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INFECTED BLOOD INQUIRY

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Red Alert!

Is regulation working for imported and CSL blood products?

Katherine Beauchamp

Australian Blood Regulators Study
First Report

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UNIVERSITY OF CANBERRA

Centre for National Corporate Law Research

Mr Laurie Glanfield
Chairman
Criminology Research Council
GPO Box 2944
ACT 2601

Dear Mr Glanfield,

As Principal Investigator for the study entitled 'Blood Pressure — the Ability of Australian Regulators to respond to a Worldwide Trend Towards Criminal Transactions in Blood', I am pleased to forward my First Report which covers regulation of processed blood products.

As you are aware, the study commenced in March 1992 but was drawn out by difficulties in access to material and intervening responsibilities of my own. I thank both the Council and Ms Lavinia Hill in the Secretariat for their understanding, patience and assistance in these matters. The study was further extended by my decision to study new regulatory schemes introduced after my application to the Council for funds.

I wish to record here my appreciation of the support given me by staff at the University of Canberra, particularly the co-applicant for funds, Professor Roman Tomasic, whose guidance, advice, assistance, and commitment to the topic and confidence in my progress have been invaluable.

I commend the Council for funding this project, which still appears to be the first of its kind worldwide, modest though it is in comparison with what still needs to be done. The importance of studies on regulating human blood supplies is readily acknowledged by many institutions globally; few have given practical support so far. My findings show there is room and need for more such support and for more scholars and commentators in this largely neglected but vital field.

Yours sincerely,

GRO-C

Katherine Beauchamp
Honorary Research Associate
June 1994

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The Centre houses the editorial offices of the
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Summary of Problems and Suggested Solutions

Main problem areas identified
The following is a summary of the main problem areas identified by the Australian Blood Regulators Study in respect of blood products for human use in Australia.

1 Lack of clear policy on human blood

Lack of co-ordination, indifference and neglect of blood policy within the Health Department was found. Within a Federal system, this is the agency which should formulate policy and encourage national uniformity amongst other regulatory bodies and stakeholders, in order to ensure the effective regulation of blood products and whole blood in the public interests of safety, equitable access, affordability and availability on acceptable clinical grounds.

Especially there is unresolved conflict within and between sections of the agency as to how to weigh claims between commercial secrecy and disclosure on one hand, and claims between profit-making and community service obligations on the other.

The combination of this policy vacuum, together with TGA's deference to commercial interests and its failure to adequately regulate blood products, mean that in effect the Health Department has been significantly captured by the interests of the commercial blood sector, at domestic and international levels. This had resulted in significant betrayals of the public interest.

The Health Department, currently the chief regulator of human blood products, is not currently well positioned to protect Australia against the increasing international trend towards unlawful, criminal and unsafe practices in the manufacture of human blood products and transactions relating to them. The failure to set, promulgate and enforce clear policy. significantly undercuts the effectiveness of current regulation and will impede the success of future regulatory initiatives.

2. Lack of clarity concerning legal powers for securing compliance with TGA and weak penalties.

While this study focussed on the role of regulation, it was evident that some regulatory failures came about because of failures in policy setting, and lack of clarity or commitment to legal provisions or principles. These deficiencies require address if regulation is to

succeed. The Therapeutic Goods Act requires amendment to strengthen compliance powers and penalties, in line with criminal offences relating to 'illicit' drugs, all defined as therapeutic goods. TGA is attracting criminals into the area of because of weak legislation.

3. Lack of Information

On the part of CSL and the Health Department, there has been a cultivated lack of access and information for most stakeholders with potential to assist the regulatory process for blood products. These include Red Cross in particular, most user and consumer groups, Ministers and parliaments, professional clients of CSL in hospitals, pathology laboratories and clinics, and the media and general public. The Health Department has failed to understand its own responsibilities in respect of accessing relevant information and in consulting, especially when evaluating applications for new blood products.

This lack of access and information is unwarranted within existing legislative and common law frameworks, and within the context of a political democracy. It has been a major factor contributing to the absence of informed public debate concerning Australia's blood supply and the absence of public participation in major decisions and regulatory moves over the last three decades. This was accentuated most recently in the passive public response to government's highly questionable sale of CSL, an act which has serious implications for the regulation of human blood product manufacture in this country.

There is also a lack of timely information to consumers about safety risks in blood products, both before the risk is realised and after contamination, supply cuts or other failures have occurred. The Health Department and CSL have failed to grasp the connection between timely release of factual information about blood products and the lessening of their legal liability for harm from the use of these products. Recently there are slight signs of change on the part of the Health Department, and some change at CSL in response to requirements under trade practices law.

4. Regulation and scrutiny of CSL

The study found chronic inadequate scrutiny and regulation of CSL by the Health Department, successive Ministers, and Parliament of CSL as the nation's monopoly processor of blood products under community service or national interest obligations. This lack was

somewhat ameliorated by the new Therapeutic Goods Administration in the nineties but remains inadequate. The inadequacies applied to CSL as a statutory commission from 1961 and later when it was also a company and then also a 'government business enterprise'. The opportunities for effective scrutiny and regulation have in some areas been diminished by CSL's sale in 1994.

5. Export/import control

There is a lack of adequate control by the TGA, the Civil Aviation Authority and Customs over blood products moving in and out of Australia, whether CSL or overseas product. The Therapeutic Goods Act regulates goods at the point of sale rather than import.

6. Control of source of foreign blood

The Therapeutic Goods Administration has insufficient powers to effectively regulate foreign blood products imported into Australia. This has particularly serious ramifications for products available to certain patients Special Access Scheme before full evaluation. The study also found evidence that existing TGA powers were not appropriately used and that it withholds information to which clinicians, users and potential users are entitled in considering use of blood products.

There is an immediate need to evaluate the adequacy of TGA's legislative powers in respect of blood products as distinct from non-biologically derived therapeutics goods. There is an immediate need for mechanisms to ensure that the Therapeutic Goods Administration is made publicly accountable for the way in which it regulates manufacturing and quality assurance for human blood products, and the way in which it deals with applications for new blood products.

There are implications for user safety and government's legal liability in the regulatory system as it now stands.

7. Regulation of supply, demand, usage and patient consent

Regulation of blood product usage, and the securing of informed consent by users (especially under the Special Access Scheme) is presently patchy and inadequate on the part of hospital boards and administering clinicians in Australia. The Health Department, despite its stated concern to ensure a safe and adequate supply of blood and blood products, has not yet assumed its responsibilities

in this field, although there are slight signs of willingness to proceed. (The role of state Health Departments is not part of this report). There are implications for safety, availability, equity in access and legal liability in the shared failure of agencies, hospitals and clinicians to regulate usage.

8. Questionable practices by CSL

This report presents evidence of questionable practices in the Bioplasma Division and other parts of CSL, Australia's sole manufacturer of blood products. CSL abused its legislative powers, its delegated authority and the trust of its clients and the public over a long period, and failed to account for its activities to relevant authorities. Regulators have too often failed to detect or act appropriately to remedy and prevent these questionable practices.

9. CSL Co-operation lacking

CSL has been reluctant and ineffective in its communication with other parties involved in the co-operative system of delivering blood products to the Australian community. Its recent efforts to remedy this fall far short of what is needed, according to evidence given to this study.

10. Red Cross Blood Transfusion Service inadequately empowered

Red Cross Blood Transfusion Services personnel have attempted with limited success to 'regulate' CSL's conduct as blood processors and suppliers back to Red Cross of blood products derived from Red Cross starting plasma. Red Cross Blood Transfusion Services are well placed to play a major role in the regulatory process and should be empowered by the Federal Government to assist.

11. CSL history of bucking regulation and accountability

CSL was found to have an attitude approaching contempt for external regulators, parliamentary and public accountability going back over more than three decades. This culture may function as a foil to regulatory success for blood products. Changes in the nineties may be overturning this ethos but the study found contemporary evidence of questionable practices continuing in the Bioplasma Division. The company's public claims to change could not be properly tested because senior management refused to communicate with the principal investigator for this study.

12. Sale of CSL questionable

The government's precipitous decision to sell CSL ruled out prior debate on regulatory implications for human blood products and the future of the company's national interest products. The sale process was unduly secretive. This prevented stakeholders, including even process participants such as the Health Department on evidence given, from scrutinising decision-making processes with implications for the regulation of blood products and CSL's other national interest products. Significant regulatory opportunities have been lost in the process to private sale. These effects, taken together with evidence of questionable practices at CSL regarding blood products and a range of other activities over three decades, give rise to real concern about the degree to which future regulation of domestic blood product manufacture can succeed.

Nevertheless, the Health Department is in a good position to expand existing powers and create new opportunities for regulation of CSL's processing of blood products.

The Health Department should:

- .accept its role as initiator and co-ordinator of a co-operative federal effort to establish a uniform national system of blood supplies in accordance with the policy of pursuing a closed national self-sufficient system based on unremunerated blood donation;
- empower other parties such as Red Cross, and health consumers, to assist with this goal;
- work co-operatively and creatively within the Federal system;
- consult experts on creative and responsive regulatory solutions to situations requiring legal, policy or regulatory know-how;
- .share information with individuals and groups who could play a watchdog role on the conduct of CSL, and on other companies and parties who deal with human blood products.

Recommendations

R.1 The Health Department should write down its policy of pursuing a national system of blood supply based upon non-remunerated blood and

publish it to particular publics with an interest in the quality of the Australian blood supply and blood products, including its own officials.

R.2 The Federal Government should take responsibility for seeing a national system for the supply and usage of blood and blood products devised, implemented and uniformly regulated.

R.3 The Health Department should assign policy responsibility for blood and blood products to a section of the agency on different command lines than the Therapeutic Goods Administration. This section of the agency should determine a program of steps designed to achieve a uniform national system, based upon co-operative federalism and according to the eight goals set out in chapter one.

R.4 A 'focal point' for Government policy and regulation on blood and blood products has been needed since at least the late seventies. The Health Department should establish a small unit within the Department to address the need for policy formulation and regulation of human blood and blood products. Consideration should be given to the need for an external National Blood Commission as well, to function as a public 'focal point' in order to better implement co-ordinated uniform national policy within the Federal system.

This new Unit should:

1. Make its presence and purposes known to all Government and non Government agencies with an interest or stake in blood policy, including all relevant areas of the Health Department and the Department of Defence, the Trade Practices Commission, the Federal Bureau of Consumer Affairs, AQIS, CAA Customs, the Australian Securities Commission, NHMRC, State Health Departments, the National Association of Testing Authorities, hospital boards, the HFA, consumer groups representing or capable of representing users and the general public, health unions, colleges capable of influencing blood usage, Red Cross, CSL, foreign and domestic companies, IVF clinics and research bodies using or processing human blood and transport unions.

2. Formulate a policy for consultation and information-sharing within these agencies, especially a standing mechanism with the States for ensuring a uniform approach to effective policy and regulation. The Unit should actively promote the need for a 'seamless government' approach, whereby agencies commit themselves to collectively and co-operatively addressing blood policy and regulation rather than committing only to areas defined

as belonging to their agency. The unit should also promote the need for a 'no surprises' operating style between agencies.

3. After consultation formulate a contemporary policy on blood and blood product supply, based upon the commitment to a national, closed system of blood derived from non remunerated donors, in keeping with the 1975 WHO resolution, in line with State and Territorial legislation banning the sale of human blood, and in keeping with the best overseas trends in Europe and elsewhere.

This policy should define the meaning of 'community service obligation,' or 'national interest', or 'public interest' as it relates to the human blood supply and the WHO Resolution. Particularly it should give in principle guidance concerning how the public interst should be weighed against commercial or other interests when decisions are made by Government officials concerning access to information and decision-making processes with bearing on blood policy and regulation.

The policy should specifically affirm the actual written principles contained in the Freedom of Information Act concerning access to official information on the dissemination of information necessary (a) for stakeholders to contribute to effective regulation of blood supplies and (b) for users and potential users of blood products to be able to weigh up the risks and benefits of blood and blood products.

4. Publish that policy through appropriate channels on an ongoing basis, including the National Health and Medical Research Council which has discontinued its previous practice of making public statements exposing international commercialisation of blood, the efforts of overseas companies to break down our system and the value of the closed Australian system. ( ) *eg Melbourne Age 21.10.79.* The value of a National Blood Commission taking on this particular role should be considered in this context.

5. Recommend and advocate for any necessary legislative amendments and initiatives needed, at Federal and State levels to give the Federal Government powers to enforce the policy and its commitment to a closed non remunerated system as stated in the World Health Organisation resolution of 1975.

6. Oversee the implementation of other appropriate policy and regulatory changes such as those recommended in this report, or otherwise found to be suitable.

R.5 Rather than wait on co-operation amongst the States for legislation to complement the Federal Therapeutic Goods Act, the Health Department should seek to regulate all blood collections under the constitutional power to regulate matters incidental to the activities currently regulated under the Act.

R.6 The Health Department should acknowledge that responsibility for uniform national regulatory controls of blood and blood products includes, as a matter of course, responsibility for ensuring sufficient resources to implement them.

R.7 TGA should conduct a cost-of- regulation impact study for its regulation of blood banks and commercial fractionated blood products.

R.8 CSL and TGA should investigate the safety implications of bringing in foreign plasma which does not conform to Australian standards observed by Red Cross and other blood collection centres and publish their findings. Foreign plasma from overseas manufacturers not vetted or not tested to Australian standards should carry warnings to that effect on the product containers themselves, rather than on certificates or other documentation relating to its shipment. The status of the material should be specifically drawn to the attention of CSL personnel who handle it during manufacture, transport workers and inspectors with the Australian Quarantine and Inspection Services and Civil Aviation Authority.

R.9 The Health Department should declare as policy that the safety of blood products derived from placentae is beyond the power of regulators to adequately control and should seek legislation prohibiting human placentae as starting material for these products. Unless the innate safety risk for blood products can be eliminated for other products derived from placentae, the legislative should prohibit placentae in all biological products.

R.10 In the meantime the TGA should inform CSL that their manufacturing license is subject to the company not making use of placental material on grounds they pose an unacceptable safety risk.

R.11 The Health Department should immediately increase its inspectors for the Code on Blood and Blood Products to realistic levels so it can adequately enforce the license requirements contained in the Therapeutic Goods Act.

R.12 Australia should rely on GMP audit reports only from countries whose inspectorates subject themselves to independent audit. In countries where significant failures in blood safety come to light the audit and product evaluation reports of those countries should not be relied upon

unless or until the overseas agency is officially cleared of responsibility for the failure.

R.13 TGA should maintain a uniform policy of not heralding inspections of blood collection centres and CSL's fractionation plant and when relying on overseas reports should require the same policy to have been implemented by the agency generating the report.

R.14 As part of a national system of blood and blood banking the Feeral Government should require uniform tests by blood collection centres and CSL. Decisions on what tests to run should be decided on clinical and public health grounds in the first instance, by appropriate scientific personnel within TGA drawing on available expertise. The tests to be run should be expressed as standards under the Therapeutic Goods Legislation and funded by the Commonwealth and States.

R.15 As a further means of preventing disease from blood and blood products, the benefits and costs of quarantine storage for blood, should be investigated by the Federal Government and the States in consultation with consumer representatives, Red Cross and other relevant stakeholders.

R.16 Therapeutic Goods Act provisions permitting manufacturers to 'grandfather' blood or blood products where their continued production could result in avoidable harm to users and handlers are unacceptable. If manufacturers are still operating without a licence in ways which pose safety or other serious risks, the Health Department should inform itself of this immediately and use its standing to have manufacturers remedy the situation, while advocating for amendment of the legislative provisions for any remaining 'grandfathered' centres still seeking licenses if applicable. If plasma has been sent to CSL from blood collection centres without adequate testing over the past two years while licensing has been progressively introduced, the TGA should make a detailed report on this matter to the Secretary of the Health Department, and patients who have received blood or blood products derived from inadequately tested material should be informed of the facts and of the possible effects of the practice for their health.

R.17 The Therapeutic Goods Act should be extended without delay to regulate collections of whole blood and its distribution as blood or platelets for hospital use. This could be done by the States and Territories giving the Federal Government the authority to regulate these activities. Any delay or lack of commitment to this task should be resolved by address from whatever level of government is necessary to expedite the matter.

R.18 CSL should review its complaints procedure in light of evidence presented in this report. It should conform to the Australian Standards Association complaints handling standard. Its complaints mechanism should then be audited by TGA GMP auditors whose auditing emphasis should be on outcomes rather than process.

R.19 Reports of TGA audit findings should be available on a public register accessible in Canberra and all States.

R.20 Further levels of accountability should be achieved by empowering Red Cross blood bankers to accompany TGA inspectors on inspections of the Bioplasma Division of CSL, especially when inspections are prompted by complaints from Red Cross or other clients.

R.21 The TGA inspectorate for blood banks and CSL should be required by law to submit itself to external audit by agencies such as the FDA's office of biologics, the reports to be made available to an external party such as a National Blood Commissioner, the Australian Health Minister's Advisory Council, or the Health Minister, and also to the general public.

R.22 There is a need for a 'mopping up exercise' by regulators and CSL itself in respect of accountability and possibly liability over the past practice of mixing plasma of difference sources.

R.23 The National Association of Testing Authorities should be required by law to submit to regular external audit for its inspection activities relating to blood testing laboratories.

R.24 The Therapeutic Goods Act should be extended to incude recall and forfeiture powers.

R.25 Since blood and its derivatives cannot be standardised as can chemical entities, evaluators should offset this liability by placing less weight on evaluation reports from foreign regulators than they would for pharmaceuticals, and less weight also on inspection reports by regulators of foreign plasma collection centres. This re-weighting could be achieved by, for example, supplementing study of foreign inspection reports with direct inspection by TGA of collection centres as a matter of routine, and by greater independent assessment of evaluation reports furnished by foreign countries. Even less weight should be placed on reports from regulatory authorities which or have been subject to inquiry and adverse findings pertinent the quality of their evaluation of therapeutic goods in general, or blood and blood products in particular.

R.26 The Health Department should seek expert advide from TGA scientists concerning the feasibility and effectiveness of requiring 'fifth phase' clinical trials for biological products.

R.27 The TGA should develop a protocol for the application of grandfathering to blood and blood products, (preferably as part of an overall protocol on biologicals). The legislation should be amended if needed to make this protocol enforceable.

R.28 Therapeutic goods which have been grandfathered under the Therapeutic Goos Act 1989 should be required by law to carry a statement that the Federal Government has (a) never or (b) not since the commencement of the Therapeutic Goods Act 1989, evaluated the goods for their quality, safety or efficacy, and this statement should be required to reach the consumer. When CPI is made a requirement it should include such statements.

R.29 Special access for blood products should be reviewed and consideration given to restricting its applicability to patients who are terminally ill only, or for those in danger of death or seriously ill. In its present form, it should require a dialogue between a TGA officer and the ordering physician before the product can be administered. If the ordering physician elects to proceed s/he should be required to inform the patient of the dialogue and its content. Hospitals should be required to ensure that an independent second opinion is given in writing concerning the status of the patient and the soundness of administering the product in the circumstances, (taking into account available alternatives) and these written opinions should be furnished to the patient before consent is given.

R.30 In a system adhering to a policy of pursuing national self-sufficiency in blood supply from non remunerated donors, any suggestion of inadequate product or supply should be referred in the first instance to an officer responsible for having the policy implemented. The first line of inquiry should be why isn't the product available in Australia. The second line of inquiry should be how it can be made available from within the Australian system. The last should be how can we bring in a foreign version.

R.31 There is a case for reviewing the use of blood products under special access schemes with a view to restricting their use unless and until more evaluation data can be tapped from other countries. Alternatively, the Secretary of the Health Department should require, under the Therapeutic Goods Act, that the TGA be responsible for monitoring patient consent much more closely. This could take the form of occasional random follow-up interviews of patients to check that informed consent was properly

obtained. If it was not, the TGA could make a submission to the appropriate medical board alleging irresponsible medical practice on the part of the relevant clinician. The hospitals in which most of these blood products are administered could also be deemed to be the body treating the patient, making monitoring and regulation much easier.

R.32 For foreign blood products from countries with whom TGA has data exchanging arrangements, where these products are allowed under the Special Access Scheme, the Secretary should instruct TGA to obtain relevant data on overseas applications which have failed or not been approved because of safety considerations. The administering clinician should be required by hospitals to inform the patient that approval has been refused on safety grounds, after receiving the relevant data from TGA (with data identifying the manufacturer excised).

R.33 The same recommendation above should apply for local products.

(The Secretary is already empowered under the legislation to require and release information which is necessary to ensure the safe use of particular therapeutic goods). ( ) *S 61(7)*

R.34 Written evidence of the patient's understanding on this point should be obtained by the clinician from the patient or a patient representative before administering the product, and should be furnished to the hospital and TGA before or at the time the product is administered.

R.35 The Federal Government should not passively permit TGA to bring in blood products on the basis of 'clinical need' as this criterion is insufficient for making decisions about products derived from blood. Decisions must also take account of the cost to the user or hospitals of these products compared to Australian products, the impact of importation on local supply dynamics and the special challenges which foreign blood products pose for regulators in respect of safety.

R.36 The Federal Government should make its purchase of CSL's existing range of blood products conditional upon CSL also producing other products for which a clear clinical need has been established, thus offering the national fractionator a financial incentive to develop home products while permitting the Federal Government to stay true to the national policy of pursuing a closed self-sufficient system of unremunerated blood supply for Australia.

R.37 Where more discretion is sought in trials systems, there should be assurance of independence of judgment, dialogue, and clear accountability for the discretion.

R.38 Biological products at an early stage of development, where a virology review is considered desireable, should go under the more stringent CTX trial rather than the CTN scheme. (This recommendation comes from a Health Department Report).

R.39 As a standing acitvity, a random audit of ethics committee deliberations, or an auditing role when negative indicators come to light, should be undertaken to augment the CTN scheme, and the reports should be public. The audit need not be done by the TGA but could be undertaken by an external body approved by the TGA and paid for by the sponsors of the trial. The external body should consist of people experienced with Ethics Committees, so that it functions as a peer review scheme.

Alternatively, TGA could tighten the approval process again, and charge sponsors for their expertise in assessing proposals, to avoid a return to the previous practice of companies exploiting Health Department resources.

R.40 Before long the Health Department should undertake a cost-of-deregulation impact study of its trials approval and notification schemes, and should not keep shoring up the system if the costs outweigh the benefits.

R.41 State and Federal governments should fund research to establish from whom the general public and donors would best receive information about the importance of unpaid blood donation and the effects of commercialisation, and should fund appropriate information programs designed to improve supply and maintain public confidence in unpaid blood donation.

R.42 The potential of Australian plasmapheresis programs to meet demand for blood products should be reviewed to establish whether their funding and development can increase supply and reduce the need for foreign imports.

R.43 The Health Department should determine an acceptable clinical level of haemophiliac treatment within the context of its health budget allowing for equity in access for other needy groups. Then it should compare the cost of local production for that level with the cost of recombinant. If recombinant is cheaper, it should not allow infrastructure for plasma derived factor VIII to be run down, because the safety of the recombinant will not be known for some time. If local production is cheaper, the Federal Government and State governments should discourage the use of recombinant factor VIII by adjustments in government funding and should educate clinicians accordingly.

R.44 There is a clear need for governments, led at the national level, to pursue compliance with guidelines on the appropriate use of blood and blood products.

R.45 Federal and State Health Departments should co-operatively and in consultation with Australian Red Cross Society and other relevant parties determine the effects of current policy, regulation and funding levels on supply and demand, and make recommendations for changes as needed.

R.46 The Health Department should actively promote the importance of clinicians, manufacturers and users reporting problems with blood products to the Department. This promotion should be done at least through the Adverse Drug Reactions Bulletin and the Australian Prescriber, in order to reach all specialist and general medical practitioners and pharmacists. The Department should investigate reported problems and publish summaries of reports and the findings in ADRB, the Australian Prescriber and to blood banks, hospital and clinics using blood products. Investigations should be extended, where multiple adverse reaction reports are received for one product, to studies designed to determine the nature and extent of risk for that blood product.

R.47 As with pharmaceuticals on the pharmaceutical benefit schedule, the Health Department should implement a consumer education program designed to show consumers how to recognise and assist in the reporting of adverse reactions. This information should be distributed to consumers through hospital pharmacies, treatment clinics for blood clotting disorders, and organisations such as the Haemophilia Foundation.

R.48 Blood and blood products should be considered to have the same status as prescription pharmaceuticals for the purpose of legislation governing the supply of patient information: regulations applying to consent should apply to both therapeutic groups.

R.49 Legislation should be framed to ensure that all relevant health professionals involved in ordering or administering blood and blood products provide appropriate patient information, and carry out their common law duties to obtain informed consent.

R.50 The National Health and Medical Research Guidelines for Medical Practitioners Providing Information to Consumers should be disseminated to all health professionals involved in ordering and administering blood and blood products; the guidelines could state that they apply where blood and blood products are given.

R.51 The Health Department and National Health and Medical Research Council should continue in its recent form of acknowledging in public

that biologically-derived products cannot be fully standardised and carry innate risks. Drawing on appropriate scientific and legal expertise they should then draw up a protocol for general patient information on blood products derived from Australian plasma and a separate protocol for foreign products, which sets out:

1. the general nature of biological products and how this sets them apart from pharmaceutical products;

2 their potential for harm from disease, other contamination and individual patient 'allergic' reactions;

3. the relative safety of paid versus unpaid donation;

4. the limits of testing to assure screening for known and unrecognised disease;

5. the limitations on regulators in assuring quality and safety, including whether the product is grandfathered or made available under the Special Access Scheme;

6 The obligation of TGA to inform practitioners if the status of an overseas regulatory body on whom the TGA relies to certify products, or of an overseas supplier, becomes questionable; (see earlier recommendations)

7 the statuary and common law duties of clinicians to inform patients of these factors when obtaining consent;

8. The importance of practitioners not degrading the status of information intended to assist the patient in giving or withholding consent on informed grounds, by adding their own opinion of the data given or overriding it with generalised reassurances not borne out by the facts available to the patient;

9. The elements involved in the process between the medical practitioner and the patient of actually obtaining informed consent, including the need to ensure by questioning and two-way communications that the patient, irrespective of any language, ethnic or other barriers, are brought by the practitioner to a state of understanding before giving their written consent; provision of written patient data is not sufficient for obtaining informed consent.

10. The need to document the process and outcome of obtaining informed consent and to obtain the patient's declaration that the process was carried out and informed consent was given.

These protocols should be disseminated on all lines currently used for pharmaceuticals and to specialist groups involved with the supply of blood and blood products, including under the Special Access Scheme, and should be given to the patient in written form at the same time as specific product information.

R.52 Patient information should be consistent with and not contain less data than product information.

R.53 The protocols should then be backed by Federal rather than States legislation, either under the Therapeutic Goods Act or as part of future law relating to requirements for informed patient consent, and included also in the National Health and Medical Research Council 'General Guidelines for Medical Practitioners on Providing Information to Patients'.

R.54 Responsibility for seeing that patient information for blood and blood products aligns with relevant regulations and product information, and actually reaches the patient and is understood by them, should not under any circumstances be left to the sponsor alone, since the sponsor alone is not capable of discharging this responsibility. The responsibility must be recognised in policy, law and practice as a mutual obligation between Federal and State governments who subsidise and regulate blood and blood products in the public interest, manufacturers, hospitals and other suppliers, accident and emergency departments, medical practitioners, nurses and ambulance paramedics, and learned intermediaries involved in their delivery to the patient, such as pharmacists.

R.55 Clinicians, nurses and others involved in delivery of these products to patients should be educated to ensure compliance with consumer product information. The cost of these programs should be born by the practitioners and other health professionals, since the programs assist them in discharging their existing legal and ethical duties to inform patients and obtain their consent.

R.56 Federal and State Health Departments, hospital boards, medical associations and consumer groups with a stake in the safe, appropriate use of blood and blood products, especially the Australian Red Cross Society, the Haemophilia Foundation and health consumer groups, should individually and co-operatively declare that practitioners must obtain written evidence that informed consent has been obtained as proof that they have met their common law obligations. The TGA must recognise its responsibilities to provide relevant information concerning blood products to permit this process.

R.57 Consumer groups should be empowered to take part in the development of consumer patient information on blood and blood products as they are the principal stakeholder.

R.58 The Federal Government should favour research aimed at developing alternatives to human blood and urge its progress in appropriate international circles.

R.59 The Therapeutic Goods Act should provide for recall of therapeutic goods and forfeiture of goods on conviction of an offence.

R.60 Legislators should appreciate that improper manufacture and supply of goods under the legislation can cause as much harm as manufacture and supply of the same goods supplied 'illicitly'. In terms of deterring criminal supply, the distinction between an illicit manufacturer and a lawful or licensed manufacture is not relevant when framing offences under the legislation.

R.61 Provisions in the Therapeutic Goods Act relating to intention in committing indictable offences and to penalties should be reviewed and brought into line with legislative sanctions for criminal and unlawful activities relating to the supply of 'illicit' drugs, all of which fall within the definition of therapeutic goods.

R.62 The Therapeutic Goods Administration should use its authority as regulators of therapeutic goods and its commitment to maintaining a closed national system of blood supply to assist the latest international movement towards uniform standards and regulatory schemes for blood and blood products based upon non-remunerated blood supply. To assist it in this, it should first actively inform itself of the nature of the international blood industry and its effects upon safety, efficacy, appropriate use and equity in access.

R.63 All TGA's consumer safety activities must be adequately staffed and resourced. In particular, there should be no shortages in surveillance and inspection resources as against product evaluations and approvals as this can invalidate the purpose of approving goods for therapeutic use and can contribute to increases in crime and unlawful behaviour.

R.64 Anti-corruption compliance systems should be introduced to the Health Department, involving duties to report ethical concerns followed by review and discussion, and resolution of the concerns in writing.

R.65 TGA officials and consultants should disclose on a register all their pecuniary and other relevant interests in corporations and other organisations involved with the manufacture, trialing and supply of blood

or blood products or pharmaceuticals and any past interests that could be perceived as a conflict with their current activities, including substantial periods of employment with CSL. The register should be available to the public without charge and without the need to apply for access under Freedom of Information legislation.

R.66 TGA's Compliance Branch should investigate the sending of Red Cross material to Hong Kong by CSL, and follow up allegations of other instances and practices of doing the same, and TGA's General Manage should provide a report to the Secretary of the Health Department. The Minister should make public the results of this investigations.

R.67 The Board of CSL should also investigate the incident and assist the TGA in establishing whether any other incidents of this nature have occurred. The Board should also publish its findings, and any procedures or disciplinary action instituted to ensure that the behaviour cannot be repeated.

R.68 The Therapeutic Goods Administration should require foreign consigners of plasma for fractionation at CSL to provide sponsor certification that the plasma coming in was collected locally and from unremunerated donation, and to specify volume.

R.69 Regulators should assume that products which pose an HIV risk also pose a hepatitis risk, which means they should all be classed as potentially infectious for the purposes of regulating them.

R.70 For human blood and blood products imported into Australia, permits should be required by law to declare (a) where the goods are of human origin, (b) whether they are for human use or otherwise (c) the country of origin of the blood or blood fraction in the product, (d) the country of manufacture and manufacturer's name in that country (e) whether there is any reasonable possibility that the goods could be infectious.

R.71 Quarantine permits should be strengthened to direct importers to use correct packaging. Consideration should be given to whether a requirement that permits meet international rules regarding infectious substances, would have the effect of rendering the permit invalid if an imported breached these conditions. The option for strengthening permits should be considered if it would have that affect.

R.72 In order to reduce product failures leading to product liability suits, the Federal Health Department should (a) assume its responsibilities for regulating testing procedures, especially the need for a uniform national policy on what tests should be run; (b) assume its responsibilities for

informing Australians of the innate risks in blood and blood products; (c) enforce informed patient consent and (d) recognise that its responsibility for establishing a national blood service includes compensating those who are harmed through use of these products.

R.73 The Federal Government should, in conjunction with the States, examine the costs and benefits of a no-fault compensation scheme for biological products provided on behalf of Government in the public interest. Carriage of this review should not lie with the Federal Health Department, because of its past unsatisfactory record in taking proper account of the public interest and the rights of consumers.

R.74 A complaints mechanism should be established within the Health Department for matters referred by Red Cross, clinicians, and other clients of CSL in respect of blood product development, manufacture and supply. Responsibility for receiving and co-ordinating complaints should not lie with the Therapeutic Goods Administration, but should lie with an official responsible for blood policy, senior to those officials with responsibilities for regulating the agency's business with CSL, or funding Red Cross via the States.

R.75 Designated Red Cross blood banking officials should be permitted to accompany TGA inspectors on inspections of CSL for manufacture of product derived from Red Cross owned starting material. Alternatively, such Red Cross officials should be given access to TGA inspection reports.

R.76 Consumer groups should be empowered by government with resources and information so they may represent the views of all users of blood and blood products.

R.77 CSL's Bioplasma division and management senior to that Division should be required by Government in consultation with the Directors of the Company, to comply with a series of external accountability exercises designed to test their responsiveness - within the framework of the national policy on blood supply - to clients, suppliers, shareholders and the community of blood product users and potential blood product users - that is, the Australian community, and governments or communities of users in overseas countries for which the country fractionates plasma into blood products. Government is in a position to secure compliance from CSL on the basis that it is the company's sole client for Australian blood products.

CSL should table for a consultative committee a plan to ensure the transformation of its corporate ethos. This should be designed to overcome secrecy, ensure government and public accountability for the manufacture of Australian blood products, and implement credible internal compliance

and ethics programs. The primary emphasis and purpose in this plan should be to enable the realisation of the eight regulatory goals postulated in chapter one of this report. The plan must include positive measures to rule out the compromising of these goals by CSL's commercial and international activities. The plan should be modified in light of consultation with relevant stakeholders. CSL should report to the consultative committee on progress with the performance indicators in the plan.

The company should commit to continuous publication of quality assurance policies and quality outcome indicators.

R.78 CSL's should consider pairing the Bioplasma Division with a 'sister' organisation from another country, preferably a state-owned fractionation facility, to permit continuous mutual peer review of its compliance with regulatory programs.

R.79 As a contractor to the Federal Government, CSL should be covered by the Freedom of Information Act 1982 to the extent that information collected relates to blood product contracts. A condition of contract should be CSL's commitment to a code on information access.

R.80 CSL should be required by law to be ISO 9000 accredited.

R.81 The Health Department should make compliance with the Australian Standards Association standard on complaint handling a condition of its plasma fractionation contract with CSL, by stating in writing to CSL that it is a requirement.

R.82 CSL should be required by regulation to keep public complaint registers and performance indicators in a Quality assurance plan for improvement in complaint resolution performance in relation to blood and blood products, vaccines and other products which Governments purchase under their community service obligations.

R.83 In the absence of legislation requiring that corporation boards include a fixed percentage of independent non-executive directors, the Board of CSL should consider appointing such a Director now, to assist the company in (a) appropriate regulation of the manufacture of biological products for government (b) the introduction of public and client accountability measures for the company's blood processing activities, (c) an internal whistleblowers office and (d) shareholder communication policies and programs which recognise the equal right of individual shareholders to the same information about the company's business as is given to institutional shareholders and pledge that individual and

institutional shareholders will have access to the same information simultaneously.

Such a Director could be called the Public Interest Director. While this Director should have skills which suit him or her to direct the design and implementation of accountability measures, he or she should not, however, be taken to be responsible for implementing or maintaining these measures as that responsibility should rest with the Board as a whole.

R.84 Corporations Law should recognise the role of a board as a body by providing that public company Board members are jointly and severally liable for the actions and omissions of any particular director.

PART ONE - PRELIMINARIES

The best regulation for human blood supplies will:

1. encourage and not work against unremunerated blood donation.

2. encourage and not work against the use of Australian blood and plasma rather than overseas material.

3. encourage and not work against the use of blood and plasma for clinical purposes only.

4. encourage minimum harm to users and people who handle blood and blood products.

5. encourage maximum efficacy from blood and blood products of the highest affordable quality.

6. encourage adequate supply without harming or exploiting donors.

7. encourage equity of access on the basis of clinical need;

8. ensure the consent of users;

CHAPTER ONE: INTRODUCTION

Concerning the manufacture of human blood products in Australia, the Australian regulatory field supports few robust life forms. The new Therapeutic Goods Administration within the Federal Department of Human Services and Health is still proving its mettle. With proper resourcing it could be effective in its role as a regulator of blood and blood products, but it has a major task because the vast majority of regulatory turf covering human blood products has long been overgrown by thickets of political expediency, rank indifference to goals other than profit-maximisation and deregulation, and by bureaucratic interventionism alternating with a hands-off approach which matured into virtual absenteeism until very recently.

Nutrients such as public health and national interest policy occur inconsistently and often in trace form or not at all in the considerations of regulators. Yet these vital elements must be spelled out and constantly reinforced if our commitment to national self-sufficiency in unremunerated blood supplies is to amount to anything in practice.

Covering much of the regulatory field is a fine bloom of secrecy, carefully cultivated and nourished. And for the duration of this study, over all activities relating to our monopoly blood fractionator, CSL, fell the long deep shadow of secrecy caste by Task Force B of the Department of Finance as CSL was put through the due diligence process to prepare it for sale.

All this secrecy prevents and distorts one's perception of what lies beneath and limits the possibilities for ordered scrutiny. The results of the study are therefore more a statement about the culture or art form of non-disclosure by principal government agencies with regulatory responsibilities for CSL Ltd and imported blood products, and non disclosure of the corporation itself, rather than being a thorough review of how regulation is working.

The findings may also well be a non-representative sample of instances of regulatory failure, absence or aberration. If this is so, it is a function of government and corporate secrecy. This would have to be cut away were future investigators to come up with any more thorough picture of the regulatory life of CSL and foreign biologicals companies selling blood products in Australia. For the now-privatised CSL, regulatory controls may be more or less effective. But the potential for public involvement in the regulatory process and public accountability for blood and blood products has without doubt been substantially lost. As potential players in the regulatory process, consumers, the media, potential consumers, the general public and the parliament have all along been little more than pawns or broken pieces in the game, and now are even more so.

1.1 Ambit of this study

This study was conducted over a time period in which major regulatory changes and other significant developments occurred. The Therapeutic Goods Administration was establishing itself as a regulator for blood and blood products under the new Act, administering the new Code on Blood and Blood Products and the code of good manufacturing practices for medicines. This latter GMP code had existed in various forms for over three decades but this study found that it had effectively not been applied to CSL up until 1991. CSL had recently been corporatised and had adopted a corporate plan; the new fractionation plant was under construction and had begun some production by the end of the study, although it was yet to be fully licensed by the Therapeutic Goods Administration. The due diligence process was under way to prepare CSL for sale, which finally occurred after the study was substantially completed.

All these unfolding developments had regulatory implications which needed to be taken into account, although the funding resources did not extend to them. Their establishment during the course of the study meant we were constantly trying to study targets which not only kept moving, but constantly changed in characteristic and sometimes disappeared altogether. This phenomenon of constant change needs to the borne in mind when reading the report, as does the fact that new developments are continuing still.

Much of the research material on how CSL was regulated as a statutory authority became in one sense historical when CSL became a private company. Yet it still retains two current values. The first is the insight it provides into how government failed to regulate one of its commissions and how the commission - and the marketplace - failed to adequately regulate CSL, particularly in respect of human blood products. The second value in the material is that it details for future regulators the history of CSL's evasion and non compliance with external regulatory schemes, which arguably has bearing on how the corporation may behave in future.

1.2 What are blood products?

As the title conveys, this particular report of the Australian Blood Regulators Study is limited to regulation for human blood products, although it was necessary to inquire into the regulation of blood collections to some degree, as these provide the starting material from which blood products are then made. The study included more detailed investigation of blood collections, which will be reported separately.

Human blood can be used in whole form or as fractions of blood, and for many different purposes. Cosmetics may contain placental blood extracts, plasma may be used as a culture medium for in vitro fertilisation of human embryos, recombinant products may be mixed with an albumin solution after manufacture, blood derivatives may be contained in minute amounts in diagnostic testing kids, blood banks may spin whole blood into various components.

In this report, the term blood products means those products for clinical use in humans, which are based on human blood fractions and are made by a manufacturing process called fractionation, which is described below.

Examples of blood products include:

> **blood clotting agents,** (now called pro-coagulants by CSL) such as factor VIII and IX for haemophilia treatment, and protein C;
>
> various proteins from plasma called **immunoglobulins** which are used to combat disease; some vaccines are made from plasma;
>
> **albumin.** used in emergency and trauma situations where blood loss must be made up; in shock, burns cases and in surgery; in haemodialysis, a technique for removing waste materials or poisons from the blood stream.

The major clotting agent is anti haemophilic factor VIII, used to prevent or stop bleeding in haemophiliacs; it comes in various forms and purities. Factor IX is another clotting agent. Albumin is known as a plasma volume expander and the albumin protein comes in a solution. The immunoglobulins are injected into veins or muscles of people who cannot produce their own antibodies to various diseases. Specific antibodies combat conditions such as tetanus, hepatitis A, hepatitis B, measles, herpes zoster and diphtheria. They are also used for some auto-immune disorders which cause the body to make antibodies that attack its own tissues and cells. Normal immunoglobulins are used for a range of conditions, although their use is disputed for many of these indications.[1] New blood products are constantly being developed by overseas companies and research bodies. Fibrin glue is used to bind wounds together in place of sutures and has been on the market overseas for about twelve years. Fibrin glue has been imported into Australia in small amounts; some is made locally at an Australian hospital and CSL claims to be developing their own brand currently.

CSL and other blood product companies also incorporate small amounts of Red Cross blood in diagnostic kits used to establish a person's blood group before transfusion. These are supplied to private and public pathology laboratories and BTS's. CSL has a long-term agreement with the Federal Government for the supply of some diagnostic products.[2]

1.3 Meaning of fractionation or processing

This is a more complex process than the component preparation that some blood banks undertake, and requires fractionation or processing technology

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[1] *Dr. Peter Schiff, CSL, in interview with the author, 1986; various clinicians interviewed; Australian Red Cross bloodbankers.*
[2] *Prospectus for Sale of CSL, p 29, p 88, AGPS 1994.*

and plant, various heating, filtering and other techniques to inactivate viruses and other disease agents, and testing equipment and processing plant for separating blood fractions, adding solutions after manufacture of the blood product, packaging and so forth.

1.4 Who makes blood products?
Manufacture may be undertaken by fractionators owned commercially, or by the state, or in mixed ownership. CSL, the sole national fractionator for this country, was part of the Health Department until 1961, a statutory authority of the Federal Government from 1961 until this year and is now a private company.

Processed or fractionated blood products available in Australia come from two sources, overseas and CSL Ltd, which is located in Melbourne. The Health Department began importing human blood products for human use by Australians in the mid-eighties. (Human blood contained in diagnostic kits and laboratory reagents has been imported for considerably longer. For these particular products, the main regulatory goals are safety -in that they are handled by transporters, laboratory workers and researchers - and efficacy - in that they are used to detect disease, allergies and other like conditions.)

1.5 Foreign products sold in Australia
Despite Australia's long-standing policy of pursuing national self-sufficiency in non-remunerated blood supplies and States' legislation banning the sale of blood and its derivatives [3] foreign blood products are being approved for sale and use in Australia by the Federal Health Department. They may be listed on the agency's Therapeutic Goods Register after evaluation for quality, safety and efficacy or used without such evaluation where the ordering clinician certifies their need for an individual patient and obtains the patient's consent.[4].

1.6 How are blood products made?
The starting material for blood products is human plasma collected in Australia by Red Cross and some hospitals, and for overseas companies by Red Cross and other unpaid donor systems, and by commercial plasma companies who pay their donors.

In Australia, Red Cross collects roughly one hundred thousand donations annually. Plasma may be obtained from whole blood donation, or by a process called plasmapheresis, in which blood is drawn from the donor and the red cells separated and returned at the same time. The blood or plasma may end up as any of approximately seventeen different forms of blood or blood product. For every thousand donations, about eighty remain as whole blood distributed by Red Cross to hospitals and clinics for transfusion and to

[3] *Sale of Human Blood Act, 1962 S.A. followed by other states and territories over next 22 years*
[4] *Therapeutic Goods Act 1989 No. 21 of 1990 S 19*

pathology laboratories. From the remainder, Red Cross separates out certain parts. These include the red cells that are suspended in plasma and are transfused as with whole blood, platelets which help arrest bleeding and must be used within five days, and a number of other components.[5]

The remaining bulk is plasma, a sticky amber-coloured fluid which is ninety per cent water and contains proteins, such as albumin. Plasma is frozen within twenty four hours to minus thirty degrees Celsius or below, and transported to CSL in Melbourne where it is turned into a range of products by the process known as fractionation. Its products are then returned, for the most part, to Red Cross BTS's for distribution. CSL claims its fractionated blood products are used by roughly half a million Australians annually.[6] CSL also fractionates foreign plasma for a fee and returns it to the originating country.

1.7 Who distributes and pays for blood products?

After returning processed material to Red Cross or other providers, CSL invoices the Federal Government for the cost of fractionation. These blood products are not listed on the Commonwealth Pharmaceutical Benefits Schedule but are distributed by Red Cross for clinical purposes without charge (at the time of writing this) to the end user, via hospitals and clinics in the main. Some hospitals also collect blood and send plasma to CSL. Regulators in government agencies and hospitals have for may years suggested a paper accounting system of 'price signals' for blood and blood products as an incentive to cut wastage and encourage rational use. Such a system, or alternately, actual charges for blood and blood products, are currently being considered by many parties involved in the delivery, funding or regulation of blood products. Red Cross is funded jointly by the Federal Government and States, and contributes a small amount to the Blood Transfusion Services from its own funds. Products used in hospitals are paid for by the hospital.

1.8 Who administers blood products?

The administration of blood products must be authorised by and is mostly undertaken by medical practitioners, who, after charging the patient a fee for administering the product can claim reimbursement for their service from the Commonwealth Medical Benefits Schedule reimbursement scheme. The patient can claim under national health insurance for the service. Factor VIII for haemophiliac treatment may be administered at home by patients or their parents, or by nurses. In some States ambulance paramedics can administer albumin plasma volume expanders which may be needed urgently following massive blood loss.

1.9 Meaning of regulation

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[5] *ACT Red Cross BTS*
[6] *CSL Information sheet, 1994*

In this study, **regulation means the influence which is exerted on an organisation by external parties or by itself to bring about compliance with goals which are considered appropriate and necessary for the organisation's production of goods or services to an acceptable standard.** As for the term 'influence' in the above definition, a wide range of activity is assumed, including the direct and intentional acts of official regulators and the indirect or sometimes incidental effects of less formally empowered regulatory 'players' trying to influence the system in various ways.

1.10 Who are the regulators?

The author looked for evidence of a range of major types of enforcement methods normally associated with official regulation - self-regulatory enforcement, pre-marketing clearance, licensing through inspections and certification, prosecution, injunctions and directives, seizure, disclosure, adverse publicity and financial incentives. The checklist of major enforcement types for the official regulators followed fairly closely the categories identified by Braithwaite and Grabosky,[7] although non-financial incentives were also borne in mind as a regulatory tool.

1.11 Official regulators

Officially-empowered regulators of fractionated blood products include the Federal Department of Human Services and Health (referred to here as the Health Department), which regulates manufacture of blood products and their registration; the Australian Quarantine and Inspection Service, which requires permits for importing and exporting blood products; the Federal Bureau of Consumer Affairs which has a role in some product recalls and compliance with some provisions of the Trade Practices Act; Australian Customs which polices blood products moving in and out of the country in association with the Therapeutic Goods Administration of the Health Department, and a range of other such agencies. The National Association of Testing Authorities is a non-government body which inspects laboratories on government's behalf. Australian Red Cross Society is subject to Health Department regulation, is also a self-regulator, and voluntarily undergoes NATA inspection in exchange for accreditation. CSL Ltd. is subject to the Corporations Law, TGA provisions governing inspections of its manufacturing activities and registration of its products, to NATA for its laboratory inspections and also has a range of self-regulatory schemes. Hospital boards and embryonic blood usage committees now being established in some hospitals, assume regulatory roles concerning wastage and appropriate usage.

1.12 'Unofficial' regulators

Parties who effect or affect regulatory goals in a less directed, intentional or official way include **clinicians** whose prescribing patterns and requests for

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[7] *Of Manners Gentle - Enforcement Strategies of Australian Business Regulatory Agencies OUP 1986*

new products shape demand for local or imported product; **Red Cross** who supplies CSL with plasma; **parliamentarians** who raise issues for debate or scrutinise regulators and blood product manufacturers; **lawyers** who bring product liability suits; **commercial companies** who promote blood products for sale; **user and donor advocacy groups**; **media workers** who shape consumer perceptions by inquiry and publication or not; **expert commentators** who seek to influence policy, law and regulatory systems; **unions** who protect the rights of workers in the industry and may take a stand on an issue on public interest grounds and also the **general public**, who may influence policy and regulatory goals in many ways.

The general public have the potential to exert the greatest influence of all these groups and their influence may complement and even exceed that of officially empowered regulators. They may question what becomes of the blood they donate; they may question their need for blood or blood products; they may require information from their doctors before they consent to use these products; they may abstain or participate in blood donation programs; they may store their own blood for anticipated future use; they may communicate their views, needs and experiences to official regulators, product suppliers, parliamentarians, journalists and others. (Currently more and more individuals are seeking to store their own blood. Autologous bleeding is a useful measure where the blood is needed for certain planned procedures but not where unanticipated need arises or where blood products are indicated. Red Cross statistics from 1991 show that less than one percent of people require a blood transfusion in any year. The vast majority of all transfused blood goes for conditions such as cancer, renal failue and leukemia treatment, where autologous bleeding is not possible.)

Parliamentarians, consumer groups, unions, the media, CSL shareholders, expert commentators and the general public were found by this study to play negligible or no part at all in influencing the regulatory process for human blood products in Australia - except insofar as their non-participation tends to further entrench secrecy and lack of accountability by more involved players. Their potential for improving regulation of blood and blood products is vast and relatively easy to translate into effective action. The study found there were no expert commentators beyond the haematology and clinical community, such as in law, political science, consumer affairs or media.

Not all players were studied uniformly because of the lack of resources and the entry of new players late in the study, including CSL shareholders, the Australian Securities Commission and the Corporations Law scheme. Greater attention was paid to regulatory schemes with the greatest potential or actual effect on the regulatory goals set out below:

1.13 Why regulate blood products?

The study attempted to go beyond a mere description of regulatory processes for blood products, although even that had not been undertaken before in Australia. If an attempt is to be made to judge the efficacy of the systems described, one must postulate some suitable regulatory goals or else judge each regulatory activity against its stated or implied goal. The latter course was a natural path to take in the Australian setting, since governments have long pursued a clear policy of aiming for **national self-sufficiency in non-remunerated blood supplies for clinical purposes**. This national policy is discussed in more detail later in this report. It is infringed upon to varying degrees yet it is sufficiently settled and agreed upon for one to be able to infer regulatory goals from it, against which the success or failure of regulatory schemes may be measured.

Drawing from the agreed policy on national self-sufficiency in unpaid blood and from other national health policy commitments, one can postulate that the most effective regulation of blood and blood products will:

- **1. encourage and not work against unremunerated blood donation** on grounds it is likely to furnish the safest supply. Testing can never be foolproof for blood contaminants, whether known, unidentified or disease agents which are not yet producing disease in their host. Those who give blood for remuneration may be reliant on the remuneration for essential survival needs. Such people are not likely to be sufficiently healthy or fit to qualify as donors. Taking blood only from the healthiest donors is a vital backstop to inadequate testing.

- **2. encourage and not work against the use of Australian blood and plasma rather than overseas material** on the grounds that this material can be screened more effectively and to minimise exotic diseases. Many blood donations are pooled; one contaminated donation can render the pool useless. Also, foreign blood harvesting is more difficult to regulate.

- **3. encourage and not work against the use of blood and plasma for clinical purposes only.** Human blood is a scarce national resource and should not be wasted on unapproved experimental therapeutic use, comfort or luxury use, or cosmetic use; nor should it be preferred ahead of a suitable non-biologically derived product.

- **4. encourage minimum harm to users and people who handle blood and blood products;** this also implies regulation of usage to minimise unnecessary exposure to blood and blood products; it implies the use of the best available affordable testing ; it implies telling the general public as potential users of the innate risks in using blood products and telling individual users of particular risks for individual products prior to administration.

- **5. encourage maximum efficacy from blood and blood products of the highest affordable quality;** this implies that those who administer and

supply blood products should establish the efficacy of the products for given indications and implies that supply should be withheld if efficacy cannot be established.

- 6. **encourage adequate supply without harming or exploiting donors.** Bleeding of donors for whole blood or plasma, and inoculation of donors for particular blood fractions should only be undertaken once the risks for the long and short term have been established, in order to avoid experimentation at the possible expense of donors health. If risks cannot be established either way, bleeding should not be undertaken, unless the donor knows the procedure is experimental and carries risks.

- 7. **encourages equity of access on the basis of clinical need;** a blood system established within a democracy, funded by public taxes, supported by voluntary gift from members of the community in trust it will reach people in need, and supplying goods for medical use in the national interest cannot then discriminate amongst its citizens by releasing these products on grounds such as capacity to pay.

- 8. **ensures the consent of users;** informed consent is needed to empower users to make clinicians more accountable and responsible when ordering blood and blood products and to allow users to be responsible for their health decisions.

1.14 The challenge in regulating biologically-derived products

As a former senior regulator with the Health Department put it:

> What do you do about regulating biologicals? They are only as good as the people they come from.

It is important to understand the challenge that biologically-derived products present to regulators and manufacturers. The Therapeutic Goods Administration of the Health Department has chosen to classify these therapeutic agents with drugs and then bring them under Therapeutic Goods Administration. Another section of the same agency groups them with human organ donation. All biologically derived or biologically based products (such as blood products, herbs, human and animal tissue and blood) differ from synthesised chemical entities in many ways that often make their sound manufacture extremely difficult, their safety liable to some disaster, and the resultant implications for effective regulation extremely challenging.

The human body cannot be compared to a laboratory or manufacturing plant in which chemicals are synthesised for drug making under strict quality controls.

1.15 What is blood?

Sometimes when people talk about blood they include meanings which derive from symbolism, patriotism and other value systems - blue blood, tainted blood, good or bad blood, family blood and so on. One commentator analysing the French blood scandal, in which HIV-infected blood was knowingly distributed to haemophiliacs, found evidence amongst even senior regulators of unwillingness to accept that French blood could possibly be bad, meaning diseased. This apparently derived in part from the French perception of blood as a symbol of past victories at war- *la gloire de France* [8] - which might even be recaptured a little if the French Central Blood Bank conquered the European plasma market and beyond? This perception did not necessarily operate at a conscious level.

Blood is a fluid tissue that circulates throughout the body via the arteries and veins. It carries an immense variety of different substances between transported between organs and tissues. As it circulates around the body, blood carries nutrients and oxygen to the tissues and removes waste products, poisons and toxins. Because of this, blood could accurately be described as 'dirty' much of the time.

1.16 Role of testing and screening

Testing for impurities and disease in human blood is only possible for specific diseases and in any event is not foolproof. Then there is the unknown quantity of other diseases which may be present. Because of this factor, harvesting only from donors in general good health is regarded as the best and only remaining backstop measure against contamination of the starting material.

Beyond screening and testing measures for limiting safety risks lies a range of other regulatory possibilities and schemes which may be introduced along the stages of production, offering for sale, distribution and administration. However, none - including virus inactivation procedures - can be an absolute compensation for compromised starting material. As a CSL official said, when asked if virus could survive inactivation, 'It is a belt and braces approach ... you never say never'.

A number of overseas blood bankers, noting that some blood products have come into widespread use without sufficient and reliable clinical evidence supporting their efficacy, have urged that clinical trials for biologicals should be even more stringent than those for chemical entities, urging at the same time a kind of fifth phase clinical trial which some have termed 'biological

[8] *The New Yorker, 11.10.93,, pp 74-95, Bad Blood, by Jane Kramer*

monitoring' [9] This phase would seek to study (and regulate, if possible) the biological interactions between donor and recipient, which can be unique and variable for the same reasons as starting material is variable and beyond standardisation. However, for the starting material itself, the only remaining regulatory device is to offer consumers the choice of protecting themselves from harm by fully disclosing to them the innate risks.

It is a major finding of the Australian Blood Regulators Study that this device, of general public disclosure for the innate safety risks in all blood, and the supply of patient information, has generally been ignored altogether or extremely poorly utilised.

As a former Director of the Melbourne Red Cross Blood Transfusion Service said in 1984:

> ...transfusion is *not* completely safe, and probably never can be; that many transmissible diseases are undetectable in donors; that the risk is minimised by the careful selection of altruistic donors from healthy sections of the community; that national self-sufficiency at least cuts off one avenue for introducing new diseases into our patients ... these facts are so clear to us who work in the field that we take them for granted, forgetting that they are not well known to our clinical colleagues, to political leaders, to the media, to blood donors or to the community in general. [10]

This rare statement was not made to the general public but in a specialist periodical for haematologists and blood bankers, when HIV had made the risks of human blood and blood product use incontrovertible. It took many more years before the innate risks began to be acknowledged routinely in public. The TGA Code on Blood and Blood Products requires that whole blood must carry a warning that it may transmit infectious agents, but this was devised only in 1992 and in any event would reach the patient once they were being hooked up to it, assuming they were conscious, English speaking, able to read, and disposed to look.

Even were the device - and duty - of disclosure fully in use, however, an important public health question arises at the point where regulation reaches its limit for biologicals: can we afford the bill when a medical accident occurs despite all available and affordable regulatory standards having been met? Put more starkly: Can we afford to use biologicals? It is beyond the scope of this study to address such a question but it is important to concern ourselves with the cost and impact of regulation and also to recognise and point out when its reach may have been exhausted.

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[9] *Vox Sang, 46 suppl 1. pp 77-80 (1984)*
[10] *J P Morris 1984 in Vox Sanguinis 46, supplement one, 1984 at pp 7-9*

This study found few people questioning the overall costs of usage or regulation of human blood and blood products. The answer to this question in a democracy should ideally be formulated after consultation with all stakeholders. Most Australians are not aware that blood and blood products may be clinically indicated for their health at some stage in their lives; many may have already received them without realising it. Their involvement in the regulatory process is as negligible as their information base. Those with a professional or financial stake in their use cannot be expected to promote unbiased or comprehensive debate on this question.

In this study, only one interviewee, a pathologist formerly in the serum business, addressed the issue of the utility of biologically-derived products head on:

> We need to look at doing without blood and blood products or only using them if life is threatened ... We can't afford to be making a product from human origins ... when one AIDS case in Australia costs ten million dollars. The problem with [the Therapeutic Goods Administration] is that they are not monitoring each batch. Each unit [of blood] is a batch. The overall problem with CSL is insoluble because if you pool donations you are in trouble. There are enormous numbers of substances in blood, and the pool of diseases will expand, even without a malicious person. It's like testing all the A's in alphabet soup. They're picking out the A's to test but what about the rest?

TGA appears to address this point but actually dismisses it. The 1992 Code on Blood and Blood Products says 'some may argue that human blood is a biological substance and no two donations are the same, ... each donation represents a batch, ... no two batches of products derived from blood ... can be the same'. However, it then says that the quality systems in its standards 'have been shown to apply to many different situations (as diverse as a solicitor's office and a bicycle factory) and have been shown to be applicable to similar manufacturing situations analogous to blood processing such as device manufacturing' citing heart pacemakers. [11] Actually, when it comes to regulating for safety, nothing is 'analogous' to biologically-derived goods for human use, especially products made from pooled material.

The same interviewee quoted above also observed that R & D on replacement products for human blood and blood products is not advancing sufficiently to offer up an adequate range of replacements for human blood, for which there is no ceiling on demand.

Other interviewees evinced much the same concerns as the pathologist but in a less deliberate and reasoned way. Numerous interviewees concluded interviews and discussions with the author, sometimes having argued

[11] *p 9 of the 1992 Code*

strenuously for the merits of the Australian blood supply, by adding more or less furtively that they would avoid using blood if possible. This echoes what Australians have been increasingly saying over the last seven years this author has been discussing this topic. The stance of avoiding use where possible is of course best for them as consumers or potential consumers, best for donors and blood bankers and best for regulators, but over three decades the public was permitted to form quite falsé expectations of the blood supply because government, Red Cross, CSL and other agencies refused to acknowledge the obvious fact that while the blood supply was relatively very good, it could never be risk free. Had people heard the truth from these players, rather than discovering it themselves from the HIV disaster, they would not feel so let down. Neither would regulators, blood bankers and manufacturers be so jumpy, at times reactionary, and vulnerable to being pushed around by their lawyers intent on avoiding damages claims.

As one Blood Transfusion Director said, the pronounced decrease in usage of blood and blood products of the last decade, which Red Cross had been seeking through clinician education measures, came about far more because of public and clinician reactions to actual harm from HIV and now hepatitis. This phenomenon, of acting only when the harm manifests although the probability of harm was glaring, is paralleled at government levels. A former NBSL regulator, speaking of the agency's desire for legislative powers to regulate drugs and blood products, they were reducing to 'waiting for a disaster: that's when you get your chance.' HIV was to the biologicals business what the thalidomide disaster was to the pharmaceutical industry. This of course, is a description of history rather than a rule of human or government behaviour. Regulatory schemes should anticipate and avert such things. Ahead of that, those who would regulate must employ, empower, respect and consult the technical experts on whom regulators have to rely in defining the possible harm their schemes should avert. In this case, this means the scientific experts - microbiologists, virologists, drug evaluators and other such professionals -who work for the Therapeutic Goods Administration.

There are really only two sensible choices when states or corporations consider supplying blood or blood products. The first is to not offer them. The second is to offer them, regulate them as well as possible and broadcast the truth about the remaining risks which no amount of regulation or processing can nullify.

1.16 Disease risks in human blood products

The biggest current health threat stems from **viruses** and other disease agents. The disease risk increases with the amount of product used, but can be real nevertheless even in the smallest amount of material: at the time of this study informants told the author of questions being raised about the safety of minute amounts of albumin used in IVF programs as culture media.

Other centres around the world are now researching a higher temperature pasteurisation to replace the current sixty degrees celcius for ten hours.

Not all diseases are blood borne. A majority of known viruses appear not to be although the great majority of **bacterial** and **parasitic** diseases are said to be transmissible in blood. [12] The above statement concerning viruses sounds reassuring and is often given as information to the general public expressing concern about the potential of blood and blood products to cause disease in recipients. However, as with so much information in this field of study, it can be misunderstood.

Unfortunately, one needs to grasp more detail to arrive at a useful statement about the potential of human blood for disease transmission. The term blood borne means in medical parlance that blood is the vehicle in which the agent is transmitted. Some examples of blood borne diseases are malaria, myxoma virus (in rabbits) and the arbo (encephalitis) viruses, all of which can be transmitted by mosquitos. However, there are many infectious diseases in which movement of the micro-organism from one part of the body to another *via* blood is an essential step in the establishment of disease. Some examples of these are polio, measles, and hepatitis. Yet doctors don't term these blood borne diseases. In fact the majority of diseases, apart from some gut or skin infections, fall in this class. Thus, if blood is taken during the 'viraemic stage', when virus particles are present in the blood, the blood can transmit the disease to a person transfused with it or, should the disease agent survive processing, to the recipients of blood products. The 'viraemic' stage precedes the acute disease and this makes avoidance of the problem very difficult.

In addition to viruses and bacteria there are the **prions**, for which the transmission route is currently unknown in some cases. A prion is the name for a disease agent, thought to be a protein which spontaneously mutates, or changes in shape. This mutated protein gives rise to more mutated proteins and this process brings about disease.[13] Creutzfeldt-Jacob Disease or CJD, a terminal disease of the central nervous system with an incubation period of fifteen to thirty years, is an example of prion disease, sometimes incorrectly called a slow virus. In 'nature', the incidence for spontaneous mutation is said to be approximately one in a million people. CJD is believed to have been transmitted in hormones derived from human organs, and via human blood products made from human placental blood other sources. Kuru, a disease found in Papua New Guinea, is the same disease, said to be transmitted when cannibals ate brain matter. [14]

Screening for disease in blood for blood products and transfusion commences with donor examination, questioning and declaration forms. The purpose of questioning is to determine the general health of the prospective donor and

[12] *ACT Blood Bank ,Dr Pembrey, 24.3.94.*
[13] *Professor Fenner, ANU, 24.3.94,*
[14] *Prof. Fenner, above.*

to exclude defined risk groups, such as people with a history of blood borne disease or people who have used various substances with a potential for disease transmission. As seen above, a donor may have contracted a disease which is in the viraemic stage but not yet presenting as disease, a particular liability in the case of slow viruses when many years may pass before disease manifests. Tests are conducted on the donated blood at Red Cross for hepatitis B and C, HIV I and II, HTLV I and syphilis. Certain tests are repeated when the plasma reaches CSL, according to official A interviewed by the author in 1992.

It is either not possible, or not always considered cost effective, to test for all potential and known blood borne diseases. Some tests detect antibodies rather than the disease agent itself. Such tests are not effective during the window period between the time of infection and sero conversion when antibodies are produced. For HIV this period may be six weeks to three months, for hepatitis C up to twelve months and for syphilis and a common herpes virus called CMV, a few weeks.

Some bloodbankers overseas are suggesting quarantine for blood fractions with a suitable shelf life, so the donor can be tested again before the material is issued. Despite the obvious expense, Germany was said to be studying the possibility in 1994. [15] Seven months later, the Lancet reported that quarantine storage was already in partial use. From 1995 blood will have to be retested for viruses four months after donation. [16]

For hepatitis B there is a test which detects the actual antigen or virus. For some diseases there is no available test. These include malaria and glandular fever. CJD can be confirmed only at autopsy and is highly resistant to known forms of virus inactivation.[17] The constant development of new, more sensitive testing kits is a major growth industry, a kind of inanimate 'regulator' which obliges bloodbankers and their official regulators to constantly review testing standards. It also gives product liability lawyers unending opportunities to challenge the validity of state-of-the-art defences against charges involving harm from blood products.

The spread of viruses and other disease agents is compounded by increased immigration, international travel and the unintended movement of biological material in the course of trade and transportation - such as virus in ballast water of cargo ships which may carry viruses from one side of the planet to the other. Clearing of forests may release viruses into communities without immunity to them.[18] Blood bankers and fractionators face a constant dilemma which is intensifying. How prevalent must an emerging disease be in the community before testing is considered mandatory, assuming a test exists?

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[15] *How Safe is Europe's Blood? New Scientist 15.1.94*
[16] *Lancet, Volume 344, August 6 1994, p 398*
[17] *Fenner, above*
[18] *A Dancing Matrix - Voyages Along the Viral Frontier, Robin Marantz Henig, Alfred A Knopf, New York 1993.*

The most recent examples are HIV II and malaria. HIV II is common in West Africa and has been detected in the blood of two exclusively homosexual men in Australia.[19]

There is currently no test for malaria (other than for one stage of its complex life cycle) but it is rapidly increasing in many countries and has been detected in one Australian case where blood transfusion is presumed to be the route for transmission. Chagas disease, a potentially fatal and effectively untreatable disease originating in tropical and temperate climates, is prevalent in children and adults in central and South American. It is transmitted to humans via contact with the faeces of a bloodsucking beetle and is also blood borne. The very high incidence of Chagas disease reported in Brazil in the early eighties was said to be mainly created by blood transfusions from paid donors. It is another disease not tested for in blood banks.

Disease may go undetected in blood during collection or processing because of insensitive or faulty tests and because of human error. Or disease agents may enter in through faulty equipment, inadequate cleaning of equipment, human error or intent. No intentional contamination of human blood has ever come to light in Australia, so far as this author is aware. A major claim made for CSL's new fractionation plant is that it is designed to obviate human error.

Even with the best manufacturing principles in place, it is easy to see how challenging the production of blood products is from the perspective of purity and the avoidance of disease agents entering in. One informant described the difficulties:

> When you see what they are up against, you wonder how it can work. Take the making of factor VIII. [CSL] did a single batch of this from something like *two and a half tonnes* of plasma. They have to get out all the plastic bags of frozen plasma; each one is only about 250 to 500 grams. The plastic is very tough. They have to breach all the bags, throw all the ice in and get the extraction process under way before the stuff starts to denature! All that without sneezing into the ice slushy.

1.17 How can regulation fail?

Regulation can fail in many ways. It may be ill-conceived in the first place, as a result of a failure to identify the true situation needing address. It may not be applied, or its application may be non-uniform. It may cost more than the benefits to be gained from it; it may solve the situation for which it was designed but create another comparable problem, or infringe rights unduly, such as when donors are bled too often for good health.

[19] *Sydney Morning Herald 28.3.94*

1.18 What can happen when regulation fails?

Where regulation fails or does not exist, one can find activities which represent a departure from any or all of the eight goals postulated above. For example, if the collection, storage and manufacture of plasma is not adequately regulated, material may be diverted into non clinical use such as cosmetic manufacture, or sold abroad, affecting goals three and six above. If levels of donation are not regulated, donors may be exploited at the expense of their health, affecting goal six. If all stages of production are not monitored, disease agents may survive the process or enter in during it. If clinical usage is not regulated, the goals of adequate supply and equity in access can be adversely affected. If a regulatory system for licensing the quality and manufacture of blood products costs more than regulated parties are willing to pay, they may contrive to subvert the system, possibly compromising the goals of minimum harm to users, and highest affordable quality. If regulatory standards are imposed in isolation from health policy, the finished product may not be affordable, jeopardising equity in access and encouraging the introduction of payment for blood products. This may in turn lead to commercialisation which will jeopardise many of the eight goals set out in this report.

Regulatory schemes should be designed to align with the achievement of positive goals, such as good manufacturing practice, adequate blood supply, equitable usage and so on. Some of the specific harmful activities which good regulatory schemes should also be able to detect or prevent include:

- 1. Excessive bleeding of donors;
- 2. Donor screening and testing failures; lack of uniformity in testing;
- 3. Inadequate storage or starting material rendering it unfit for use;
- 4. Mixing starting material of different qualities;
- 5. Failures in manufacture and testing by the fractionator;
- 6. Diversion of material at any point in the process for unauthorised purposes, such as export or non-clinical use;
- 7. Substitution;
- 8. Sabotage;
- 9. Inappropriate or wasteful usage;
- 10.Sale or other for-profit transaction in blood or blood products;
- 11. Recall failures;
- 12.Failure to adequately inform users and potential users (the general public) of risks in blood products.

Evidence of points two, four, five, six, nine, eleven and twelve and of the above harmful activities were found during the Australian Blood Regulators Study this study. Other activities have occurred overseas. A disgruntled former employee of a voluntary blood bank in South Africa stole material in the eighties and shipped it to Europe marked as animal plasma. No cases of sabotage have been reported, however, failure to store blood during the window period for various diseases provides a point of vulnerability. US

police have raised the possibility that an HIV positive dentist deliberately allowed his patients to become infected. A prison officer in New South Wales became HIV-infected when a prisoner injected him with contaminated blood. In 1994 the officer told the Supreme Court that the Department of Corrective Services had told him there was no risk of being attacked with a syringe 'because it had never happened and therefore it could not happen'. The Department had failed to segregate an HIV-infected prisoner who had threatened or assaulted prisoners in the past. [20] The possibility of anti social and criminal conduct has to be taken into reasonable account in regulatory schemes.

1.19 Main problem areas identified

The following is a summary of the main problem areas identified by the Australian Blood Regulators Study in respect of blood products for human use in Australia.

1 Lack of clear policy on human blood

> Lack of co-ordination, indifference and neglect of blood policy within the Health Department was found. Within a Federal system, this is the agency which should formulate policy and encourage national uniformity amongst other regulatory bodies and stakeholders, in order to ensure the effective regulation of blood products and whole blood in the public interests of safety, equitable access, affordability and availability on acceptable clinical grounds.
>
> Especially there is unresolved conflict within and between sections of the agency as to how to weigh claims between commercial secrecy and disclosure on one hand, and claims between profit-making and community service obligations on the other.
>
> The combination of this policy vacuum, together with TGA's deference to commercial interests and its failure to adequately regulate blood products, mean that in effect the Health Department has been significantly captured by the interests of the commercial blood sector, at domestic and international levels. This had resulted in significant betrayals of the public interest.
>
> The Health Department, currently the chief regulator of human blood products, is not currently well positioned to protect Australia against the increasing international trend towards unlawful, criminal and unsafe practices in the manufacture of human blood products and transactions relating to them. The failure to set, promulgate and enforce clear policy. significantly undercuts the

[20] *Sydney Morning Herald 13.9.9 4*

effectiveness of current regulation and will impede the success of future regulatory initiatives.

2. Lack of clarity concerning legal powers for securing compliance with TGA and weak penalties.

While this study focussed on the role of regulation, it was evident that some regulatory failures came about because of failures in policy setting, and lack of clarity or commitment to legal provisions or principles. These deficiencies require address if regulation is to succeed. The Therapeutic Goods Act requires amendment to strengthen compliance powers and penalties, in line with criminal offences relating to 'illicit' drugs, all defined as therapeutic goods. TGA is attracting criminals into the area of because of weak legislation.

3. Lack of Information

On the part of CSL and the Health Department, there has been a cultivated lack of access and information for most stakeholders with potential to assist the regulatory process for blood products. These include Red Cross in particular, most user and consumer groups, Ministers and parliaments, professional clients of CSL in hospitals, pathology laboratories and clinics, and the media and general public. The Health Department has failed to understand its own responsibilities in respect of accessing relevant information and in consulting, especially when evaluating applications for new blood products.

This lack of access and information is unwarranted within existing legislative and common law frameworks, and within the context of a political democracy. It has been a major factor contributing to the absence of informed public debate concerning Australia's blood supply and the absence of public participation in major decisions and regulatory moves over the last three decades. This was accentuated most recently in the passive public response to government's highly questionable sale of CSL, an act which has serious implications for the regulation of human blood product manufacture in this country.

There is also a lack of timely information to consumers about safety risks in blood products, both before the risk is realised and after contamination, supply cuts or other failures have occurred. The Health Department and CSL have failed to grasp the connection between timely release of factual information about blood products

and the lessening of their legal liability for harm from the use of these products. Recently there are slight signs of change on the part of the Health Department, and some change at CSL in response to requirements under trade practices law.

4. Regulation and scrutiny of CSL

The study found chronic inadequate scrutiny and regulation of CSL by the Health Department, successive Ministers, and Parliament of CSL as the nation's monopoly processor of blood products under community service or national interest obligations. This lack was somewhat ameliorated by the new Therapeutic Goods Administration in the nineties but remains inadequate. The inadequacies applied to CSL as a statutory commission from 1961 and later when it was also a company and then also a 'government business enterprise'. The opportunities for effective scrutiny and regulation have in some areas been diminished by CSL's sale in 1994.

5. Export/import control

There is a lack of adequate control by the TGA, the Civil Aviation Authority and Customs over blood products moving in and out of Australia, whether CSL or overseas product. The Therapeutic Goods Act regulates goods at the point of sale rather than import.

6. Control of source of foreign blood

The Therapeutic Goods Administration has insufficient powers to effectively regulate foreign blood products imported into Australia. This has particularly serious ramifications for products available to certain patients Special Access Scheme before full evaluation. The study also found evidence that existing TGA powers were not appropriately used and that it withholds information to which clinicians, users and potential users are entitled in considering use of blood products.

There is an immediate need to evaluate the adequacy of TGA's legislative powers in respect of blood products as distinct from non-biologically derived therapeutics goods. There is an immediate need for mechanisms to ensure that the Therapeutic Goods Administration is made publicly accountable for the way in which it regulates manufacturing and quality assurance for human blood products, and the way in which it deals with applications for new blood products.

There are implications for user safety and government's legal liability in the regulatory system as it now stands.

7. Regulation of supply, demand, usage and patient consent

Regulation of blood product usage, and the securing of informed consent by users (especially under the Special Access Scheme) is presently patchy and inadequate on the part of hospital boards and administering clinicians in Australia. The Health Department, despite its stated concern to ensure a safe and adequate supply of blood and blood products, has not yet assumed its responsibilities in this field, although there are slight signs of willingness to proceed. (The role of state Health Departments is not part of this report). There are implications for safety, availability, equity in access and legal liability in the shared failure of agencies, hospitals and clinicians to regulate usage.

8. Questionable practices by CSL

This report presents evidence of questionable practices in the Bioplasma Division and other parts of CSL, Australia's sole manufacturer of blood products. CSL abused its legislative powers, its delegated authority and the trust of its clients and the public over a long period, and failed to account for its activities to relevant authorities. Regulators have too often failed to detect or act appropriately to remedy and prevent these questionable practices.

9. CSL Co-operation lacking

CSL has been reluctant and ineffective in its communication with other parties involved in the co-operative system of delivering blood products to the Australian community. Its recent efforts to remedy this fall far short of what is needed, according to evidence given to this study.

10. Red Cross Blood Transfusion Service inadequately empowered

Red Cross Blood Transfusion Services personnel have attempted with limited success to 'regulate' CSL's conduct as blood processors and suppliers back to Red Cross of blood products derived from Red Cross starting plasma. Red Cross Blood Transfusion Services are well placed to play a major role in the regulatory process and should be empowered by the Federal Government to assist.

11. CSL history of bucking regulation and accountability

CSL was found to have an attitude approaching contempt for external regulators, parliamentary and public accountability going back over more than three decades. This culture may function as a foil to regulatory success for blood products. Changes in the nineties may be overturning this ethos but the study found contemporary evidence of questionable practices continuing in the Bioplasma Division. The company's public claims to change could not be properly tested because senior management refused to communicate with the principal investigator for this study.

12. Sale of CSL questionable

The government's precipitous decision to sell CSL ruled out prior debate on regulatory implications for human blood products and the future of the company's national interest products. The sale process was unduly secretive. This prevented stakeholders, including even process participants such as the Health Department on evidence given, from scrutinising decision-making processes with implications for the regulation of blood products and CSL's other national interest products. Significant regulatory opportunities have been lost in the process to private sale. These effects, taken together with evidence of questionable practices at CSL regarding blood products and a range of other activities over three decades, give rise to real concern about the degree to which future regulation of domestic blood product manufacture can succeed.

Nevertheless, the Health Department is in a good position to expand existing powers and create new opportunities for regulation of CSL's processing of blood products.

The Health Department should:

- accept its role as initiator and co-ordinator of a co-operative federal effort to establish a uniform national system of blood supplies in accordance with the policy of pursuing a closed national self-sufficient system based on unremunerated blood donation;

- empower other parties such as Red Cross, and health consumers, to assist with this goal;

- work co-operatively and creatively within the Federal system;

- consult experts on creative and responsive regulatory solutions to situations requiring legal, policy or regulatory know-how;

- share information with individuals and groups who could play a watchdog role on the conduct of CSL, and on other companies and parties who deal with human blood products.

1.20 Background to this study

The Australian Blood Regulators Study, of which this is the first report, was conceived as part of a larger study on the regulation of world human blood supplies which the author commenced in 1986. The aim of my initial inquiries then was to test claims that world blood supply systems are insufficiently regulated and that this lack of regulation is a significant factor in the corruption of the integrity of our stock and sources of whole blood and blood products. There was no current comprehensive description of the world situation in 1986. Nor is there one now. Certainly there was no thorough description of the Australian system. Preliminary research was undertaken in 1986 and 1987 and summarised in an report entitled Red Gold - The Price of Worldwide Commercialisation of Human Blood, written in 1991. The report was incomplete in numerous parts and distributed only on a limited basis. Its tentative conclusion was that the original claims being tested were apparently substantially true but that more research was needed in order to make a sound case.

The 1991 report held that scientific advances of the last thirty five years have transformed blood transfusion and the use of fractionated blood products into an indispensable part of modern medicine but have 'produced many new and unsolved problems for biological and medical scientists and laid out a trail of social, economic, ethical and regulatory consequences of profound significance for individuals, governments and communities around the world. The Blood industry is highly fragmented into the unpaid and paid donor sector, the pharmaceutical industry, the cosmetic industry, large programs run by defence forces, and brokers trading within and across national boundaries. Trade in blood may be a fully legalised transaction, or a not unlawful transaction, or a fraudulent transaction or it may be entirely illicit as with the black market'.

In almost any terms the Australian system looked good from preliminary research undertaken then. But if the Australian system was as good as it looked, then how well were Australian regulators placed to protect our system from the worldwide trend towards criminal and unlawful transactions in blood? If one looked at how well Australians were regulating our system in accordance with the policy on national self-sufficiency from unremunerated blood donation, one might be able to make conclusions about our ability to withstand international movements towards commercialisation, unlawfulness or crime.

This is not saying that commercialisation is intrinsically linked to unlawfulness, or that crimes are not committed within unpaid non commercial systems. I simply accepted, as do the WHO, Red Cross and even blood brokers and commercial fractionators speaking privately, the fact that any system built on bought blood begins with an inbuilt liability, that is, the mixing of a commercial motive with the act of giving. [21] Besides, this was the system to which Australia had committed itself for most of this century.

1.21 Funding

Prior to the commencement of the Australian Blood Regulators Study component, the Blood Project had received a small amount of funding. The Australian Consumers' Association contributed $660 towards expenses associated with the 1991 report. Essential Information Inc., a Ralph Nader organisation which funds investigative journalism and research, contributed US$5,000 towards research costs in 1991 and then funded the author to study in the United States for one month in 1992. In March of that year the author, as principal investigator, received a grant for the Australian Blood Regulators Study from the Criminology Research Council, the first government agency to fund an aspect of the blood project, (which is also the only study of its kind in the world, as far as this author is aware). $17,500 was granted by the Council for expenses and the employment of a research assistant to the principal investigator, who had been appointed to the University in an Honorary capacity. The Council grant did not allow for the provision of a salary for the principal investigator, who has not received a salary since the inception of the Blood Project in 1986. Since the CRC grant, Quaker Service Australia raised $4020 towards expenses for the next phase of the project, a book on the international blood market. This was used to purchase a computer, tape player and answering machine, all of which were used for the Australian study as well as for ongoing international research.

1.22 Study process

Before beginning the Australian Blood Regulators Study, the author had obtained endorsement from organisations and individuals in Australia and overseas, and established a list of expert advisers in law, blood transfusion medicine, criminology and social studies. The Australian study, which builds on earlier research in 1986 and 1987, was housed within the Centre for National Corporate Law Research at the University of Canberra. The author, as principal investigator for the study was appointed by the Vice Chancellor, Professor Don Aitkin, as a Research Associate within the Centre for the duration of the Australian Blood Regulators Study.

The study commenced with a written approach to senior executives in CSL, Federal and State Health departments, Red Cross, the Federal Bureau of Consumer Affairs and other agencies, seeking personal interviews. The aim

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[21] *eg Spain imported 90% of blood clotting products from US commercial companies and 82% of its 3,700 haemophiliacs became HIV-infected; Belgium imported none and 4% of its haemophiliacs became infected; from Canadian Medical Association Journal, 15 February 1993, 148(4), p 612*

was to speak face to face with official regulators to record their experiences in administering regulatory schemes.

The Health Department official nominated as a first contact point, Official C, the Principal Medical Adviser to the Therapeutic Goods Administration, refused to give the author such direct access. He and more senior people in the agency, such as a former Secretary, and a Deputy Secretary, spent a good deal of time telling the author that the refusal was because the agency was too busy. Three face to face interviews eventuated over fifteen months, one of which was taped, the other two recorded by note taking. A fax of supplementary questions was sent in early 1994. Three and a half weeks later the TGA Manager replied by letter saying parts of the fax were unclear, he was waiting for the original and would discuss the questions with officers when it arrived. By this time, the reporting stage was well under way.

Many efforts were made to overcome official Health Department lack of access, all of which are documented. The author finally ran out of time and resources for the process, marked as it was, more often than not, by hostility, criticism, belligerence, indifference, lack of assistance or delay.

There are also difficulties built in to the official responses given. For example, in one face to face interview, when the author quoted verbatim from notes of an earlier preliminary telephone interview she had with Official C in 1992 as part of the study, he did not remember the interview. This official declined to permit face to face interviews to be taped. Instead, extensive notes were taken by the author and another individual who accompanied her for that purpose. These notes were then immediately debriefed, checked for accuracy and signed by both.

One could ponder as to whether fuller or better data might have been given in better circumstances, and can wonder how much weight should be given to some of the responses within such strained relationships, but there is no clear resolution for these questions. In this report, the author simply took the evidence as given. Many other officers and former officers of the Health Department assisted the author with information which was unobtainable on official lines. Quite a number of these people had already been of assistance during her preliminary research in 1986, 1987 and 1991, including Official C, who had been very helpful to her. Others who assisted unofficially were people whom the author approached newly. All were told that she had been denied access by the official contacts given for the study. The vast majority were most willing, co-operative and interested in the study.

The author was also very greatly assisted by former officials and scientists with a keen interest in the subject, who spent many hours contributing perspectives, technical knowledge and information and in helping the author assess claims made by official interviewees. Many of these individuals are too close to the official system to be named in this report. Their contribution has been invaluable. After countless hours of study, the author concluded

that students, regulators, lawyers and others who would contribute to the subject of blood regulation, cannot avoid the task of themselves understanding the technical and scientific background. Merely recording claims as to product safety, the soundness of testing procedures and so on, is a perilous course to take. The technology, safety standards, and even the meaning of terms are constantly changing. Parties disagree over what inactivation methods are adequate for rendering material safe; some parties will give incomplete or misleading information to avoid the disclosure of past or present practices and methods that could reflect upon them adversely. Scholars who merely gather advice and opinion without taking the trouble to unravel the meaning, context and intentions of the witness can find themselves trapped between cross flows of contradictory fact and opinion. They may be thus used without realising it, and, just as importantly, may do considerable harm by reporting assertion as fact. It was not always possible to get to the bottom of research findings in this report. However, considerable effort was made to do this and where it was not possible, the author has been mindful of the need to restrict her conclusions to what the data support.

State Health agencies, the Federal Bureau of Consumer Affairs, the Trade Practices Commission, Australian Quarantine and Inspection Service, the Civil Aviation Authority, other government agencies and Red Cross co-operated with the author's requests for interview. So did CSL, except when the author sought interviews beyond the Bioplasma Division. Many agencies were extremely frank. Numerous interviewees went to some lengths to assist the author, particularly those of the Federal Bureau of Consumer Affairs (from 1992 to late 1993 when some officials were hampered by censorship of the Bureau from the Minister's office), the Civil Aviation Authority, the Trade Practices Commission and many of the Red Cross Blood Transfusion Directors.

Quite a number of government officials volunteered that interview questions had raised their awareness of the need for better inter agency communication on policy, implementation and information sharing. Many remarked that the study was valuable in getting the many parties involved in regulating blood to focus on overall policy goals, their role and their relationships with each other. A number of agencies used the interview as an opportunity to speak about their lack of resources for more effective regulation, including the Therapeutic Goods Administration and the Civil Aviation Authority.

Official interviews were face to face where resources permitted, some being by telephone. Many were taped. Supplementary interviews were conducted in quite a number of cases to clarify data given or seek more. Interview time for the study, including official and unofficial interviews, exceeded 500 hours and was supplemented with study of relevant legislation, agency publications, clinical literature, parliamentary and other records, media files and some overseas inquiries. Four of the expert advisers to the Blood Project, Professor John Braithwaite, Mr. John McMillan, for advice and Professor

Robert Beal, and Dr. Richard Pembrey for technical information and understanding. Further expertise was sought from relevant experts as needed.

CHAPTER TWO : PAST REGULATION OF CSL, THE NATIONAL BLOOD FRACTIONATOR

The history of regulation of CSL and its blood product manufacture is largely a history of omission until very recent times. It is essential for contemporary regulators and others with an interest in CSL's regulation to appreciate this point as the history of the organisation is relevant to its culture. This is not to deny changes that have occurred in recent years, nor that strong leadership cannot reverse an ethos of noncompliance with internal and external efforts to regulate it, but understanding the past is a necessary step in understanding the present. Beyond that, it is a matter for judgement and evidence when one assesses how fast the organisation can undergo reform.

What follows is an outline of CSL's regulatory history until recent times. Some readers may be more interested in consumer safety issues than regulatory details. They would be best to either skim or skip this chapter, or else read only the chapter summary at the end.

2.1 Original purpose of CSL

CSL was a Federally-owned biologicals manufacturer until 1994 when it was floated on the Australian Stock Exchange. It was established During World War One when European and American supplies were cut off, CSL was established to make Australia self-sufficient in biological products, particularly vaccines and sera, for war and peacetime. When World War Two cut Australia's supplies from the German BASF giant, government had to address the need for local blood supply systems. Out of this the current system grew.

The growth of human blood supplies, blood processing systems and the regulatory regimes governing them have always been driven far more strongly by crises such as war, sensational product failures and technological advances than any conscious or planned activity by governments or regulators.

CSL began manufacturing human blood products in 1952. Later the organisation sought authority to make chemically derived drugs as well and now describes itself as a pharmaceutical company, although its core products are still biologicals.

However, in Australia's case, there was a conscious move made to regulate products of biological origin. In the late fifties the Federal Government established the National Biological Standards Laboratory within the Health Department with the intention of doing this. In Australia these products were manufactured almost exclusively by the then Commonwealth Serum Laboratories, also the only processor of human blood products for Australian use.

It is a massive irony - some say a scandal - that of all the regulatory measures established within the National Biological Standards Laboratory which were applied progressively to the entire pharmaceutical manufacturing sector in this country from the sixties through to the nineties, none were applied uniformly to the country's monopoly manufacturer of biological products, CSL. How this situation came about is partly of historical interest, but just as importantly it is relevant to regulators with responsibilities for the quality and safety of human blood products still being manufactured by CSL. The history of CSL in these decades is very much a case study in how to buck regulators and in what happens to the products of an organisation which functions beyond the reach of regulators and of public scrutiny. Case studies on some of these product failures are set out in chapters six and fourteen.

The history shows also how unimportant to CSL its manufacture of blood products have been, that is, until the new fractionation plant was finally finished in 1994 and overseas plasma fractionation became CSL's great hope for commercial success. CSL had begun fractionating overseas plasma sometime in the sixties but did not promote the fact. Media searches show little communicated to the general public about CSL blood products at all, apart from small bunches of bland fact. When AIDS hit in the early eighties, CSL's blood products received some publicity. Little was heard in public about blood processing again until 1993 when CSL was slated for sale. Then the authority suddenly began talking with pride about its 'key core expertise in plasma products and vaccines'.

But despite neglecting their research, development and quality manufacture in many cases, these had *all along* been the organisation's core products: highly subsidised, fully protected national interest activities with assured markets. Before the building of the grand new blood processing plant, blood products were a relatively silent partner to CSL's other products, a welfare product, reliable for bringing in government money, not worth researching to any considerable degree, and pretty much the runt of the litter. The 1990 official history of CSL devotes only ten of 266 pages to plasma fractionation. In regulatory terms, blood product manufacture might as well not have existed until 1991, when the Therapeutic Goods Act came into operation.

2.2 1961 CSL becomes a Commission

The then Commonwealth Serum Laboratories was part of the Health Department from 1921 until 1961 when it became a statutory authority. At the time, its director, the late Percival Bazeley protested at government moves to restructure it. Bazeley went to the Opposition party, the Prime Minister and the media, claiming government was responding to pressure from international drug companies wanting to buy CSL. [22] Following a review, CSL was converted into a statutory authority constituted as a Commission, a move which was intended to give it 'flexible and efficient management'.[23]

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[22] *Melbourne Age 11.4.84.*
[23] *Hansard 11 5.61, p 1780*

Bazeley fell into disgrace in the eyes of the government for a number of reasons, especially his unwillingness to account to the Department for his and the Commission's activities. This unwillingness had far more to do with Bazeley's demise than the generally held reason of his having gone public about a suspected takeover attempt: that merely provided the provocation. Bazeley's ruin was simply that he never asked who was to be master; he just knew he was.

Under the Commonwealth Serum Laboratories Act 1961, which stood unamended until 1980, CSL was to continue production of prescribed biologicals for sale, to stockpile these products against emergencies and to undertake research to improve existing products; to import certain vaccines for sale to the Federal Government and to research other biologicals as directed by the Minister. These functions are generally termed 'national interest' or 'public interest' activities (although these terms are not in the legislation) or, latterly, community service obligations.

The legislation provided for the Minister to determine prices paid to CSL by the Federal Government or the States for these products. [24] For as long as government was a monopoly buyer of CSL's products and also its owner, prices paid for blood and other biological products were kept low relative to the commercial sector. Now CSL is sold it has obtained much higher government prices for blood products, but remains heavily dependant upon Federal reimbursement for its manufacturing activities since government is still the sole buyer of products made from Australian plasma. This should give regulators a perfect opportunity to control the entity by means of financial incentives, but the opportunity has never been effectively exploited and is not being now.

2.3 Role of the Australian National Audit Office

When CSL was a statutory authority, the Commonwealth Auditor-General was to inspect and audit the Commission's accounts, reporting to the Minister annually and reporting any sufficiently important irregularity 'forthwith'.[25] Little scrutiny took place by this means, apart from routine annual review of CSL's accounts. In 1978 the Auditor-General found that CSL had spent $416,000 in 'a way' that did not comply with its Act; the expenditure had been incurred before determinations were made by the Minister under national interest provision, a common irregularity for statutory authorities according to an audit office source. Later, CSL was chosen at random for an audit office project looking at internal audit standards in a range of government instrumentalities. [26] The author was informed that CSL had never been put forward for a performance audit or any other form of audit office scrutiny and nor had the Health Department's funding or reimbursing role for CSL been subjected to a performance audit. The Audit Office made

[24] S 22;
[25] S 41(1)
[26] *ANAO Report no 50 of 1991-2*.

two attempts to conduct an audit of the CSL Sale process while it was under way; both these failed because personnel left, but the ANAO remained committed to the idea. [27]

(Under new legislation, introduced in June 1994 the Auditor-General may conduct performance audits on Government Business Enterprises only at the request of a Minister or after a resolution of both Houses of parliament. He should have the authority to conduct these audits on his own initiative, as was possible in the past, and this should be extended to statutory authorities incorporated as companies. The theory that the market governs such bodies adequately, without need for Audit Office intervention, is not borne out in the instance of CSL who, while a statutory authority, sold much of its product to a Government agency which took no practical interest in its performance at all.)

2.4 Annual report requirement

On becoming a statutory authority the new CSL commission was also required to comply with requests for information by the Minister and 'from time to time' inform the Minister concerning the general conduct of its business, the genesis of annual reports to parliament. [28] Financial statements were to deal specifically with any national interest operations of the Commission coming under Ministerial determination and were to show their results separately. [29] Again, annual reports did not adequately fulfil the function of keeping Ministers or the parliament informed of CSL's activities, particularly in relation to blood product development and manufacture.

2.5 Internal cross-subsidisation provision

The Commission legislation made explicit provision for a system of internal cross-subsidisation within CSL, a device also used in other instrumentalities responsible for public interest products or essential services such as Telecom and Australia Post, although in most cases it is assumed rather than spelled out in legislation. If CSL's national interest activities - the production of blood products, vaccines, anti venoms against spiders and the like - resulted in a loss in the same year as the Commission recorded a loss from its whole of its operations, the Federal Government would reimburse the CSL Commission to the extent of whichever loss was smaller.[30] This device is normally accepted as a sanction against capricious Ministerial interventions in the workings of statutory authorities. The Act, though, made no provision for government to determine whether the loss arose from the nature of the activity as opposed to possible manufacturing failures by CSL, a point which takes on some significance in the light of CSL's poor performance in blood product and other manufacturing areas, and its success at sidestepping NBSL regulation.

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[27] *interview June 1994.*
[28] *43(1),&(2).*
[29] *S44 (1) &(2).*
[30] *S 38*

2.6 CSL's early antagonism towards government/regulators

But if CSL sustained a loss from blood processing, vaccines, anti venoms or other national interest areas in a year of overall profit, the loss had to be financed from the profits of the Commission that year. The CSL Commission hated this provision with a passion. This may be seen in lengthy protests in annual reports, the CSL official history and media statements; it is also reflected in parliamentary speeches by the few who took more than a superficial interest in the Commission over the next two decades.[31]

It is clear from Commission statements that they saw the cross- subsidisation provision, as well as government's refusal to broaden their charter to include pharmaceuticals - and eventually the very presence of government itself in the life of CSL - as the principal barriers preventing them from the pursuit of mercantalism as the highest good.

2.7 Style of CSL's Commissioners

The first Commissioners were involved in the authority's activities through a system of subcommittees, and they committed the organisation to increased marketing and overseas sales. By the close of the sixties, Commissioners were no longer relating directly to personnel in the Commission but dealt through the chief executive.[32] From this time on, they normally acted as advisers to the various chief executives and monitored their performance, rather than addressing day to day problems. 'The chief executive has been left free to run the place, and whilst he does not have anything approaching freedom from the many intrusions of government, he certainly is spared many of the day to day influences which so infuriated Val Bazeley' says Brogan. The style of the current Commissioners could only be inferred from publications and other sources as CSL's chief executive officer refused to be interviewed for this study.

2.8 CSL's goals for internationalisation and profitmaking

During the sixties, there was a progressive decline in CSL's financial performance, bar a brief reversal from windfall influenza vaccine profits late in the decade. The decline continued into the early seventies. CSL frequently complained of indifference and lack of funding from government and of the hated provision for recouping from 'profits'. The organisation's extreme dislike of government regulators may be bound up in its perception that the same source was starving it of funds and the power to do what it wanted. In 1974 CSL's vision to make money from pharmaceuticals became better known outside the organisation, with the appointment of a new chief executive, previously employed by a large pharmaceutical company. Dr. Neville McCarthy mostly avoided lay media and the general public but ceaselessly promoted his vision of CSL to health professionals and influential public

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[31] *annual reports 1961- 1980, media files and eg. Hansard, House of Reps debate on amendments to the Commonwealth Serum Laboratories Bill 1970 , Mr Hayden, pp 2179- 2183.*

[32] *Brogan p 171*

figures in all levels of government, science and industry. [33] The staff author of CSL's official history writes that Dr. McCarthy believed four crucial points must be satisfied if CSL was to succeed. It must have a shareholder who was committed to being in the business and had a deep pocket. Manufacturing had to be competitive in markets larger than Australia. There had to be a way of becoming an integral part of a global manufacturing and marketing network and a way of having better access to technology than in the past. [34] It seems an improbable manifesto for a government-owned body wishing to stay that way, yet CSL protested at suggestions to sell it off during the seventies and eighties, while McCarthy professed to have no view either way on privatisation. CSL's manifestos for expansion and internationalisation never excluded blood products. Officials travelled abroad during this period, seeking plasma fractionation business, and bringing in foreign serum.

[33] *Committed to Saving Lives, a History of the Commonwealth Serum Laboratories, A.H.Brogan, Hyland House, 1990., p 241.*
[34] *Brogan p 258.*

2.9 Major independent review of CSL 1978

In February 1978 the Melbourne 'Age' reported that the Prime Minister, Malcolm Fraser had ordered a confidential review of CSL's internal operations and finances. 'Senior Government sources' alleged that CSL 'has been gobbling up millions of dollars and the Prime Minister wants to know what is happening to the money'.[35] This major Inquiry [36] was established seven months before the Age learned of it. It reported to Parliament in May 1980. It was headed by a prestigious and senior scientist in Australian medical research, Professor Sir Gustav Nossal CBE, and included senior Health Department personnel. This was the only major independent inquiry into CSL ever conducted and provides a useful window on the statutory authority as a self-regulator and on government's oversight of its performance.

2.10 Indecision concerning CSL's purpose

Nossal's terms of reference included inquiring into CSL's purposes as well as its overall financial viability in terms of the legislation, and the basis of the commercial aspects of its operations. It was common to find people with an interest in the organisation trying to decide what it should be and do. A prime feature of the organisation and its regulators has been insufficient agreement concerning its purpose. The lack of constant purpose was less a function of changing governments than might be expected; it seems to have arisen more from the fact that much of the time CSL didn't much want to be what government wanted it to be. CSL was not interested in merely making a 'reasonable return' to the government, as required in the legislation. It voiced its dissent from this meagre goal so loudly that the appearance of a dilemma was created. Was CSL to make money or serve the national interest? Few believed it could do both. CSL was convinced that it was supposed to 'be commercial', and that to CSL meant profits from pharmaceuticals at 'proper' market prices. Ought it to be (and could it be) a research-based institution, or a developer of others' discoveries and a warehouse for others' drugs? Should the fruits of its research be retained at home for local production or sold abroad? Government, CSL and the public have never been aligned on this issue - not that the public have ever really appreciated what was going on at CSL, thanks to the organisation's lack of commitment to public information and accountability.

2.11 Degradation of national interest functions

CSL's national interest functions of blood processing and research, vaccines manufacture and indeed most of the biologically derived products, which typically did not make big profits, became casualties to quite a degree of constant irresolute push and pull between purposes perceived as conflicting. Indecision and competing purposes, plus the tendency of government to leave CSL alone unless it were blatantly in crisis or causing major

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[35] *Melbourne Age 4.2.78.*

[36] *The Independent Inquiry into the Operation and Capital Works Program of the Commonwealth Serum Laboratories*

embarrassment, made the implementation of purposeful regulation all but impossible.

2.12 Inappropriate Federal regulatory intervention

And sometimes what little regulatory intervention did take place was inappropriate in any case. For example, as seen in chapter fourteen, when CSL was chronically failing in production or development of Salk polio vaccine, the Health Department or Minister asked an advisory body, the National Health and Medical Research Council, to review the situation. Such a committee of eminent and varied medical or scientific experts, meeting briefly and infrequently, meagrely serviced and swamped with paper at short notice, often had little hope of grasping the issue. There is evidence also over the last four decades that such committees have too often proceeded from the unscientific assumption that data on manufacturing problems submitted by the manufacturer must be presumed sound.

Some informants said TGA's predecessor NBSL should have been permitted to regulate testing for HIV blood products and set standards and minimum requirements, as it was the most experienced body when it came to quality control of these matters. This didn't happen because, as one said 'too many big names got involved' in influencing government decision-making.

This quirk of Health Department officials, to bypass its own scientific experts and first call on the NHMRC, was marvellous fuel for CSL executives who were ever keen to paint in public a picture of government as the lice that even heroes must put up with. From government's perspective, such ineffective regulatory measures, taken together with the other trials CSL presented them, decreased their tolerance for the whole subject of regulating CSL to the point of near apathy. By the time the privatisation refrain was heard again in the early nineties, with indemnities for product liability mounting, it was the Health Department, backed by CSL's Board, who went to Cabinet suggesting that CSL be sold off.

2.13 CSL ordered to submit to manufacturing inspection

The Reid Nossal inquiry of 1978 made many recommendations with bearing on regulatory issues for blood products as a national interest activity; the need for these recommendations shows that the Minister and Department were exercising little scrutiny and control. Most significantly, Nossal recommended that CSL should adhere to the Code of Good Manufacturing Practice and be 'examined immediately and reported on'. During debate on legislative amendments giving effect to Nossal's recommendations a Member told the House that 'a check with the National Biological Standards Laboratory has confirmed that CSL has now been included'.[37] But it had not, according to evidence given this inquiry.

[37] *Reps Hansard 27.2.80 at p 467, Mr Lloyd.*

CSL Official A told the author that CSL 'voluntarily adopted' the code of good manufacturing practice developed by the National Biological Standards Laboratory and said that inspections 'would have taken place every few years' between Nossal's inquiry and the new TGA of 1991. He described the inspections as 'pretty thorough'. In May 1994 the author asked for evidence in writing showing how often CSL's blood products activity was inspected. A response was promised but was not furnished. [38] CSL's claim was put to former Health Department officials involved in the regulatory area. All informants contradicted CSL's claim most emphatically. They insisted that blood product manufacture was conducted with negligible external scrutiny up until 1991 when the new Therapeutic Goods Act was passed and the NBSL was replaced by the new Therapeutic Goods Administration. Inspections were described as 'very slight', virtually non-existent', even after the government accepted the recommendations of the 1978 Reid-Nossal Inquiry that CSL immediately submit to inspection. [39]

Here is a representative statement from these informants:

> Even before we had the first [Therapeutic Goods Act] we were encouraged through our testing programs to bring to the attention of manufacturers things that were sub-standard. We went visiting the manufacturers - nearly always with their co-operation - and informally we went about putting things right. It was in their own interests [to co-operate]. The codes of good manufacturing practice were based on best practices amongst the US pharmaceutical manufacturers. We got a lot done on a voluntary basis. ... CSL were never part of that process. They isolated themselves from all that knowledge over all those years. They weren't even sensible enough to see that if they got their products approved by the government it could help them if they got into trouble, although all the rest of the pharmaceutical industry was wise enough to see. I am talking about quality control, chemistry, safety, efficacy ... all the tests that should be done before a product is inflicted upon the public.
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> I think they realised their standards were so bad, and it would have cost them so much to put it right. Anyway, they felt they knew all about it. ... everybody else in the pharmaceutical industry liked to have the government approving of what they were doing, because when things went wrong they could say the government approved it, and could share the guilt. CSL didn't think that way - and now it is coming home to roost I suspect [reference to current product liabilities]... **They developed new products from time to time but they NEVER routinely came to the Health Department for approval or evaluation - unless evaluation was required so they could export them, of course. The pituitary hormones never came across to NBSL**

[38] *Telephone interview 3.5.1994*
[39] *Hansard 27.2.80 at p 467*

for evaluation, yet they were supposed to be sterile products and NBSL could have evaluated them. All the blood products - they were NEVER referred to NBSL.

After the first code of good manufacturing process was written we used to go around touting it to industry. We went to CSL and saw [key scientific officer]. **He told me that he did not subscribe to some of the principles behind the code of good manufacturing practice and had no intention of implementing these. For example, he didn't believe in having a quality control department independent of the production departments.**

A former senior official in NBSL said that CSL simply side-stepped the external regulatory process altogether, apart from a few inspections in the eighties. He said CSL claimed they were not subject to the licence provisions of the States who had the official inspection powers under the new therapeutic goods legislation of 1966, that CSL claimed Federal Government privilege in effect and thus avoided scrutiny.

Another official said it was quite common for government, semi-government and government-assisted bodies to avoid GMP inspection, citing CSL and repatriation hospitals as examples. Another cited CSL and the Atomic Energy Commission as 'feeling they were part of the and didn't need to be inspected - until near tragedy came along'. One regulator got as close to CSL as any regulator could, and said of their GMP:

CSL only subscribed to the principle [of GMP surveillance and inspections] when they became a public company [1991]; until that time they were only subject to internal scrutiny -ha ha ha!
KB Which was?
Hopeless! Up the s..t!

Where inspections by NBSL were contrived or ordered because of a crisis, CSL was said to be 'happy for NBSL to document the findings if they were favourable, but if they were going to be adverse the whole of Australia would have to think about it first.' CSL generally perceived outsider expertise not as help but as a threat. NBSL officials would have to wait upon a foreign government with an interest in a CSL product to ask NBSL to inspect CSL on their behalf. Or if CSL was bringing in a foreign product for packaging and sale here, NBSL would rely on CSL's product responsibility as an excuse to see if CSL's specifications were up to standard. An inspector from the United Kingdom, which, according to informants, does not have particularly good procedures itself, yet said of CSL's manufacturing processes during an inspection in the late eighties: 'God, it's awful'.

One source said that from attending monthly scientific seminars at CSL he formed the opinion that there was an unwritten agreement between the participants not to ask each other tough questions. This informant considered

a major cause of CSL's scientific weakness was its infrequent exposure to a 'proper hothouse research environment; they spent much of their time trying to follow a recipe obtained by licence, working from cookbooks instead of scientific principles. CSL would undoubtedly say this was the fault of government for never giving them enough money.

'Good scientists tended to want to get out of CSL' said one NBSL informant. Another senior scientist, himself working within a resource-poor government agency, said 'they were not good scientists. They were inbred, did a very limited amount of work, humdrum work, they didn't read the literature. We ran out of steam ourselves when we had to do too much of their lab work. We had to do over their whooping cough and polio vaccines.'

While CSL wanted to keep regulators out, at some levels of the Health Department there was a reluctance to go in. This was for a number of reasons, partly a widespread belief that they hadn't the necessary powers under therapeutic goods legislation, first passed in 1953. NBSL staff would write the technical reports of inspections for pharmaceutical companies and have them authorised by State government or foreign inspectorates.

But regulatory disinclination was also fuelled by the perception that CSL, as a division of the Department and later a statutory authority, was still part of the family. In other words, the Health Department was captured to that degree, not by CSL, but by its own wrong headedness. This attitude often originated with the medical doctors who were running the Health Department at the time and did not understand the science involved in CSL's or NBSL's work, or weren't interested or perhaps aware of its regulatory significance. That the Health Department should take an understanding view of CSL's departures from grace clearly suited CSL who habitually saw the pater of the family as an interfering and irrelevant spoilsport, even when he was rescuing them from disasters of their own making. Others in the Health Department turned this same concept of paternalism to regulatory account, using it to send inspectors into CSL on a grace and favour basis whenever possible.

This failure of the Health Department over seventy years to regulate CSL at arm's length, (or at all), likely also contributed to the growing acceptance that CSL should be freed of its government bindings through successive moves toward full privatisation. However, privatisation is not a logical solution to failed regulation, especially in a field of natural monopoly such as human blood product manufacture.

2.14 Blood products not regulated during HIV period

Concerning the manufacture and inspection of blood products in particular, another former NBSL official was questioned about inspections during the eighties.

KB How long have they been inspecting for blood products?

They have been inspecting ... for a few years.

KB: What did NBSL inspectors find in looking at the old blood products plant [pre 1994]?
They found they were looking at old plant! It was ... not up to current standards.

Another senior official, asked what were CSL's main problems in the blood processing area, cited 'worn out equipment' and 'CSL didn't know enough about viruses in blood'. A further senior NBSL informant told the author that CSL had not been inspected adequately in the eighties when they were inactivating HIV in blood and blood products. Yet another independently reported that inspections were slight. This informant told the author of a meeting at CSL over factor VIII and HIV in 1984. He said CSL's process was a compromise between killing the virus and maintaining potency and that it was a compromise which had not struck the right balance. The process, he said, was weighted in favour of potency and thus increased the risk of live virus ending up in the final product. This informant was indignant at the slight amount of research CSL had undertaken on the subject.

He outlined some research and action which could show CSL how they could increase the temperature and thus significantly improve safety without greatly reducing the yield. He did not know if CSL accepted the advice but at that meeting they finally agreed to conduct some more detailed studies on the stability of factor VIII. (Evidence from the Haemophilia Foundation of Australia shows that CSL told the Foundation senior executive in 1989 that they would raise the heating temperature for some clotting factors to better destroy virus, but said CSL had still not done so at the time of interview with the author in December 1992.)

2.15 Buildings not conforming to GMP

The Reid-Nossal Inquiry had also recommended that the National Biological Standards Laboratory (NBSL), a division of the Health Department which inspected the pharmaceutical industry, should be consulted by CSL on any major new production facilities at an early stage in production. Past officials claimed to this author that CSL operated as if the Department didn't exist; when the inspectorate managed to get into the facility they found newly completed plant construction which had to be rebuilt because it did not comply with the good manufacturing principles in the code. (Buildings are supposed to be located, designed, constructed and used so as to ensure the products are protected from contamination, to permit efficient cleaning and maintenance and to minimise the risk of manufacturing error.) [40] CSL saw NBSL's insistence on changes in the buildings as yet another reason to hate the Health Department. This evidence aligns with copious evidence maintaining that CSL was not inspected under the code of GMP which all other manufacturers submitted to in the sixties. As former government

[40] *Australian Code on Medicinal Products, TGA p 10*

inspectors said, had they been permitted into CSL on inspections they would have discovered that CSL was constructing plant without reference to the code and could have assisted them in meeting its requirements, thus saving them time and money in rebuilding - quite apart from achieving regulatory goals.

2.16 Inadequate peer review

Nossal also recommended that depreciation on buildings should be charged and shown on the accounts. In 1978 the Auditor-General reported that CSL had not provided in its statements for depreciation on buildings.[41] Given how often CSL spoke of its need for new blood fractionation plant, this omission is surprising. It said CSL should show more initiative in recognising and rewarding scientists, and should strengthen recent arrangements for external peer review of its research. If the principal recommendations were adopted, CSL should not be subjected to further general inquiries but be encouraged to pursue its prime objectives without diversion.[42] CSL's official history, published in 1990, described Reid Nossal's findings as 'a triumph' for the organisation.[43]

2.17 CSL allowed to enter pharmaceuticals field

Amending legislation in 1980 reflected the government's 'general acceptance' of the Reid Nossal recommendations. After kicking at the stable door for decades, CSL was finally permitted to move into pharmaceutical production and sales in Australia and overseas,[44] and to import pharmaceuticals. This was indeed a triumph for CSL. The products had to be for therapeutic use, as defined within the Therapeutic Goods Act 1966, and must be prescribed in regulations under the Act. At last CSL was not required to allocate costs arising from national interest activities against its commercial activities.[45] They were expected to pursue profits sufficient to enable the to receive a 'reasonable return' on its capital, the amount to be determined annually and in advance by the Minister after consultation with the Commission.[46]

2.18 CSL's idea of commercial

CSL management thereafter appear to have recast this provision in their own minds to mean that the statutory authority was supposed to be nothing more or less than an unconditionally commercial for-profit enterprise. Their concept of what this meant is illustrated in many ways which are dealt with in chapters dealing with questionable practices and chapter fifteen on the ethos of the organisation. Certainly it meant that the national interest activities were to be even more neglected, or exploited in the interest of commercial gain or viewed merely as public relations kudos for the

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[41] *Canberra Times 23.2.78.*
[42] *CSL annual report 1978.*
[43] *Brogan 203*
[44] *S 19 (1)(a-c) Commonwealth Serum Laboratories Amendment Act , no. 7 of 1980*
[45] *S24*
[46] *S 34B (1-3)*

enterprise as a whole, such as the anti-venoms against funnel web bites and the like.

2.19 Further commercial restrictions lifted

The 1980 amendments did not deliver to CSL the unrestricted freedom they sought. But in 1984 Health Minister Neil Blewett, who paid an unusual amount of attention to CSL compared with many Health Ministers, introduced legislative amendments giving CSL 'the same flexibility as any other trading enterprise to use its plant and equipment as technology changes and market opportunities arise'.[47] It could now form subsidiaries, enter commercial relationships with other firms, form a company, buy or sell shares in a company, at last have access to an unrestricted range of pharmaceutical products, and enter into partnerships or other profit-sharing arrangements.

In the same year Prime Minister Bob Hawke said at a major CSL function honouring the previously disgraced CSL head, the late Val Bazeley : 'I give you one guarantee ... CSL will not be sold off to private enterprise'.[48] CSL's name featured on candidate lists for privatisation over the next decade.

2.20 Blood Products Division established

In 1987 a separate Blood Products Division was created, renamed the Bioplasma Division just before CSL was sold in 1994. In 1989 the present government introduced a 'reform package' to convert CSL to a public company and make it an independent Australian-based company by 'expanding its domestic base and developing internationally competitive biological products.'[49]

Regulation of blood business by a contract

The Minister for Housing and Aged Care, Peter Staples, stated in 1989 that 'CSL can succeed in these areas only if is allowed to operate as a truly commercial enterprise that can respond quickly in the marketplace free from day to day government regulatory controls'.[50]. thereby furthering the almost universal public and parliamentary misconception that CSL had ever been substantially regulated by government. The Minister then referred to new planning and accountability mechanisms: a three year corporate plan defining financial targets, strategies and goals, with annual reporting of its performance. The Minister retained the power to appoint and dismiss the CSL Board and could issue guidelines to it. As a public company CSL would operate in accordance with the Company's code. 'Serum [ie blood] fractionation will be made more efficient and accountable' by means of a

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[47] *Ministerial media release and Commonwealth Statutory Rule No 81 of 1984*
[48] *Brogan p 265*
[49] *CSL annual report 1989-1990; Commonwealth Serum Laboratories (Conversion to a Public Company) Act 1990.*
[50] *Hansard Reps 22.11.89 p 2679*

contract, he asserted. Nothing was said about the possible impact upon Australian blood product manufacture of CSL's increasing internationalisation and commercialisation.

In 1990 the staff author of CSL's history wondered if incorporation was simply a clever back door strategy to achieve privatisation by stealth.[51] 'Will Arthur Calwell's 1960 prediction that the sale of CSL would be "an act of criminal folly so great that in itself it should cause the defeat of the government responsible" prove prophetic?' he asked, with characteristic CSL overstatement, and 'will CSL be reduced until it consists only of the plasma fractionation plant?' But at that time, any evidence that CSL was heading away from being a qango to a commercialised 'nongo' was coming from CSL itself, manifested in its profit-seeking ethos, running down of national interest activities (with some help from government) and looking to the international blood and drug market.

McCarthy retired in June 1990. He is succeeded by a much younger Chief Executive, Dr. Brian McNamee, aged 33, formerly of Pacific Biotechnology Limited in Sydney, and the pharmaceutical company F H Faulding. CSL committed itself to a future of internationally competitive biological products.[52] Incorporated in the Australian Capital Territory the same year as Commonwealth Serum Laboratories, an unlisted company, it changed its name to CSL Limited in 1991.

2.21 Regulation by corporate plan

In June 1993 the Department of Finance distributed to all government business enterprises its new guidelines for the formulation of corporate plans. Under these arrangements, which are intended to 'make control more strategic than to focus it on trivial concerns', the Board goes to the Minister and negotiates the corporate plan, after which the statutory authority is expected to meet targets but with considerable autonomy in doing so. The process is overseen by the policy section for Government Business Enterprises of the Department of Finance.

The potential for public and parliamentary involvement in regulatory processes is massively reduced by the introduction of these guidelines because the statutory authorities themselves determine whether their plans will be published. Naturally most are commercial in confidence.[53] Some GBE's publish their corporate objectives in summary form in their annual report but this is as far as their public accountability extends. In CSL's annual report for 1991 to 1992 the corporate objectives are mentioned:

> to build a sustainable international business by developing, manufacturing and marketing value-added pharmaceutical products,

[51] *Brogan p 265 .*
[52] *CSL annual report 1990.*
[53] *interview with Finance Department official,*

whilst at the same time successfully competing in an environment dominated by several large transnational companies ... new products and world class facility to meet strategic objectives are of paramount importance.

Professor Roger Wettenhall, of the University of Canberra, an expert on regulation and accountability of statutory authorities, says 'The creation of the term government business enterprise has led people to think that they have created an entirely new thing. But it is still a statutory authority'.[54] The confidentiality of corporate plans from such bodies he says, is completely unacceptable.

A Health Department official involved in CSL matters, before being censored by the department from speaking further with the author, expressed concern over community service components like blood products, vaccines and anti sera produced in Government Business Enterprises. 'What if the States don't order enough because they want to cut corners? The Federal Government has absolutely no control assured over such a development'.

The new Ministerial Oversight Arrangements say that GBE Boards are clearly responsible and accountable for the performance of the GBE and are to examine performance against world best practice. The Board is to be fully accountable to the Minister for the GBE's performance , including for any 'undue or unusual risk which may have significant implications for the owners of the business.' Information on any material variations, and other changes which would require disclosure to the Australian Securities Commission or the Australian Stock Exchange, are to be reported immediately to the Minister. If the GBE is not performing satisfactorily, the responsible Minister is to 'initiate prompt remedial action, in consultation with the Minister for Finance'. Ministers may commission independent advisers in assessing the performance of the GBE. Dismissal of Board members, according to the Guidelines, would be considered, particularly in any case of failure to keep Ministers adequately informed and in situations of ongoing under-performance.

2.22 Ministerial oversight of GBE inadequate

For this measure to have worked in the case of CSL for its blood fractionation activities, it would have required the Minister to take an informed interest in CSL, which was not done. The Health Department, based on evidence given to this study, judged CSL's performance principally on whether profits went up. When factor VIII supplies were short, they believed CSL's claim that the difficulties were principally with the volume of supply of plasma from Red Cross and to a lesser extent the capacities of the old fractionation plant. That CSL's yield of Factor VIII from Red Cross starting material was up to forty per cent less than fractionators overseas did not figure. Thus CSL paved the way for government to look kindly on the introduction of the expensive

[54] *8.12.93 personal interview*

alternative recombinant factor VIII from overseas, for which CSL had already secured a licence in 1992.

2.23 Role of current commissioners, and self-regulation

The role of the Commissioners of CSL is dealt with to some degree by the author of the official history 'Committed to Saving Lives', but there was no objective material available for study - nor of CSL's success in self regulation over the past four years since it was transformed into a company before being sold off. Professor Wettenhall has observed that, 'apart from anecdotal evidence, not much is known about the behaviour of public enterprise board members, and ... there has been little effort anywhere to formalise their role or offer guidelines to assist their effective functioning.'[55] What does seem clear is that much of the authority is delegated to the full-time Commissioner, CSL's managing director. This arrangement is fairly standard in Australian companies.[56] Under the Ministerial Oversight Arrangements of June 1993 the Board is responsible for the appointment of the CEO, who is directly accountable to the Board. Over five months the chief executive refused interview for this study and thus could not be questioned about his or the Commission's state of knowledge of various questionable practices in blood products which came to light during the Australian Blood Regulators Study, nor about the role of the Commissioners in regulating CSL. However it probable that the chief executive officer is the primary channel for communications between the Board and CSL staff.

2.24 Backgrounds of current commissioners and executives

The current eight commissioners have backgrounds or existing posts or interests in banking, mining, steel, insurance, timber milling, energy resources, pharmaceuticals (Syntex, Mead Johnson, Searle, F H Faulding), biotechnology (the managing director), medicine (teaching, clinical and publishing), medical diagnostics manufacture, legal practice, accountancy, marketing, Austrade, Council of the Australian Defence Force Academy, the Australian Securities Commission, and the Council of the Australian Institute of Company Directors. Published details do not show any substantial professional background or training in public administration, public health, public information, trade practices, consumer affairs or regulatory issues, although a former Commissioner from the eighties had previously been Secretary of the Federal Health Department for a short time.

The new Head of the re-named Bioplasma Division, official B, is an overseas appointee with decades of experience at executive level in small and large biologicals companies.

2.25 Oversight role of Commissioners over GBE

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[55] *Public Enterprise in an Age of Privatisation, Wettenhall in Public Affairs Bulletin, Volume 69, Number 9, February 1993, p 9*

[56]

In this report, evidence is presented of questionable practices within CSL's blood products division, and in other parts of the organisation over time. Some could be said to constitute 'undue or unusual risk which may have significant implications for the owners of the business' as defined in the Ministerial Oversight Arrangements requiring accountability to the Minister. Others appear to come within the Guidelines as under-achievement (though it may not show in generalised financial statistics). Some questions that arise from these practices are how much the Board knew of them and how much they did to address these practices, and under the new guidelines from June 1993, how they went about discharging their responsibility to keep the Minister informed of these matters.

2.26 Role of Ministers in regulating CSL

Ministers, apart from appointing Commissioners, have had little role in regulating CSL, on their own admission. A former Health Minister from the eighties told the author that he had noticed how little information he had on CSL and wanted to find out what was going on. The authority was on his list of things to look into, but his government lost office before he could do it. Neil Blewett, as already mentioned, gave considerable attention to CSL's commercial viability. Brogan says in the official CSL history 'sundry Ministers for Health have admitted that CSL ... seldom rates Ministerial attention and even less frequently rates unprompted Ministerial thought.'[57] Health Minister Hunt was lobbied to remove the restraint on non-biological products. Before taking the matter to Cabinet he sent it to a government members' health and welfare committee, where Mr. Fraser asked CSL why the government shouldn't sell it off.[58]

A spokesman for former Health Minister Richardson, approached by the author to arrange an interview, said the Minister's office had had almost no contact with CSL, apart from requesting a bit of information on anti venoms. The opening of the plasma fractionation plant in 1994 was 'the only thing [the Minister] has done'. At the spokesperson's suggestion, written questions were formulated for the Minister's consideration but he retired the following week. Prior to publication of this report, the current Health Minister, Carmen Lawrence was invited to discuss the study and findings via her media officer and again directly in a personal interview with a contact of the Blood Project but she did not respond to the offers.

The legislative powers of Health Ministers under the CSL Act and the Therapeutic Goods Act have given them ample opportunity to regulate the organisation through such means as appointment of commissioners, fixing of salaries, determination of national interest products and so on, and the mechanisms available under the 1993 Accountability and Ministerial Oversight Arrangements for Commonwealth Business Enterprises, referred to above, offer further opportunities for scrutiny and regulation. Brogan

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[57] *Brogan p 197.*
[58] *according to Brogan, p 201*

claims a former MD and commissioner initiated quarterly meetings with the Minister to report at firsthand on current events and plans and to 'seek from the Minister any input he desired to make - this latter search being a fruitless one'.[59] Perhaps Ministers assumed that the Health Department was in touch with CSL's workings.

Whether Finance Ministerial scrutiny of CSL's corporate plan under the new guidelines of the nineties was effective is unknown, since the process and the plan are secret.

2.27 Parliamentary scrutiny

Parliamentary scrutiny of CSL's blood product performance and of CSL in general was a potential means for improving the quality of regulation. It was not realised in CSL's case, neither when it was a division of the Health Department, nor a statutory authority constituted as a commission, nor a government business enterprise and government owned company.

When the Laboratories became a statutory commission in 1961 even a parliamentary member from the Government party complained that Government had not told parliament the reasons for the legislative changes or the results of the independent Reid- Nossal review leading up to them.[60] (As seen above, the major review only became public when the Melbourne Age reported on it halfway through its life. In 1970 the Opposition spokesperson on health, Mr. Hayden, complained of not knowing how the Minister struck the price of stockpiled and other national interest products.[61]

Evidently, neither Ministers nor anyone else, including parliamentarians, have been concerned about how CSL accounted to the parliament. Indeed, one of former CSL Director Bazeley's sins in the eyes of government was that in addition to vesting his grievances in journalists he also briefed representatives of the parliamentary Opposition party. In chapter sixteen it will be seen that parliamentary understanding concerning blood products and CSL had bottomed by the time of its sale. Members had ceased complaining about lack of information, as by this time most no longer realised that they didn't know what was going on at CSL.

The Public Accounts Committee took evidence from CSL late in the sixties under its Chairman Davis, a former member of the Committee. The Committee considered the national interest activities should be funded and accounted for separately, partly to facilitate parliamentary scrutiny. Separation did occur later. In 1990 Senator Watson on the same Committee said 'I think there are a few people within the [Government Business Enterprise] sector and statutory authority areas that believe they have a new

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[59] *Brogan p 197*

[60] *Mr. Stewart 16.9. 61, at p 869?, in 'The Administrative Vocation', Selected Essays of R S Parker, Hale and Iremonger.*

[61] *Hansard Reps 14.5.70 debate on National Health Bill, p2179.*

found independence from parliamentary scrutiny ... their new found status hasn't diminished the interest of either the Senate Estimates Committee or the Joint Committee of Public Accounts.'[62] Nevertheless CSL sailed right by. Besides, CSL had already been enjoying independence from parliamentary scrutiny throughout its career as a state-owned body.

Parliamentary debate of any substance concerning CSL's blood products and CSL itself, does not appear in Hansards. Mr. Hayden made a speech in 1970 about CSL's economic conditions and the funding of national interest projects. During the sale debate in 1993, Senator Coulter asked some considered questions of the Minister representing in the Senate. Senator McMullan's response stands out from the way in which most Ministers responded in the Parliament concerning CSL. He made no attempt to brush the questions aside and every effort to provide informative and reasoned responses from the little information available to him. These instances aside, most parliamentary debate has been ill-informed and meaningless. A 1970 Senate debate covers an unprecedented thirteen pages. Ten of these are devoted to a turgid and ramshackle debate on remuneration and allowances of the commissioners, while in the remaining three the Senators readily approve importation of foreign vaccines.[63] The general standard of debate probably seemed to be approaching farce in the eyes of CSL, already impatient with democracy. Parliamentary questions mostly cover matters such as shortages of influenza vaccines. The level of debate is unsurprising, since the Parliament has never been adequately informed about CSL or the issues relating to blood products and human blood supply.

2.28 TGA involvement

The limited evidence available concerning the regulatory role of the new Therapeutic Goods Administration, together with evidence of their audits in blood banks, suggests that CSL is no longer able to evade inspections and evaluations of at least their new products. (This is not because of privatisation, although one possible advantage of privatisation ought to be that preferential treatment for CSL becomes even less likely.)

However, strong inspectorates are only a limited part of the answer. A former senior scientist who believed profoundly in the need for external regulation from NBSL/TGA type agencies said at an ANZAAS meeting in the eighties: 'Government control has been found necessary throughout the developed world. Nevertheless, while standards for products, codes of GMP, inspections and random and selective programs of sample testing by the national control authority both guide and assist manufacturers and are an important factor in consumer protection, the prime responsibility for the safety and efficacy on a batch by batch basis lies with the company and its staff.' CSL's role in self-regulation is dealt with later in this report.

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[62] *ABC Radio The World Today 7.9.90*
[63] *Senate Hansard 10.6.70 2216- 2229*

2.29 Summary and Conclusion

This chapter shows that CSL began making blood products on behalf of the Federal Government in 1952, who remained its only client for Australian-sourced products. While all other pharmaceutical companies were subject to scrutiny through inspections under a good manufacturing practices (GMP) code written by the National Biological Standards Laboratory from the sixties onwards, CSL was not. When CSL became a statutory authority in 1961, constituted as a Commission, the Parliament, successive Health Ministers and the Health Department continued to have little control over the organisation and were generally uninformed about its manufacture, research and development of blood products.

The organisation treated blood products as a lowly part of its activities, constantly bucked the efforts of NBSL officials to make it conform to good manufacturing principles, and preferred to pursue pharmaceuticals manufacture for the international market, often at the expense of national interest activities such as vaccine, blood product and antivenom manufacture. The Health Department was reluctant to intervene in CSL and rarely did so until its failures became extreme. Regulation by corporate plan was applied in 1993 but the process is not public, nor is the plan. Parliamentary knowledge of the workings of CSL was almost non-existent by the time the Government announced its intention to sell the organisation after this was recommended by the Health Department. Parliamentary scrutiny of the decision and of the two-year process leading up to sale did not occur.

CSL has long been at odds with both its regulators, government and the public's concept of what it does and should do. National interest activities such as blood products and vaccines, while providing most of the organisation's income stability because of government subsidy and purchase, have for most of the organisation's history been even less than also-rans in the product portfolio or organisation's plans, until the advent of the new fractionation plant, when new opportunities for overseas trade arose. Blood products have received even less attention than vaccines, whether in terms of research, development or regulation - even despite the HIV calamity of the eighties. Later chapters show that manufacturing failures, wastage and compromises of product safety occurred in CSL human use products from at least 1960, and in the case of blood products continued to occur throughout the time of this study.

It should be understood that CSL is a neophyte in the field of compliance with external regulation and accountability, CSL for long regarded these matters with contempt, and its history of self-regulation shows profound deficiencies. The regulator would be wise to take these factors into account when assessing the organisation's behaviour. Much reform is claimed to have occurred at CSL in the last three years. However, common sense tells us that no organisation becomes a band of angels overnight.

CHAPTER THREE: GENERAL STANCE OF FEDERAL HEALTH DEPARTMENT ON BLOOD AND BLOOD PRODUCTS

This chapter shows the general stance of the Federal Government Health Department, the chief regulator for foreign and Australian manufacturers of blood products and supply of blood, in relation to blood and blood products. Understanding the Department's stance on law, policy and regulation in this area is helpful in formulating appropriate recommendations for improving regulation, just as understanding CSL's regulatory history helps in recommending changes pertinent to that field. The chapter also serves to briefly introduce the reader to how blood products are regulated and the law and policies governing them.

The policy on **national self-sufficiency in unremunerated blood supply** has always been accepted in Australia, ever since Red Cross first began wartime collections of blood. In 1975 the commitment was strengthened 'from above' by a WHO resolution to which Australia became an automatic party. In May 1975 the twenty-eighth World Health Assembly noted the increasing activities of commercial blood firms in developing countries, which it said may seriously interfere with efforts to establish unpaid blood donation systems. The Assembly was aware that blood acquired commercially posed higher disease risks and led to donor exploitation.

The Assembly passed a Resolution urging Member states:

> 1. to promote the development of national blood services based on voluntary non remunerated donation of blood;
> 2. to enact effective legislation governing the operation of blood services and to take other actions necessary to protect and promote the health of blood donors and of recipients of blood and blood products.[64]

As seen in chapter seven, the failure of the Federal Government to pass legislation giving effect to this Resolution at the Federal level, has been used to justify bringing in foreign blood products, despite their sale being banned in all States and territories of Australia.

3.1 Denial of general responsibility

Various Health Department officials interviewed by the author said it was not the responsibility of the Commonwealth to regulate blood. The official in charge of funding the Blood Transfusion Services outrun funding through the States, said in formal interview in 1992 'we only fund it, we're not responsible for the regulation. It's a matter of state legislation'. Some were looking to wrap the funding of Red Cross up in a composite grant to the States so they would not even have to be involved in that aspect, even though the funding

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[64] *WHA 28.72*

of agencies to provide or process human blood is an obvious lever for enforcing regulation. As another officer said:

> We just wandered into the field of blood supply, only because Red Cross wrote to the Prime Minister in the fifties and got funding. You can't then switch the money off. From 1954 to 1989 we just handed over money without worrying. We never collected a single, solitary statistic. Read the annual reports- they never tell you anything more [than that we handed over the money].

The author conducted two interviews with Officials C and D. Official C had been nominated by the Secretary as an appropriate contact and interview subject because he was said to know more about blood and blood products than anyone else in the Health Department. Official C confirmed this and so did many other Health officials interviewed formally or informally. Official C is Principal Medical Adviser to the Therapeutic Goods Administration. Official D joined the Health Department as National Manager of the Therapeutic Goods Administration in December 1991.

Official C wears a number of hats, as a medical adviser to the TGA, and also as the Federal Government representative on the National Blood Transfusion Committee of the Australian Red Cross Society.

Officials C and D were shown a copy of the WHO Resolution and asked if Australia had undertaken any activity approaching the conditions contained within it. Official D said the document was foreign to him. Official C said nothing at first but looked at it and then said he would have to be able to go over it. After looking at it further he said 'That's the basis for the Commonwealth funding of forty per cent for the blood bank - to support the States and keep ourselves abreast of the State's policy - the basis for kicking in the forty per cent funding of blood banks'. He then raised the 'constitutional problem' which limits Commonwealth power. He was invited to elaborate on what this problem is and said he was 'not going to discuss it'.

When asked about the policy on national self-sufficiency in non-remunerated blood supplies Official C, said 'What policy ... I've never been sure of what you've been referring to'. Another senior official in charge of funding the BTS's, interviewed officially by the author, said the policy has been 'a matter of practical politics' for many years,( ) although he did not know of anywhere it was written down. A former senior official from NBSL, (TGA's predecessor), said the policy was so well accepted 'it didn't need to be written down. 'An official of NBSL referred to it at a symposium in 1986, when he said that until recently foreign blood had not come into Australia because the 'Australian Government supported the 1975 World Health Organisation resolution ... on the development of national blood services based on voluntary, non remunerated donation of blood.'[65] Later, Official D referred

[65] *Joint IABS/CSL Symposium on Blood Fractionation, Melb 1986*

to the policy in an ABC interview. In a subsequent interview with officials C and D, Official C spoke of the policy and referred the author to a TGA publication containing the policy. This had been written in 1992. This statement forms Appendix Two of this report.

The need for officials to understand and promulgate the policy on blood is clear. When officials C and D were asked if they had heard any suggestions to further commercialise blood and blood products, official D, the General Manager of TGA said 'CSL is a commercial organisation that sells their blood', whereas actually CSL is merely paid to fractionate plasma belonging to governments or other parties such as Red Cross and the sale of blood is prohibited throughout Australia.

R.1 The Health Department should write down its policy of pursuing a national system of blood supply based upon non-remunerated blood and publish it to particular publics with an interest in the quality of the Australian blood supply and blood products, including its own officials.

In 1992 WHO Guidelines for the Organisation of Blood Transfusion Services said the ultimate responsibility for these services rests with the national government. Even if the Federal government had no constitutional power to regulate human blood, this does not mean that in a Federal system the Federal Government is entitled to assume no responsibility. There are many common sense reasons why regulation of blood should not be undertaken by individual States and Territories acting in isolation.

Turning specifically to regulation of CSL, in a preliminary interview in 1992 Official C volunteered that little was done to regulate blood product manufacture prior to the new Therapeutic Goods Act : 'In the past before CSL was corporatised [1991] they were beyond our control. In theory they could have been [controlled] by the Minister but it never happened ... they were in the same position as a local manufacturer. Before [the new TGA became operative in] February 1991 all Commonwealth controls were mediated via import control, not local control. CSL was not much controlled. CSL is now perceived as a private drug company.' This was said before CSL was due to be privatised.

A general lack of regulation of CSL's blood activities by the Health Department at large was a key finding of this study. It was found to be symptomatic of the agency's approach to blood products in general. One Department official involved with CSL said in 1993: 'we own CSL, we are their customer and their regulator' but when questioned further said 'we don't really regulate in effect.' A former official said to know most about regulation of CSL, when asked who was their regulator before TGA, replied pointedly 'I've no idea!'

Between 1992 and the present there were two people involved specifically with CSL customer and financial matters in the Corporate Services Division.

Documents from 1980 show a staff allocation of point five of one person - twice the Red Cross allocation at the time.

3.2 Lack of agency co-ordination

A lack of co-ordination on blood issues within the Department was also found, often affecting the quality of regulation or whether it occurred at all. Most CSL matters come under the Therapeutic Goods Administration for GMP's, evaluation of products and for access to unapproved products under the Special Access Scheme. Corporate Services deals with CSL's supply to the Federal Government and finance matters, including the funding of CSL blood products available under the Special Access Scheme for individual use. The Health Care Access Division deals with adequacy of supply and access, which includes funding arrangements for Red Cross. This is the only division of the Health Department where there appeared to be any practical or effective interest in overall policy and co-ordination on blood and blood products, and in the quality and nature of regulation. This is also the division which will 'regulate' CSL post-sale, in the sense that it will seek to enforce its supply contract with CSL for blood products.

As one official put it when asked about agency co-ordination on blood policy 'there are Chinese walls in this Department'. A senior legal officer commented on a tendency until recently for policy makers and administrators to consult agency lawyers only if it suited their cause. The Chairman of the Red Cross National Blood Transfusion Committee, a powerful advisory committee which was found to have a key executive and policy making role for blood banking practice in Australia, was asked if there was a representative in the Health Department to whom Red Cross could refer on transfusion matters. He replied:

> I have not been, as Chairman of the NBTC, given by the Federal Department of Health the name of a person who is seen to be responsible for transfusion matters.
> KB: Could there be a role for someone there who you would have as a regular contact?
> There is an attitude that the development of that may be desirable.
> KB: Where is the awareness of that desirability coming from?
> Right throughout all of the Blood Transfusion Services.

In interviews face to face with officials C and D, little further evidence of regulation of CSL before or beyond TGA was given. The author's and her recorder's notes show the following:

> KB: Was any attempt ever made to enter more control in (of CSL); how did the Commission regulate itself and how was it regulated?
> C: Ask CSL.
> KB Would anyone else know about departmental involvement with CSL [before TGA]?
> C: Don't recall. Don't know the answer to the question of who would

have.
KB: Who is responsible [for CSL] in this department?
D: TGA has regulated CSL. There's company regulation [ed: Corporations Law] Sorry, can't answer that, not TGA's role to do that.
KB: What forms of consultation exist between the Department and CSL regarding financial, legal and technical matters?
Same [type of] response.

Up until the sale of CSL, Government had many opportunities to fulfil its normal watchdog role over the statutory authority. A most effective way of obtaining regulatory compliance is through budget adjustments up or down as indicated. Appointments to the authority's board may be used, or arranging for parliamentary and government inquiries, the taking of annual reports, taking an authority to court for crimes or offences, putting the authority under political pressure through criticism in the media and in parliament (such as when the government criticised the Civil Aviation Authority in the media) and by enacting and using statutory powers for Ministers to give direction.

In many cases, awareness of the need to use any of these will arise first from within the relevant Ministers' department. It is here also that the most effective method of regulating a statutory authority through informal and ongoing contact, can be exercised. The mere fact of the department learning of a regulatory failure or contemplated breach in the statutory authority may be enough to induce self-correction or maintain compliance. However, there was little evidence that the Health Department exercised or cared to exercise an effective watchdog role over CSL's manufacture of blood products, despite the many opportunities available.

CSL official A, asked about Health Department regulation by non-TGA staff, said that he was not knowledgeable about regulation of financial matters but that;

From my contacts it certainly hasn't been a question of regulation. The sort of contact I have with these guys (Corporate Services Division), it's more from them to me than from me to them. They'll call up about Ministerial questions and technical advice on products that doctors have written in about and asked if they can import ... If Official X rings up and says Dr Y wants some pure factor IX, he doesn't know who to get it from or where the manufacturer is situated and so forth, we'd help out.'
RS: Any other products [that you know of coming in]?
Fibrin glue, made by the Immuno Company. Instead of stitching you they glue the little structures like blood vessels and so forth, quite an interesting product which we're also having a look at ourselves.
KB: Could you make that possibly in the new plant?
Yes ... we're doing a little bit of preliminary work on it now.

If one accepts the Health Department's commitment to maintaining the national policy of self-sufficiency in blood products from unpaid Australian donors, one would be surprised by such instances of the Department passing up regulatory opportunities in favour of using the national fractionator as an information and referral service for individual doctors wanting to import foreign blood - and also by CSL's seeming willingness to be used to that end.

3.3 National Blood Transfusion Committee

The Health Department and CSL are both represented on the National Blood Transfusion Committee, the Red Cross committee where CSL issues are raised if necessary. This Committee provides the Federal Government with opportunities to inform itself on Red Cross and CSL operations which could lead to regulatory initiatives or routine activity. The Health Department representative is Official C, also Senior Medical Adviser to the Therapeutic Goods Administration.

CSL's official A, an established member of the Committee, was asked:

> KB: How much real scrutiny do you think the Commonwealth representative can exercise, or what do you think he is trying to achieve by being there?
> A: I've no idea! He doesn't really contribute very much. He probably reports back to his superiors.
> KB: Do you know who that is?
> A: I would imagine the Chief Medical Officer and/or the Secretary but I don't know that for sure ...
> KB: Does he tell you of any thinking that they have, or don't they think independently of what comes to them from Red Cross and yourselves?
> A: Usually he doesn't on the spot ... you tend to get the answer in correspondence.
> KB: Do you think it is adequate for such a representative to be merely a doctor or should they be more highly qualified in haematology or-?
> A: That's a hard question. I don't think the Department would normally employ someone highly skilled in transfusion medicine ... I'm not quite sure what the Commonwealth rep. is there for quite frankly. I mean I know that the Commonwealth pays thirty five per cent of the running costs [of Red Cross] ... really he doesn't, how should I say, enunciate Commonwealth policy on issues that come up before us.
> KB: How do you find out about the government's thinking?
> A: By writing to the Secretary (laughs) ... and then waiting a sufficient length of time for an answer. Oh, you know, you usually get a response ... It takes a while ... I mean I really wonder from a technical or medical point of view whether we should expect *anything* from the Commonwealth Department of Health ... since I have been on the Committee the Commonwealth rep. has tended to be someone in the medium hierarchy of the Department and really I think they've just acted as - it sounds terrible - a messenger boy.

On reading the transcript of this interview later, CSL official A volunteered that he had formulated an answer to the question about the role of the Health Department representative. He said that 'his particular role is to act as a bridge between the bureaucracy and the BTS and CSL. He represents the views of TGA and TGAL (Therapeutic Goods Administration Laboratories)'.

When Red Cross tripped over CSL's long-standing practice of mixing plasmas of different origins without telling them, the matter was raised at a subcommittee meeting of the NBTC. Official C was asked if he routinely attends subcommittee meetings of NBTC. He said that would not go into such detail, saying 'pass on that question'. CSL official A said they stopped mixing plasma of different country origins because they were 'forced to' by the government but clearly it was at Red Cross' behest. What role, if any, the Health Department played is unclear. However the practice was reported as having occurred over some decades, during the time that CSL as a statutory authority was legally obliged to report to the Minister for Health and when the Minister's Department was supposed to be its chief regulator. If they did not know of the practice, it could only have been because of extreme indifference.

As for CSL sending Red Cross material to Hong Kong without Red Cross authorisation, this was brought to the attention of the Chairman of the NBTC unofficially, probably by a Health Department official or less probably by a CSL whistleblower. CSL claimed the blood product was sent with Department approval but Official C, asked if there were any instances of material getting export approval when it had not been approved by Red Cross, said 'not to my knowledge'. It is unclear exactly what the Department knew and when, and what if anything they did to regulate the Commission after the incident, although a number of informants inside the Department and beyond said Department knew of the incident, at least after it occurred. This was during the process of fitting CSL for public sale. This matter is dealt with further in chapter sixteen.

Official C said in 1993 of his role on the NBTC:

> If [something] is clearly in breach of Commonwealth law I would take the matter up. I attend as an officer of the Commonwealth, not just as a good fellow. I report back to the Department.
> KB: Do you routinely send minutes of the NBTC to any other part of the Department?
> Not routinely; if it required a statutory decision [I] would refer it on. [I am] not obliged to raise a matter which has no statutory implication .... [the minutes] are placed on file. I draw officers' attention to what I believe is relevant.

3.4 Regulatory legalism

Official C's assertion that he is not obliged to raise matters which have no statutory implication is an example of what Braithwaite calls regulatory legalism. 'Regulatory legalism construes business regulation as an enterprise that is fundamentally about the just enforcement of law. The job of regulatory agencies is to enforce the laws that are passed on to them by the parliament'.[66] Professor Braithwaite himself claims 'the obligation of regulatory agencies is to use their resources strategically to find the least cost ways of maximising regulatory objectives while respecting the legal rights of alleged offenders.'

Australian Health officials like to insist, and likely believe, that they had no power to regulate blood before the new Therapeutic Goods Act, however it is not true. Those that so insist tend to be caste in the mould of Braithwaite's regulatory legalists, those who say their hands are tied for lack of a law to administer. In respect of the Health Department, regulatory legalism has also been found to be a mask for simple lack of interest in doing the job.

For example, the therapeutic goods legislation which preceded the current Act only applied to products where there was a relevant standard in the British Pharmacopoeia, or where the Health Minister had proclaimed a standard. As one official put it 'the Department received complaints about why they had taken no action against various things and they replied that they had no power because there was no standard'. There was clearly a desire in some parts of NBSL to formulate a standard for biologically derived products. The lack of interest seems to come mostly from executive levels of the agency.

Lawyers and non-lawyers alike, the really dyed-in-the-wool Health Department legalists share absolute convictions about the limits of their constitutional powers and will readily lecture other people, the author included, about how those powers prevent them regulating Australia's blood supply. This issue is pursued more in later reporting on this study but it is interesting to note here, in light of claims by current Health Department officials that 'blood is a States matter "because" health is a States power under the Australian Constitution', that their own legislation governing the CSL Commission between 1961 and 1993 was created under Constitutional powers including the provision by the Federal Government of *'medical ... services.'* Few blood products can be administered without there being a medical service involved.

Other officials, present and past, cite different reasons for the agency's failure to regulate than perceived lack of constitutional power. A former senior regulator said 'the capacity to introduce good manufacturing codes for blood was there all along. They chose to link them to the new Therapeutic Goods Act but they didn't have to ... they could simply have introduced them

[66] *Business Regulation and Australia's Future, Ed. John Braithwaite and Peter Grabosky 1993, Australian Institute of Criminology, pp 81-4)*

through the National Biological Standards Laboratory. Blood products would be very low on their agenda and that is why they would know very little about it. They wouldn't care about it.'

Another former senior regulator said 'The government has had the authority to deal with blood and blood products since the [sixties] when the first Therapeutic Goods Act was passed ... they were not seen as a priority until the sixties as to whether there should be intervention by the National Biological Standards Laboratory (The predecessor of TGAL) Intervention was because of the evolution of NBSL ... and the question arose concerning the quality of CSL's product'.

3.5 Safety of government laboratory staff

Even where human blood posed a direct threat to their own staff, policy makers in the Health Department were slow to act. In early 1976 hepatitis b antigen was found in significant numbers of human sera imported into Australia for use as controls in diagnostic work at NBSL, according to documentation obtain during this study. Three years after this discovery a draft standard for tests involving this virus in laboratory environments was still receiving comments within the Health Department.[67] In 1987 Official C had told this researcher that the standard had been finalised and was due to receive approval from Health Minister Neil Blewett. In 1992 the author asked official C whether NBSL workers were tested at any point, why it took eleven years to introduce the standard, and how it was working in practice.

> Official C: I don't have a view.
> Official D: We assume it is [working] OK ...
> KB We understand that a worker at NBSL found HIV positive batches of control plasma to be used as laboratory reagents for quality assurance factor VIII assays. Is this true?
> No answer given.
> KB Have recent tests been run on imported materials for diagnostic or laboratory use and were any undesirable results found?
> Official C: Can't recall any.

Nor was any evidence given of Health Department awareness or concern about of the many manufacture and supply deficiencies alleged in this report by clinicians, Red Cross and hospitals.

3.6 Conclusion

The stance of the Health Department in relation to policy, legislative needs and opportunities, and regulation of blood products, has in general been to either neglect these matters or explore ways of giving away responsibility under the guise of delegation. Corporately, the agency long ago formed the view that it has no responsibility for regulating this area, despite committing itself to the policy of national self-sufficiency in unremunerated blood

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[67] *Health Department documentation*

supply, despite funding Red Cross through the states to collect blood and despite being the agency responsible for CSL as a statutory authority and monopoly manufacturer of human blood products.

The predecessor to the Therapeutic Goods Administration, the National Biological Standards Laboratory, attempted to regulate CSL despite CSL's resistance and with variable support from executive levels within the Health Department.

The Health Department's indifference and weak stance on policy and regulation for blood and blood products to date has been the principal factor leading to the erosion of Australia's long-standing commitment to a national system based on unremunerated blood supply and freedom from the harms associated with unregulated commercialised foreign schemes. This claim is further borne out by particulars presented in Part Two, which deals with regulating the manufacture of blood products.

There are many conscientious, very talented and dedicated staff in administration, policy, scientific and technical areas at middle and junior levels of the Health Department. These officers could readily use or create law, policy and regulatory schemes to further the eight goals postulated for human blood supply within the Federal system. However, lack of adequate knowledge , confusions about law and public duty, undue deference to industry, and the simple indifference exhibited by their executives needs to be remedied before these officers can be managed and directed effectively.

R.2 The Federal Government should take responsibility for seeing a national system for the supply and usage of blood and blood products devised, implemented and uniformly regulated.

R.3 The Health Department should assign policy responsibility for blood and blood products to a section of the agency on different command lines than the Therapeutic Goods Administration. This section of the agency should determine a program of steps designed to achieve a uniform national system, based upon co-operative federalism and according to the eight goals set out in chapter one.

Professor Roger Wettenhall describes an interesting overseas development of 'focal points' - specialised sections of the central Government service which exist in some countries to coordinate/harmonise government control over or interventions in the affairs of the corporate enterprises ...[this is] a big advance on systems where the Government interest is divided in an unintegrated way among a miscellany of sectoral ministries - Treasury, Minister of Finance, audit office, planning commission and special legislative committees. The concept of a focal point could be adapted for use in regulating blood and blood products.

R.4 A 'focal point' for Government policy and regulation on blood and blood products has been needed since at least the late seventies. The Health Department should establish a small unit within the Department to address the need for policy formulation and regulation of human blood and blood products. Consideration should be given to the need for an external National Blood Commission as well, to function as a public 'focal point' in order to better implement co-ordinated uniform national policy within the Federal system.

This new Unit should:

1. Make its presence and purposes known to all Government and non Government agencies with an interest or stake in blood policy, including all relevant areas of the Health Department and the Department of Defence, the Trade Practices Commission, the Federal Bureau of Consumer Affairs, AQIS, CAA Customs, the Australian Securities Commission, NHMRC, State Health Departments, the National Association of Testing Authorities, hospital boards, the HFA, consumer groups representing or capable of representing users and the general public, health unions, colleges capable of influencing blood usage, Red Cross, CSL, foreign and domestic companies, IVF clinics and research bodies using or processing human blood and transport unions.

2. Formulate a policy for consultation and information-sharing within these agencies, especially a standing mechanism with the States for ensuring a uniform approach to effective policy and regulation. The Unit should actively promote the need for a 'seamless government' approach, whereby agencies commit themselves to collectively and co-operatively addressing blood policy and regulation rather than committing only to areas defined as belonging to their agency. The unit should also promote the need for a 'no surprises' operating style between agencies.

3. After consultation formulate a contemporary policy on blood and blood product supply, based upon the commitment to a national, closed system of blood derived from non remunerated donors, in keeping with the 1975 WHO resolution, in line with State and Territorial legislation banning the sale of human blood, and in keeping with the best overseas trends in Europe and elsewhere.

This policy should define the meaning of 'community service obligation,' or 'national interest', or 'public interest' as it relates to the human blood supply and the WHO Resolution. Particularly it should give in principle guidance concerning how the public interst should be weighed against commercial or other interests when decisions are made by Government officials concerning access to information and decision-making processes with bearing on blood policy and regulation.

The policy should specifically affirm the actual written principles contained in the Freedom of Information Act concerning access to official information on the dissemination of information necessary (a) for stakeholders to contribute to effective regulation of blood supplies and (b) for users and potential users of blood products to be able to weigh up the risks and benefits of blood and blood products.

4. Publish that policy through appropriate channels on an ongoing basis, including the National Health and Medical Research Council which has discontinued its previous practice of making public statements exposing international commercialisation of blood, the efforts of overseas companies to break down our system and the value of the closed Australian system. ( ) *eg Melbourne Age 21.10.79.* The value of a National Blood Commission taking on this particular role should be considered in this context.

5. Recommend and advocate for any necessary legislative amendments and initiatives needed, at Federal and State levels to give the Federal Government powers to enforce the policy and its commitment to a closed non remunerated system as stated in the World Health Organisation resolution of 1975.

6. Oversee the implementation of other appropriate policy and regulatory changes such as those recommended in this report, or otherwise found to be suitable.

PART TWO - REGULATING MANUFACTURE

There is a balance to be struck, between giving markets free rein and safeguarding the public interest. Often we try to strike this balance using a 'carrot and stick' approach. However unless regulators have a very deep knowledge of the activities or businesses to be regulated, they will get it at least partly wrong. To put it simply, a carrot and stick will not do the job if you do not know which way the donkey should be facing.[68]

[68] *Eric Mayer p 97 Business Regulation and Australia's Future.*

CHAPTER FOUR: GENERAL OUTLINE OF ACTIVITIES TO BE REGULATED.

Part Two looks at the actual and potential regulatory role of key agencies, especially the Health Department and its Therapeutic Goods Administration, in a number of major activity areas, with a view to assessing the effectiveness of regulation against the eight goals postulated at the beginning of this report. These major areas of activity which regulation should seek to affect are:

1. **Blood collection and storage for local and overseas blood products.**
2. **Manufacture, from receipt of starting material to release for sale, and product recalls, to ensure quality, safety and availability.**
3. **Sale, and use in trials.**
4. **Supply, demand and usage, including user consent.**

Each of these activities has the potential to enhance or detract from the eight goals put forward in this report. Blood collections should be unremunerated, Australian sourced, obtained without harm to the donor or those who handle them, and of the highest affordable quality; manufacture should eliminate or minimise health risks and maximise yield; sale should only take place after evaluation of the products for safety, quality and efficacy with attention also to relative cost; trials of blood products should not unnecessarily harm participating subjects.

The main regulatory mechanisms available include:

For blood collections: the licensing of local blood collection centres; requiring certification by sponsors bringing in foreign material for processing into blood products; inspecting foreign collection centres.

For manufacture: the implementation and enforcement of good manufacturing practices (GMP) for quality, safety and efficacy of local manufacture by CSL, as a basis for licensing their manufacturing plant.

For sale and use in trials: pre-marketing clearance for local and foreign blood products; trial approval and monitoring mechanisms; product recall schemes using voluntary codes backed by legislative provisions.

For supply, demand and usage: promotion and encouragement of blood donation, education, voluntary guidelines, price controls, persuasion and other such means through hospital peer review committees; and **for user consent**: clinician education, product information supplied by manufacturers, information and warning disclosures by government and other bodies, public information programs, consent forms, and protocols governing the actual process of ensuring informed consent.

As tools to ensure compliance or monitor the market post-sale, regulators may use financial incentives, random sampling and testing, ongoing inspections, injunctions, directives, seizure, disclosure orders, adverse publicity through media and consumer networks, and prosecutions. To test the effectiveness of regulation personnel may use audit, review, cost-of-regulation impact studies and consumer feedback mechanisms such as complaint hotlines.

The Health Department, particularly the Therapeutic Goods Administration (TGA) is the principal agency addressed in respect of these activities. The Therapeutic Goods Administration regulates blood and blood products by requiring good manufacturing practices of blood banks and processing companies, regulating trials, and to a certain extent by affecting user consent. Its potential to regulate the major activities of collection, manufacture, sale, trials, demand, usage and user consent is considerably greater than its current activity level. The principal limitations are weak and defective law which doesn't account adequately for the particular challenges of regulating blood and blood products, too few staff in key areas such as compliance, and unwillingness to supplement the legislative powers to use non-legislative means to improve regulation.

4.1 Blood classed as a therapeutic good

Blood and blood products are taken by the Health Department to be therapeutic goods. They come under the Therapeutic Goods Act 1989 and the associated Code for Medicinal Products 1990 and Code on Blood and Blood Products of 1992. Both codes are linked to the legislation by Ministerial determinations.[69] However, observance of GMP standards is not required by law as condition for obtaining a manufacturing license, although many people appear to assume that it is. This author could find nothing in the legislation that makes it an offence for a manufacturer to not observe GMP codes, although the TGA may refuse a license to a manufacturer who doesn't conform to them. (Ironically, this bears out claims that the Health Department could have introduced this form of regulation decades ago, rather than waiting for legislation).

4.2 Blood classified with drugs for regulation

Official C, the Principal Medical Adviser to TGA, said in interview that 'from a regulatory point of view blood is the same as any other drug'. (Another Health official said it was 'no different to organs'). Whether the classification of blood with drugs is of concern depends on whether regulators take proper account of the distinctions between the two in practice. For example, the classification of vitamins, which are food supplements, as drugs, can lead to inappropriate solutions for wrongly defined problems. Regulators especially need to know if a therapeutic product is derived from or contains a human blood component when it comes to regulating the quality of the starting

[69] *for the Blood Code, Determination 1 of '94; for the Medicinal Code, No 1 of '92 and No 2 of '92.*

material. This can become particularly important where the TGA tries to control the quality of blood products from abroad, as seen later.

4.3 Therapeutic goods legislation aims at national controls

The new Therapeutic Goods Act shifts the former legislative emphasis on importation across to supply and aims to regulate the product at that point. The new legislation seeks to establish a framework for a national system of controls relating to the 'quality, safety and efficacy of therapeutic goods.'[70] and 'timely availability'[71]

4.4 Limitations

The Act states in S 6 that it applies only to incorporated bodies, and persons or corporations trading across State or Territory boundaries.[72] This means that if an individual were collecting placentae from a hospital and using the tissue in cosmetics sold within their State, for example, they would not be covered by the legislation, although the selling would be prohibited under State laws. Another individual could be doing exactly the same thing and *would* be covered by the therapeutic goods act if he or she were incorporated.

Blood collection centres in hospitals or other facilities, and Red Cross centres who collect plasma and blood not intended to be sent to CSL for fractionation are not considered to be subject to the legislation in respect of that material. They can collect plasma, process it, and distribute it without a manufacturing license and without having to get the goods evaluated for their safety, purity and efficacy and then entered on the register of therapeutic goods set up under the legislation.

The power to regulate incorporated trading corporations such as CSL is held concurrently by the Federal Government and the States. As TGA sees it, complementary State legislation would be needed to cover unincorporated parties which manufacture or supply blood products within a State or in the Northern Territory. A national committee on therapeutic goods was said to be addressing the need for complementary legislation at the time of this study. By the end of the study, some advances had been made but uniform legislation had not been achieved. One State was believed to be in disagreement with draft law.

The situation whereby blood collection centres take blood which is subject to regulation alongside blood which is not, and whereby a consumer benefits from human regulated for safety if it happens to have been processed at CSL but not if it is issued by Red Cross, affects the integrity of the whole system of blood safety in Australia. In some cases, outdated whole blood collected by Red Cross, which is not subject to TGA regulation, is then processed for

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[70] S34

[71] *The Pink Book p 2*

[72] *and under Commonwealth law relating to the provision of pharmaceuticals or in relation to the Commonwealth or its authorities., 6(I)(a) and (b)'*

issue to CSL and so becomes subject to the testing standards required for material being issued to CSL.

R.5 Rather than wait on co-operation amongst the States for legislation to complement the Federal Therapeutic Goods Act, the Health Department should seek to regulate all blood collections under the constitutional power to regulate matters incidental to the activities currently regulated under the Act.

As seen earlier, blood manufacture, whether that term applies to Red Cross collections and component separation, or to CSL's fractionation of plasma into blood products, was scarcely regulated by the Federal Government at all until the new Therapeutic Goods Act came into operation on February 15 1991. CSL neither regulated itself adequately nor tolerated attempts at external regulation or help, except in crises when it had no choice.

That is the regulatory history inherited by the new Therapeutic Goods Administration. Added to that is a history of incompetence on the part of CSL, the evidence for which is presented in chapters six, fourteen and *inter alia*. Since the ultimate responsibility for the quality and safety of blood products rests with the manufacturer, and depends heavily upon the personnel of the corporation, this history needs to be borne in mind by regulators of CSL's Bioplasma Division.

Shortly after the new Act became operative, the government accepted the recommendations of the Baume report on drug evaluation, which has led to substantial deregulation and 'harmonisation' with regimes of other countries.[73] Australia is progressively moving towards accepting drug evaluation reports and data from other countries, exchanging inspection reports, and allowing more drugs onto the market with less evaluation. Responsibility for certain patients obtaining access to certain drugs, including some blood products from CSL and overseas, has been passed by the Department to hospitals.

Thus, at a time when the need for tighter regulation of blood has finally begun to be recognised worldwide, blood and blood product manufacture in this country, for so long neglected, have been brought under the umbrella of a regulatory regime characterised by weakening controls.

There are also major weaknesses in the Therapeutic Goods Act. These will be addressed as they become relevant to the different activities of blood collections, manufacture, product registration and controls on demand, usage and patient consent.

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[73] *ref bibliography*

CHAPTER FIVE: REGULATING LOCAL AND OVERSEAS BLOOD COLLECTIONS

This chapter examines the extent of regulation over collections of blood overseas and in Australia and shows how plasma coming to CSL for fractionation does not meet Australian safety standards. The practice of deriving blood from human placentae is also discussed.

5.1 Local collections

Australian material is collected - 'harvested' - mostly by Red Cross blood collection centres and somewhat by hospitals. Red Cross Blood Transfusion Services in all States and Territories are administrative units of the Australia Red Cross Society set up to collect and supply blood and in part to separate certain blood components unsuitable for CSL processing, which are distributed to hospitals and clinics. Red Cross collects blood and plasma from unremunerated donors on behalf of Federal and State Governments, who fund its operating and capital costs, bar ten percent contributed by the Society. The greater part of collected material is transported as frozen plasma to CSL for processing into various blood products, and returned to Red Cross (BTS's) who distribute it to clinicians and hospitals.

Until very recently Red Cross had long been its own chief regulator, despite clear opportunities from the State and Federal spheres to regulate it. Now its manufacturing processes are regulated by the Health Department via the Code on Blood and Blood Products.[74]

This code is intended for Red Cross and other entities who send plasma to CSL for processing from mid 1992. By contrast, the US Food and Drug Administration (FDA) regulated American Red Cross as a 'pharmaceutical manufacturer' from the early eighties.

That TGA is applied only to plasma sent to CSL leaves a major regulatory gap relating to the blood which Red Cross and others spin into components or distribute in whole form for hospital use. In 1989 the Canadian Bureau of Biologics extended its own regulatory control beyond blood products to cover all blood sold or distributed in Canada. A number of witnesses, including some TGA personnel speaking unofficially, expressed their concern about this gap in the regulatory system; some officials at TGA were looking at ways to cover it.

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[74] *Australian Code of Good Manufacturing Practice for Therapeutic Goods - Blood and Blood Products, July 1992.*

Some Health Department officials gave the onset of AIDS as the reason for regulatory intervention in Red Cross blood bank activities and CSL blood fractionation. Officials from TGA's predecessor, NBSL, often cited disasters as being the best opportunities they had for obtaining increased general regulatory oversight. But the code was published in 1992, some eight years after AIDS emerged. If it was the Health Department's response to AIDS, it was a delinquent one.

The WHO resolution of 1975 requested member countries to develop a code governing blood. In 1978 the WHO published requirements for regulating human blood and blood products.[75] The Health Department took another fourteen years to develop a code.

The Department claims the Code was developed as a collaborative project between themselves and others, including the National Blood Transfusion Committee and Red Cross Blood Transfusion Services. Red Cross interviewees objected to this, saying the code was taken out of their hands when still a working draft. 'We didn't realise what was happening. Bits and pieces came and went from it and the way it was put together has created a nightmare'. A Red Cross informant said the UK model itself was a working draft that 'got put on the wrong desk and then published'. (Both the UK and Australian versions were being rewritten during this study; in 1994 the TGA's blood bank auditor had standardised the Code on Blood and Blood Products to the format of the international ISO 9000 standard. This co-incided with a move to harmonise blood codes of many overseas countries to the same standard. One Red Cross interviewee said the ISO 9000 standard was too low.

The implementation of the Code for blood collection centres within Australia is addressed further under the section on inspections later in this report, but not in great detail as this report focuses more on blood product manufacture.

Upgrading to comply with the Code cost millions of dollars for some centres. The Health Department saw no need to assist, although in one case they were persuaded. State Health Departments came under great pressure to provide funds, in some cases for things Red Cross had wanted to improve before but couldn't because State governments didn't recognise the need. Other blood centres say they cut corners in their operations to pay for the TGA-dictated upgradings, some even cutting on blood collections to free up the money. The exercise caused a great deal of friction and demonstrated an appalling lack of co-operation within the Federal system on policy and regulation for human blood collection, particularly a lack of concern over the cost of the new regulation and its impact on production in the blood collection centres.

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[75] *WHO expert Committee on Biological Standardisation's Technical Report Series No 626, Annex 1 'Requirements for the collection, processing and quality control of human blood and blood products.'*

This issue must be addressed by government if regulation is to succeed. According to TGA regulators, Red Cross is going to need a national computer system to permit effective operations, and effective self and external regulation towards the goal of a uniform national system as called for under the WHO convention. The national government cannot demand regulation and ignore its cost.

R.6 The Health Department should acknowledge that responsibility for uniform national regulatory controls of blood and blood products includes, as a matter of course, responsibility for ensuring sufficient resources to implement them.

R.7 TGA should conduct a cost-of- regulation impact study for its regulation of blood banks and commercial fractionated blood products.

5.2 Overseas collections

Overseas plasma entering Australia for fractionation and re-export is not required to meet the same standards as Australian plasma.

Therapeutic goods have to be entered on TGA's Australian Register of Therapeutic Goods after vetting by the Therapeutic Goods Administration. The definition of therapeutic goods includes ingredients for manufacture, which would include overseas plasma for fractionation by CSL. But where the goods are for export-only, the status of any contributing overseas manufacturer is not reviewed, nor does TGA require any documentation about the overseas manufacturer. These goods are merely listed on the TGA register with the comment that 'The status of the overseas manufacturer of this product has not been reviewed'.[76] Starting materials for manufacture or goods for export only[77] - both these apply to foreign plasma - are exempt from the listing and registration requirements of the Act. Nor are the standards required for overseas plasma the same as those contained in the Code on Blood and Blood Product or Red Cross Guidelines for the Selection of Blood Donors. As one Health Department official said: 'CSL would have no business if that was strictly applied'.

The Australian code and guidelines require the health of donors to be closely ascertained and they must be in very good general health.[78] Donors must report illness subsequent to donating blood or plasma.[79] Their blood must be tested by the blood collection centre.[80] Where the donation is for fractionation, each donation must test negative for hepatitis B and C and HIV

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[76] *TGA News March 92, no 9 p 11 ;*
[77] *ref Schedule Five*
[78] *paras 502, 505, 510,*
[79] *paras 513, 514.*
[80] *per Annex 7 and the Technical Guidelines of the Code*

1 and 2, HTLV1 and syphilis.[81] Plasma donors in Australia may not give more than the WHO standard of fifteen litres a year.

This compares with donors in the US who may give fifty to sixty litres of plasma a year, with harmful results.[82] CSL indicated during the float of their company in 1994 that they wish to enter the North American plasma fractionation market. Much of this material comes from paid donors who would never qualify to give in Australia. As one US informant told the author 'Whatever the plasma centres and the FDA tell you, much of this bought plasma comes from the very lowest people in the community'. Overseas blood collection centres who send plasma to CSL may avoid paying for blood and may question donors concerning their health, but no measures can negate the lower general standards of health in these countries. Even the healthiest donors are more likely to carry disease than Australian donors.

CSL official A was questioned in 1994 about overseas donor screening for plasma sent to CSL:

> KB Must it comply with the Code?
> Not to the same extent; the Code is written for Australian requirements. The plasma we import is not imported for therapeutic use *per se*. But it must [conform] in terms of the testing of the material. We don't impose rules on the qualifications of the donor but the material before it is shipped has to undergo the same sort of tests as in Australia. And we can't export the product back unless it is licensed for use there.
> KB Is there any written policy on how all this works?
> Good question. We've taken the attitude that we will manufacture to the Australian Code, that is both the Code for GMP for pharmaceuticals and the Code for Blood and Blood Products, unless there's an exception.
> KB Have you concerned yourselves with whether the material is paid for or donated?
> We haven't come across any paid material. That is a different thing ... some evidence that paid donors are worse.
> KB Why do you have to care at all about the quality of plasma coming in?
> Because of the safety of the operators and the risk of accidental contamination. There are always people involved. There is a possibility of splashing.

The later case study on CSL sending Australian blood products to Hong Kong brought to view that the company also imports plasma from Hong Kong which, contrary to what Official A maintains above, is not tested to the same standard as in Australia. CSL official B, the Head of the Bioplasma

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[81] *Code on Blood, paras 901-903*
[82] *Red Gold, 1991 Beauchamp K, p 45*

Division, himself suggested that hepatitis C testing, (required in this country since 1990), is not carried out on Hong Kong plasma.

There are two possible harms in allowing overseas plasma which doesn't meet Australian testing standards. Personnel involved in transporting or handling the plasma during manufacture may be harmed by exposure to infectious or contaminated material, and manufacturing safety may be compromised. The plasma may become mixed with Australian feed stock if machinery cleaning systems fail, material becomes lodged in machinery parts, mixing of batches occurs for any reason, or mix up of processed blood products occurs during distribution. The latter two failures have already occurred. CSL recently despatched New Zealand product to an Australian BTS, and pooled Australian plasma with foreign material during manufacturing over a very long period.

TGA manufacturing licences are issued for the manufacturing site itself. Product in transport to or from the site is less easy to control, particularly when it goes overseas or has come from overseas. This provides more reason still to regulate the quality of foreign plasma moving in and out of the fractionation facility.

It is unclear why the legislation and the Administration have given such little consideration to the special properties of foreign plasma; perhaps it is a result of classifying blood as a drug and then ignoring or overlooking the fact that starting materials for chemical entities are easier to regulate than biological material; perhaps the need to maintain CSL's overseas business market weighed more heavily on government than considerations of safety; perhaps regulators think that accidental, misguided negligent or wanton behaviour of the kind that could compromise blood safety just wouldn't happen in Australia and therefore does not need to be guarded against.

R.8 CSL and TGA should investigate the safety implications of bringing in foreign plasma which does not conform to Australian standards observed by Red Cross and other blood collection centres and publish their findings. Foreign plasma from overseas manufacturers not vetted or not tested to Australian standards should carry warnings to that effect on the product containers themselves, rather than on certificates or other documentation relating to its shipment. The status of the material should be specifically drawn to the attention of CSL personnel who handle it during manufacture, transport workers and inspectors with the Australian Quarantine and Inspection Services and Civil Aviation Authority.

5.3 Human placentae as a source of blood

After the Australian Blood Regulators' Study was completed it came to light that CSL had also made blood products from human placentae. Human placentae pose very obvious disease risks because they can be contaminated

during the birth process, may carry disease themselves, and cannot easily be tested at source. Testing on pooled material would not be effective.

The discovery that CSL had used human placentae for this purpose came from the CSL Prospectus. In its closing pages, under 'additional information'[83] there is a very brief, adventitious mention of a Federal Government indemnity for:

> blood products manufactured by CSL and derived from human placentas. This indemnity applies to claims by persons who contract or have contracted CJD because of the use of these products.

No mention of CJD or placentae was found anywhere in the earlier references to indemnities arising from the use of blood products[84] This was the first time this author had come across a public admission in this country of blood products being linked with CJD and the first time any corporation had openly admitted manufacturing blood products from human placentae in Australia, although circulate constantly about overseas companies wanting Australian placentae. One interviewee claimed that an Australian hospital offered him human placentae when he work with a large cosmetic company. Another suggested there were backyard processors of placentae in Australia but did not know if the material was human origin. Thus, although the Principal Investigator and her Research Assistant routinely asked witnesses for evidence of placental trade or manufacture, none came to light in seven years. The matter was not specifically investigated however, due to lack of resources.

The buried admission in the Prospectus came as a surprise: the former managing director of CSL, interviewed by the author in 1986 about CSL's practice of mixing Australian and foreign plasma, changed the subject to placental trade, suggesting the author should investigate overseas practices:

> If you want to talk about *that* sort of thing then why don't you talk about the world market in placental blood, and the fact that Merieux ... is trying to get material in Australia ... They are getting placentas from India! You can't convince me that blood is being tested! Have you had children? ... Well, it is not uncommon for a mother giving birth to defecate and that material will be mixed in with the placentae ... my own intuition tells me they are not being tested.

He was also asked by the author if (then) Institut Merieux would succeed in getting supplies of placentas from Australia and said 'I'd like to believe they'd have Buckley's'. These statements could be taken to imply CSL disapproval of the practice. One could even infer from them that CSL had not

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[83] *p91*

[84] eg. *Prospectus p 85*

dealt in placentae themselves, or at least untested placentae. It would be odd if it transpired that CSL had collected vast quantities of placental material to make blood products, yet the managing director from 1974 onwards did not know of this.

Asked about possible trade in placentae, Health Department official C, said in interviews before the Prospectus was floated that he did not know of any trade occurring but 'maybe some bush hospitals might do it'. He said that anyone can apply to export placentae and that the Secretary of the Department had given him the power to approve or disapprove an application. Asked how he had dealt with the most recent application for export of placentae by Pasteur Merieux, he would 'neither confirm nor deny' that an application had been received.

When the author said the study had heard an allegation that placentae may be being collected in Australia he became enlivened for the first time, seizing upon this and demanding immediate details. If he heard of placentae being collected in Australia he would suspect it was for export, which was a Commonwealth matter on which he would wish to take action. He and Official D both emphasised that the author was asking them for 'all this information' yet she would not give them details of a possible breach of the law. She replied that she did not have the information with her at the interview. They asked whether she would furnish the information if they wrote asking her for it. The author said she would. No request was received. Official C also asked 'what did placentae have to do with blood?' and said he was unaware the material could be processed for blood fractions. This is surprising in view of the notoriety of the Dijon plant in France.

From all of this evidence the author had inferred, perhaps invalidly, that the Health Department and CSL knew of no placental manufacture in Australia. Soon after the Prospectus revealed this practice, the Sydney Morning Herald referred to Health Department statistics showing that two hundred thousand kilograms of placentae had been processed into blood products between 1961 and 1968.[85]

For some time the public has known that the fatal CJD disease may be transmitted in products derived from pituitary glands. As to transmission through blood, the possibility is there at least,[86] and has been verified between humans and animals[87] although just how blood may transmit is not known. One informant suggested the neural tissue which carries the disease causing prion would have to be present in blood for transmission to occur by this route. The size of the risk could also partly depend on the prevalence of

[85] *Jennifer Cooke, SMH, 21.5.94 , p 3.*
[86] *Lancet Vol 341: 23.1.93, p 205-207*
[87] *Transmission to Animals of Creutzfeldt-Jakob Disease in Human Blood, The Lancet, October 19, 1985 p 896-7*

the disease in the community. This is almost impossible to judge at this point because iatrogenic CJD is still coming to light.

The Sale Prospectus linked 'blood products manufactured by CSL and derived from human placentae' with CJD but failed to specify the actual products implicated. Human chorionic gonadotrophin, or HCG, is a hormone similar to the pituitary gonadotrophins, produced by the placenta during pregnancy, and secreted in urine. This hormone is given by injection to treat delayed puberty, undescended testes and premenstrual tension. It is also given with follicle stimulating hormone for sterility due to lack of ovulation.[88] Follicle stimulating hormone is also contained in HPG, a growth hormone linked with CJD. However, it is unlikely that HCG is the product referred to in the Prospectus. Despite being derived from human placentae, it is not generally termed a blood product.

Human placentae are rich in a blood protein called albumin. A number of overseas companies have dealt in placental albumin A principal processor was for long Pasteur Merieux, based in Dijon, France, although the plant was recently closed down. Merieux advertising literature says the company secures placentae from 'over thirty countries', said a Red Cross Official. In 1993 an Australian businessman told the author that when touring the Dijon plant he was informed of a series of subjects on which it would be appreciated if he did not ask questions. Whether the placentae were tested was on the prohibited list. Once on the tour, he asked and claimed he was told the placentae were not tested, something which has long been assumed but not before asserted in such a way. (It is a fascinating insight into the politics of non-disclosure that information which is potentially vital to the health of millions of people, can be withheld on the strength of an agreement concerning mannerly conduct. French regulators could presumably compile an entire interrogatory from the single repetitive query: 'What question shouldn't we ask you?' It might not be such a bad question for TGA regulators dealing with CSL either.)

Another informant claimed Merieux approached the Health Department and CSL hoping to have placental albumin sold in this country and distributed by CSL. He understood the Health Department had told Merieux to go away. Recently, Merieux abruptly ceased processing placentae, according to a Red Cross source. The reason was believed to be 'concern about contamination'. Why Merieux should suddenly feel concern over safety risks which have existed all along is likely to do with the sudden interest French regulators had to show in these blood products once the CJD transmission scandal became public knowledge in France.

The company has also tried to obtain placental material in Australia over the years. Intermediaries for overseas placental processors try as well. A State Health Department official told the author of a mysterious Middle Eastern

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[88] *Concise Medical Dictionary OUP 1984.*

gentleman who asked for permission to collect placentae from State hospitals for a company he declined to name. Approaches are well known within the industry and various government agencies. State legislation enacted between 1965 and 1983 prohibits trading in human tissue.

The Federal Government indemnity covers CJD, which can take fifteen to thirty years to manifest. If cases are a real enough prospect now for the government to indemnify CSL and 'disclose' the fact on page ninety one of the prospectus, it may be inferred that CSL's involvement with these products may stretch back fifteen to thirty years, or even longer.

In Australia, the use of any placentae are accepted as risky. In 1980 the Medical Journal of Australia published a report by the Australian Society of Blood Transfusion which referred to two drawbacks in the extraction of plasma from placentae to produce the blood product albumin. One was that ' "foreign proteins" may cause side effects'.[89] The working party included a representative from CSL. The past managing director of CSL attached this MJA published report to a letter written in August 1975 to the Secretary of National Health and Medical Research Council, in which he refers to it (though not the placental reference within it).

If CSL processed placentae and then learned that it posed risks, what did they do with that information? The Health Department has established a unit to trace people who received pituitary hormones through its program. At what point did they and the Health Department learn that blood products derived from placentae could pose a risk for CJD and what action did they take? More importantly, perhaps, if blood products derived from human placentae can attract a government indemnity covering CJD, what is it about blood products derived from placentae that sets them apart from other blood products in terms of the risk for CJD? The answers have not been furnished by government or by CSL. That cases may be pending for placental blood products is not a sufficient reason for government to withhold information. Why was the reference so deeply buried in the sale Prospectus?

There are signs that Government is evading the issue of CJD links with human blood, whether from placentae or otherwise. On May 27 last year the Shadow Minister for Finance asked the Minister for Health when the Department and CSL became aware that there could be a link between CJD and blood and what steps were taken to ensure that possibly contaminated blood was not used in the manufacture of any products derived from blood. The questions were posed when CSL was being put through due diligence in readiness for sale. Health Minister Howe refused answers, but claiming the issues 'may be sub judice, being the subject of writs lodged with the Supreme Court of Victoria' by parties claiming harm from pituitary hormones. Pituitary hormones were not the subject of the questions. But litigation was

[89] *Med J Aust., 1980, 1 205-207.*

clearly the subject in the Minister's mind when answering, or the minds of Health Department officials who wrote his reply.

The Minister also quoted from a *Lancet* article in 1993 which concluded that certain evidence 'does not suggest that blood transfusion is a major risk factor for CJD'. This was also not the question asked. The article he referred to[90] actually contains more than the Minister's quote. It in fact says 'every precaution' should be taken to ensure that blood is not taken from people at risk for CJD.

The first and simplest preventive measure would be to ensure blood banks defer blood donors who had used growth hormones associated with CJD. Clearly the Health Department and CSL Limited knew of the risk of CJD in 1985; At that time the hormone program ceased worldwide because of it; (France excepting - that delay is now the subject of a manslaughter investigation).[91] A blood bank source told the author that the BTS was warned to refuse donations from individuals who had received the risky hormones by means of a Health Department 'brochure' only in 1992, after a reported death in Australia.

More information became known about the placental business after this was written. The author was informed that CSL began processing human placentae from before the mid sixties for its albumin content. Red Cross drivers did what was known as the 'placenta run' to major obstetric hospitals once a week. Placentae were collected from deep freezes installed by CSL and sent frozen to Melbourne. There was no evidence from this informant of the placentae being tested before reaching CSL. Then a CSL source suggested the placentae were not tested at all. From one account the practice ceased in the late sixties, and from another possibly in the early seventies. Cessation was prompted by the finding that the product had an unacceptably high level of serum alkaline phosphatase. Phosphatase is an enzyme or protein, presumably the 'foreign protein' referred to in the Report of the Australian Society of Blood Transfusion referred to above.

Are the Health Department and CSL attempting to trace individuals who received blood products made from human placentae, to advise them of the possible CJD risk from these products? Albumin is used for many conditions, although absolute indications for its use are few according to some experts in the blood banking community.[92] Albumin is used to maintain plasma volume and protein content in burns patients and is used in cardiovascular surgery, for treatment of shock and has been used in kidney dialysis. The literature of blood transfusion in the eighties is littered with strong protests at worldwide wastage, misuse and gross overuse of this blood product in that

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[90] *Lancet Vol 341: 23.1.93, p 205-207*
[91] *Guardian, UK, 21.7.1993*
[92] *eg Vermylen C in Vox Sanguinis 46, Supplement One.*

and the previous decade.[93] Earlier research by this author showed that Australian clinicians had not used albumin as excessively as some other developed nations, but wastage and misuse did occur. In 1991 the Australian Society of Blood Transfusion was due to issue 'Recommendations for the Use of Albumin Products'. Both this and an earlier version issued in 1981 were prompted by perceived wastage of albumin and albumin products in this country.[94]

Who can say how many shock, burns or surgery patients used CSL processed albumin in the sixties, and who can say whether the albumin they used came from blood donors as opposed to human placentae? The products themselves evidently didn't reveal whether they were derived from placentae or from blood donation, or the practice surely would have come to public notice at the time.

There is no evidence that the blood banks were informed until very recently of the CJD risk from albumin products of any source, nor that they were told to refuse donors who have used products which might carry the risk. CSL could easily have done this via its representation on the National Blood Transfusion Committee of the Australian Red Cross Society, or by informing communicable diseases officials in State or Federal Health Departments.

While this study was being conducted, there were persistent rumours of the possibility of placentae again being used as a source of albumin to supplement inadequate supplies from donors. A BTS Director said he reported a request for placentae by an overseas company to the Health Department in the late eighties. He said 'the attitude I got was that they were likely to sell it to them.' The possibility of CSL again turning to placentae as starting material for blood products was also raised by an informant in 1994. TGA reported hearing rumours concerning efforts to import placentae.

Chapter fourteen addresses CSL's pituitary hormone program, and makes another suggestion as to how blood products made from placentae might have become contaminated with CJD.

R.9 The Health Department should declare as policy that the safety of blood products derived from placentae is beyond the power of regulators to adequately control and should seek legislation prohibiting human placentae as starting material for these products. Unless the innate safety risk for blood products can be eliminated for other products derived from

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[93]*for example, Vernylen C. and Tony Britten and Wagstaff W in Vox Sanguinis 46 Supplement One; Proceedings of Conference on Socio Economic Aspects of Blood Transfusion, 1983, published 1984, European Health Committee, cited by Piet Hagen in Blood: Gift or Merchandise - Towards and International Blood Policy 1982, Hiss, NY; and Hagen , at p 345 citing Swisher, US 1979 and others..*

[94]*Red Gold - The Price of Worldwide Commercialisation of Human Blood, Katherine Beauchamp 1991, p 6.*

placentae, the legislative should prohibit placentae in all biological products.

R.10 In the meantime the TGA should inform CSL that their manufacturing license is subject to the company not making use of placental material on grounds they pose an unacceptable safety risk.

Consumer health groups could also mount a very effective and colourful campaign advising women to ensure their placentae don't get whipped away for vague 'research purposes'.

CHAPTER SIX: REGULATING MANUFACTURING

6.1. Definition of Manufacturing

Manufacturers of blood and blood products must be licensed by the TGA and the legislative definition of manufacturer includes blood collection centres. The Code on Medicinals, against which CSL is assessed, defines manufacture to include everything from **compounding, processing, assembling, packaging, labelling, sterilising, and releasing for sale.** (In this discussion manufacturing also takes in **product recalls.**) A licence may be refused, cancelled or suspended if the manufacturer cannot comply with manufacturing practices contained in the applicable code. A suspended licence may be restored where TGA is satisfied that corrective action has been taken and will continue. A revoked licence cannot be reinstated, but an application for a new licence may be considered under certain circumstances.

The recent introduction of the revised medicinals code and the new blood code co-incides with a national movement towards **total quality management.** Emphasis in manufacture generally is moving away from testing as a judgment on materials or products of essentially unknown quality to testing as a confirmation that standards have been met by addressing quality throughout the manufacturing process. The medicinals code advocates that manufacturers prepare a Quality Manual.[95]

The medicinals code is very detailed, stressing the need for appropriately educated, trained, skilled and experienced people, appropriate buildings properly utilised; quality assurance procedures through quality control sampling and testing; fault analysis and complaint handling; authorisation before the release of products; product recall procedures and audits of quality; and especially tight control of the manufacture of sterile products such as blood products. The new 1990 medicinals code contains completely new requirements for regulating water used in processing. Water must be pure enough to be added to products and for cleaning processing machinery used to make sterile and other goods for human therapeutic use. Water purity was a common problem at CSL for many years, according to informants. The new code also expands requirements for qualifications of senior staff.

For CSL's manufacturing site, regulation under the medicinals GMP code includes TGA inspecting plant during construction, further inspections on completed plant during pilot production and before licensing and regular follow-up inspection. Each separate production area in the plant, designated for one type of blood product, requires a separate licence from TGA. The TGA was closely involved with the construction of the new plasma fractionation plant from its beginning. This was not the case for previous CSL plant, as seen in chapter two, and led to substandard plant.

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[95] *code p 5.*

6.2. Overseas manufacturers

Apart from export-only products, therapeutic goods made overseas and imported for use in Australia must be manufactured to a standard 'similar' to those for products made in Australia. Certification from the regulatory authorities of countries with a similar standard of GMP to Australia may be considered suitable evidence for TGA registration of the product. If suitable evidence is not available, the sponsor of the goods must agree to a TGA audit at their expense.[96] This condition was not automatically imposed on all goods registered or listed before February 1992.[97]

6.3. Testing

TGA regulators must be able to test products for such things as sterility, viral and microbial content and must also be able to evaluate the efficacy and adequacy of tests run by manufacturers in blood banks and fractionation plant. TGA undertakes directed and random tests on CSL's blood products. Selection of samples for testing is made on the basis of the history of the product, its therapeutic importance, complaints about products, advice from auditors concerning the manufacturer's GMP performance or as a condition of supply in the case of some blood products and vaccines. Much recent testing of CSL blood products has been in association with licensing each new separate blood product manufacturing facility at the new Broadmeadows plant.

A TGA source said that currently most testing for potency and purity is on goods as they move through the warehouse because historically many pharmaceuticals were formulated overseas and only the last stages of manufacture, such as bottling and labelling, was done in Australia. TGA testing is now beginning to invite itself into earlier and earlier areas of manufacturing.

A former NBSL official said testing staff felt obligated, for fear of being open to legal suit, to carry out all available tests on therapeutic goods, whether they had an effect on potency and safety or not. This went against the principle of targeting areas with greater potential effect on regulatory goals and could lead to testing officials adopting a robotic attitude towards their work, which is incompatible with the investigative spirit required to do their job well.

Of nine hundred and fifty five human drugs tested in 1992 to 1993, two hundred and ten were failed, fifty nine of these for inadequate labelling.[98]

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[96] *The Pink Book TGA November 1992 p 21*
[97] *TGA News March 1992, no 9 p 7*
[98] *Program Performance Statements 1993-4, Health Housing, Local Government and Community Services Portfolio, Budget Related Paper No 7.8A, sub-program 1.5 p 110*

6.4. Good Manufacturing Practice Inspections

A former NBSL official ranked the agency's inspectorate as the most important regulatory measure for ensuring the quality and safety of biologically-derived products:

> **The regulatory authority should use its inevitably inadequate resources to prepare enabling legislation; standards for pharmaceuticals; minimum requirements and standards (where practicable) for biologicals; code(s) of good manufacturing practice for both fields; and establish laboratories to carry out random checks of products; research better test methods; and carry out research in new problems affecting products - safety in particular. But, *above all*, set up an effective inspection service to monitor the operations of manufacturers, the goal being to anticipate and solve problems before they affect consumers. The laboratories need to participate in this particularly in relation to biologicals, because pharmacist inspectors are not equipped to spot problems in the biological area. Laboratory scientists should be involved in inspections, particularly the biologists.**

The 1990 medicinals code[99] constitutes the criteria to be used by inspectors in evaluating manufacturing establishments. TGA describes the code as a distillation of national and international experience regarding the principles, requirements and precautions necessary to safeguard product quality. It is meant for use in inspection and self-audit by CSL as well, following the flow of goods from receipt through storage, processing and packing to final testing and release. However, it is not assumed to cover all aspects of manufacture. The manufacturer bears the ultimate responsibility, the code states. Audits take place when a manufacturer applies for a licence and at regular intervals after the licence is granted. Complaints about a manufacturer may also prompt inspectors to be sent in, as happened with CSL when it sent overseas product to an Australian blood transfusion service.

6.4.1Resources and qualifications

Resource rich inspectorates such as the US Food and Drug Administration have individual offices devoted to regulating each blood product or blood protein. In 1992, when the author asked the newly-appointed head of CSL's Bioplasma Division,with long experience with blood regulators overseas, who was TGA's expert on blood at TGA he replied 'It's hard to say'. The TGA is still building expertise. Prior experience in blood banking is considered mandatory for blood bank inspectors; inspectors for CSL and overseas fractionators may be drawn from the general pool. For inspections of CSL's blood products, a team of up to four inspectors with expertise in different

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[99] *Australian Code of Good Manufacturing Practice for Therapeutic Goods - Medicinal Products, August 1990, reprinted 1992, ISBN 0 644 13763*

areas, such as sterility, microbiology, water quality and computers, is required, and includes the inspector for blood banks.

One senior Health official claimed there was already 'a fair pool of experience with blood products amongst the GMP inspectors' when the Therapeutic Goods Administration was established under the new legislation in 1991. Another source close to the area said, however, that resources for inspecting blood banks are extremely inadequate. There is only one blood bank inspector,who must also rewrite the code and carry out educational work, such as speaking at meetings of bloodbankers. There are roughly one hundred and twenty blood collection centres and some five hundred mobile units nationally. An audit of one centre can take days. It should be repeated within six months where the centre does not fully comply, and regularly thereafter even when licensed - clearly an impossible task for one person. It is also unsound practice for an inspector to work alone and may unnecessarily invite appeals.

As inspection is a key principle in the legislative requirement to license manufacturers according to defined standards and practices, this deficiency in resources could conceivably invite legal challenge if a fault in a blood bank was not detected through lack of inspection and harm resulted to a user, or if a granting of a license was delayed because of failure to inspect. In fact, a legal case in the eighties recognised that there can be a duty on government to enforce its laws. Government was refusing to inspect the Mudginberee meat processing plant because of union disputes affecting its inspectors. The Company obtained an order compelling government to inspect.[100]

R.11 The Health Department should immediately increase its inspectors for the Code on Blood and Blood Products to realistic levels so it can adequately enforce the license requirements contained in the Therapeutic Goods Act.

6.4.2 Reliance on overseas inspection reports

Australia recently became a Member of the Pharmaceutical Inspection Convention (PIC), the first outsider amongst sixteen European members. The TGA inspectorate was itself audited by a PIC team of eight inspectors beforehand. Membership permits GMP audit reports to be exchanged between member countries, as a mechanism for regulating import control and saving on the need for travel to the country of origin of the products. The proposed harmonisation of national codes on blood should further increase the effectiveness of this mechanism. However, the phenomenon of overseas inspectorates or licensing bodies failing in their tasks should be accounted for by the TGA. This is sound in principle and the need for it is particularly evident as present, as blood scandals and regulatory failures continue to come to light in European countries and North America.

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[100]*Mudginberee ats Langhorne PL*

R.12 Australia should rely on GMP audit reports only from countries whose inspectorates subject themselves to independent audit. In countries where significant failures in blood safety come to light the audit and product evaluation reports of those countries should not be relied upon unless or until the overseas agency is officially cleared of responsibility for the failure.

6.4.3 Prior notice of inspections

Interviewees said that in its early days the new TGA gave manufacturers warning of inspections. One TGA official did not think this lessened the value of the inspection process 'because there are now so many hundreds of points on which they may pass or fail, being given notice makes little difference to their preparedness'. A former NBSL official disagreed strongly, saying the glossing over of faults that precedes heralded inspection can invalidate the whole exercise:

> The inspection should be of operating procedures, with *all* their faults, in effect when no one is looking. The inspector's aim should be to catch them with their pants down. If a company is competent and careful, it has nothing to fear from an unannounced inspection.

While the study was underway, a Director of a Red Cross blood transfusion centre told the author that TGA had omitted warnings on subsequent inspections. This is understood to be the practice now.

R.13 TGA should maintain a uniform policy of not heralding inspections of blood collection centres and CSL's fractionation plant and when relying on overseas reports should require the same policy to have been implemented by the agency generating the report.

6.4.4 Rating of manufacturers

TGA inspectors rated blood collection centres which already operating when the Code on Blood and Blood Products was introduced either acceptable, marginal or unacceptable on their first inspection and them put on notice to improve before the next audit. Licenses were not refused unless the centre had failed on more than one occasion. If improvements were occurring at an acceptable rate on the second inspection, a second time period to meet the requirements is given. The inspectorate informed the National Blood Transfusion Committee of its strategy and rules for implementing the code in blood collection centres and issued a newsletter. A source told the author that Red Cross did not abuse this openness, which TGA believed was helpful in building trust between the inspectorate and blood banks.

This contrasts with US commercial plasma collection centres, where the same approach by US Food and Drug Authority inspectors was abused. A number of centres exploited the time given to comply by repeating offences,

including the issue of HIV-contaminated plasma and continued interstate plasma trade in defiance of specific FDA directions.

6.4.5 Quality and style of inspections
Most large blood banks in capital cities were interviewed during the first and second round of inspections. All reports said that the inspections followed the code closely and were strict with blood collection centres and CSL.

Red Cross blood bank Directors criticised TGA inspectors who treated the codes as absolute, to be enforced to the letter, rather than as the guidelines they are intended to be. 'TGA is using them as tablets off the mount' said one. Other inspectors were said to be measured, knowledgeable and constructive in their approach. However an element of point-scoring, officiousness and heavy handedness was reported by quite a number of blood bank interviewees. A CSL official reportedly claimed in 1993 that 'fighting with a TGA inspector is like wrestling with a pig in mud. After an hour or so you realise they like it'. An informant on the other side of the process said, the approach was mostly carrot and a bit of stick when necessary: 'Once you can see they are not going to reach compliance you go by the book, but before that you don't so much have the legislation in the front of your mind.'

Since blood collection centres and CSL have not long been under inspection, the combative approach alleged by interviewees may be a deliberate strategy to create a certain attitude in those inspected. But some manufacturers considered the approach interfered markedly with effective regulation and created a derisive or skeptical attitude towards the inspectorate.

Some Red Cross centres criticised inspectors for not being able or perhaps willing to differentiate the important from the unimportant in the inspection process. Former NBSL inspectors told the author that in their own inspections they preferred to focus on manufacturing practices which were most likely to cause harm if improperly conducted, rather than treat every indicator as equally important. They regarded the rare opportunities they got to inspect CSL as an opportunity to help them improve their processes rather than to 'catch them out' or be strict about physical indicators without addressing the principles behind their regulation. One cited the example of a laboratory (not in a manufacturing facility) where window ledges had been eliminated so that dust couldn't accumulate. However, the real issue was how much dust there was in the air in the first place, and the managers would have been wiser to install air filtration rather than eliminate ledges. Undue concentration on the look of things, or too close a specification of physical arrangements, may discourage manufacturers from thinking independently about cause and effect and may cause them to lose sight of the purpose of their facilities - and of the proper purpose of regulation.

6.4.6 Evaluating manufacturers' testing
TGA inspectorate staff must also be equipped to evaluate the quality of tests which manufacturers run on their product and the adequacy of the tests as

well. This is particularly important for blood products, when it comes to deciding what disease tests should be run. If a blood bank or CSL were neglecting to run tests which could detect disease, this could result in both harm to consumers and the risk of product liability suits against the blood banks, CSL and the regulators.

6.4.7 Deciding what tests should be run

The job of deciding what tests ought to be conducted on blood and plasma should be the responsibility of experts within TGA after consultation with Red Cross, other blood banking and public health experts, but in practice this important process is being subverted by the premature involvement of parties driven by legalistic, financial and political considerations. Government has repeated its earlier error of packing issues meant for TGA off to inappropriate quarters such as the National Health and Medical Research Council, as in the case of HTLV 1 testing.

Blood banking expertise and the expertise of TGA has been degraded in this process and the States have been pulled in more on the basis of how they can avoid the costs of more testing rather than what testing means for the health and safety of users.

While TGA inspectors are trying to regulate this vital area and build expertise to do it effectively, at the same time Official C said he did not think it was the role of the Federal Government to regulate what tests were conducted. He was unaware that a surrogate test to detect hepatitis C in the window period had been discussed at the NBTC, and was being used for some blood collections but not others - a potential legal minefield for Red Cross, governments and CSL if hepatitis C infected blood led on to product liability suits - which it did. (A 'surrogate' test is one used on a disease that is known to often occur alongside the disease that can't be tested for; donors positive to the 'surrogate' test are then excluded on the basis they may have the other disease.)

The author asked official C what obligations he considered he had towards the Federal Government as a representative on the NBTC:

> C: What are you referring to?
> KB Obligations to keep them informed on issues which could have bearing on them. One BTS may have a different procedure from another on, say, testing of blood. The others who may not use a test may be legally liable at some point for failure to observe the same standard. ...
> D We don't know that happens.
> KB It does happen.
> C [Questioned] that it happened.
> KB It does happen.
> D Would [it] come up through the [National Blood Transfusion] Committee.
> KB [I was informed] it had come up through the NBTC.

C I don't feel at liberty to discuss Red Cross business.

This surrogate test was used recently to 'detect' a case of hepatitis C in the window period. The units of blood were quarantined and after the window period tested positive for hepatitis C. The interviewee giving this evidence said that the contaminated donation could have been processed into three units for distribution from Red Cross and three units of plasma for fractionation at CSL into blood products, all of which would have cost more in liability suits than the cost of running the surrogate test on all the blood bank collections.

R.14 As part of a national system of blood and blood banking the Feeral Government should require uniform tests by blood collection centres and CSL. Decisions on what tests to run should be decided on clinical and public health grounds in the first instance, by appropriate scientific personnel within TGA drawing on available expertise. The tests to be run should be expressed as standards under the Therapeutic Goods Legislation and funded by the Commonwealth and States.

R.15 As a further means of preventing disease from blood and blood products, the benefits and costs of quarantine storage for blood, should be investigated by the Federal Government and the States in consultation with consumer representatives, Red Cross and other relevant stakeholders.

6.4.8 Inspection findings - blood collection centres
Most blood collection centres did not obtain a license on the first inspection. The commonest deficiencies found by audit in blood collection centres were in storage, documentation and records, quality management systems, donor interview conditions and screening tests. Many centres had to secure large amounts of funding in order to meet requirements relating to upgrading of donor interview rooms or refrigeration and this took time to arrange.

In that time centres could still send their plasma to CSL, since they had applied to be 'grandfathered' under the TGA provision allowing continued manufacture of products existing when the legislation was passed. Yet some centres were on notice because of code irregularities which have safety implications, such as deficient screening of blood.

R.16 Therapeutic Goods Act provisions permitting manufacturers to 'grandfather' blood or blood products where their continued production could result in avoidable harm to users and handlers are unacceptable. If manufacturers are still operating without a licence in ways which pose safety or other serious risks, the Health Department should inform itself of this immediately and use its standing to have manufacturers remedy the situation, while advocating for amendment of the legislative provisions for any remaining 'grandfathered' centres still seeking licenses if applicable. If plasma has been sent to CSL from blood collection centres without

adequate testing over the past two years while licensing has been progressively introduced, the TGA should make a detailed report on this matter to the Secretary of the Health Department, and patients who have received blood or blood products derived from inadequately tested material should be informed of the facts and of the possible effects of the practice for their health.

Only one blood collection centre, and a separate testing laboratory in NSW, has so far been refused a license, according to this author's information. The blood collection centre had been given time to meet the code requirements. When the TGA inspector returned unannounced, none of the previous deficiencies were found to have been corrected and the director was believed to be out fishing.

This blood collection centre was effectively stopped from supplying plasma to CSL, but was not stopped from collecting blood and issuing blood and platelets to hospitals, despite failing to comply with GMP.

R.17 The Therapeutic Goods Act should be extended without delay to regulate collections of whole blood and its distribution as blood or platelets for hospital use. This could be done by the States and Territories giving the Federal Government the authority to regulate these activities. Any delay or lack of commitment to this task should be resolved by address from whatever level of government is necessary to expedite the matter.

6.4.9 Inspection findings - CSL

The author was informed that GMP inspectors were very critical of some procedures in the CSL area which receives Red Cross plasma for fractionation. For example, the small tubes of plasma from each donation unit were not kept with the bags. Both items have matching bar codes so this failure presumably was correctable.

In the case of CSL it wasn't a matter of TGA refusing to grant a license as an incentive to elicit compliance. The TGA appears to have worked closely with CSL to ensure they met the code requirements by the time they sought to commence manufacture in the new plant. Much of this activity occurred during the period the company was up for sale, and was likely driven as much by government's determination to have CSL ready for sale as anything else.

A senior source said that CSL's performance had improved markedly. He maintained the culture of the organisation had changed in recent years. He attributed this to the fact that the new Managing Director had experience in the pharmaceutical industry, and that new personnel at CSL could see the benefits to the company of quality assurance systems, including GMP inspections.

6. 5. This study's findings concerning CSL manufacture

What follows is a summary of evidence given to this study concerning alleged supply inefficiencies and manufacturing failures by CSL Bioplasma Division, many of which also breach principles or requirements contained in the code of good manufacturing practices. Some of this evidence came forward in the course of ordered questions put to Red Cross blood bank directors prior to the interview with CSL. Much more was given later. Allegations also came from other parties.

The author attempted unsuccessfully between December 1993 and April 1994 to obtain an interview with the chief executive of CSL, after failing to secure an interview with a quality assurance executive. The intention was to put these and other questionable practices before the CEO in order to tap a response at a level more senior than the Bioplasma Division officials who had already been interviewed. Because of the volume of the allegations and the fact that the Bioplasma Division officials had made little reference to these matters when interviewed in late 1992, it was considered relevant to test the state of knowledge and degree of responsiveness of executives. The managing director and chief executive is an important link between the staff and the governing body.

When the chief executive officer would not be interviewed, the author undertook a review of annual reports, CSL media files from 1960 onwards and other CSL publications to see if these claims were borne out from any CSL source. There was very little disclosure of any such matters relating to the blood products activity of CSL in the media files. Annual reports and some other in-house CSL publications appear to acknowledge certain difficulties at times, mostly in non-specific terms and at other times obliquely, but without explaining whether the cause lay with CSL as opposed to the inherent difficulties in biologicals manufacture. Sometimes, as in the case of failing plant, the cause is attributed by CSL to its chief external regulator, the Health Department, or to Government for not responding to calls for adequate equipment.

The following is a summary and sample of the matters which came up in interview. Evidence from hospital administrators, laboratory staff and clinicians came to light indirectly as a result of the author's questions concerning use of foreign blood products. Interviewees were questioned about whether they knew why such products were coming in. The question was designed to test their awareness of the Federal government commitment to a closed national system, free of commercial and overseas product. Instead, interviewees volunteered instances where overseas products were coming in because of CSL difficulties in producing an adequate 'home brand'.

6.5.1 Apparent loss of material

The GMP Code requires all products to be traceable through written records, from starting materials through to the product ready for issue.[101] These records must be readily available.

Considerable concern was expressed by BTS Directors in 1993 and 1994 about disparities between the amount of material they send to CSL and the amount received back. They claimed to be receiving back less than they should. Disparities cannot be clearly established without statistical records from CSL showing what they claim on paper to have received from Red Cross and returned. According to evidence given this author, such statistics have in the past been deficient or absent. That situation began improving in late 1992:

> 'We get monthly statistics back from CSL ... they're a bit hard to interpret but at least we're starting to get them. This is only quite recently. And that gives us a number of parameters: how much we're holding, how much we're due to have issued ... input per head of population for ... fractionation.'

After these statistics began coming through the blood bank Directors began to refer to their concerns.

> **BTS Director**
> There is no reconciliation between what we send and what is returned.
> KB: What do you think is happening?
> We think they drop stuff on floors. [Another BTS] has figures and they show a marked discrepancy .... It is difficult to reconcile the product returns with the plasma input. We are trying to work it out for factor VIII now. I don't believe all the figures add up. We have been increasing our input to CSL. A shortage of albumin made me look at the figures recently.
> KB: Is the disparity great or chronic over time?
> There is a significant difference ... I am not the only person [BTS Director] of that opinion.
> KB: Did you take this up with CSL?
> We spoke to them and they said they believed they were sending it back and would look into it.
>
> **BTS Director**
> They send us letters saying: this is what you sent to CSL and this is what we will return to you. They never can and they never do.
>
> **BTS Director**
> KB: Is there a significant disparity between the amount of serum sent by you to CSL and the amount returned?
> I think so. I wrote them a letter and got nothing back. But they have just appointed a Quality Assurance Manager. It could be just a lag

[101] *gmp Code, paras 510 and 511.*

delay. Or maybe they are using it all for quality control, or sending it overseas - or what.

(The Director's surmise is published here only as evidence of distrust of CSL by Red Cross blood banking officials.)

6.5.2. Interruption of supply

BTS Director
They stopped making tetanus immunoglobulin and didn't even tell the blood banks ... we were chasing tetanus immunoglobulin in EUROPE!...It's not a cohesive organisation. I'm not sure anyone could make it cohesive. But someone could have a try.

6.5.3. Faulty testing
Many blood banks have long operated on a policy of informing donors of 'bad news' test results only when the result is unequivocal. First-line tests can be inaccurate, false negatives or false positives. During the AIDS scare, one Director was informed by CSL of a donor's blood being positive for HIV and was 'forced to tell the patient ... because we were scared. The CSL testing was wrongly conducted ... In fact the man was not positive for AIDS. You only need one of these a year to give your supplier a reason to lose confidence.'
(See also under 4. below - anti-D.)

6.5.4. Manufacturing failures/lack of prediction of supply/contaminants

BTS Director
A big problem is not knowing how much product you're getting and when. You have hospital administrators ringing up and complaining. They have done a lot of damage.

BTS Director
There must be hardly anything that we haven't had to pull them up on in the last twelve months. Failure to produce five consecutive batches of Intragam (an immunoglobulin)[without problems].
KB: What was the problem?
Problems with pyrogens. The problem was that they didn't tell us. We lost batches of factor VIII for contamination reasons and we weren't told until we asked.
KB: What sort of contamination?
Hep B on one occasion.

The GMP Code contains extremely strict and lengthy guidelines for the manufacture of sterile products, making clear that the risks of hazards to patients from failure are particularly high for these products.[102]

Clinician
CSL's Intragam did terrible things to some patients.
Clinician
Sandoglobulin [a rival product] got in because CSL couldn't provide an adequate product.
Former senior Health Department regulator
You ask why was Sandoglobulin brought in. It was because CSL's product was so bad.

Albumin

BTS Director
CSL had problems with the manufacture of albumin ... in the last six months. We ... decided to ration it to about sixty per cent of normal, which has been done. Then we decided to distribute it according to usage in the previous year rather than on a population basis, and I went backwards. Last week I had to twist arms to get it ... It is still being allocated sparingly to hospitals.

Clinician
Because of problems with this product, CSL is now producing Normal Serum Albumin to replace the old Stable Plasma Protein Solution (SPPS).

BTS Director
The SPPS albumin had problems with causing low blood pressure so they have come up with five per cent albumin and it still has the same problem.

In April 1992 CSL issued an 'Important Drug Warning' concerning the risk of hypotension from Stable Plasma Protein Solution, saying some cases had been severe and 'our current knowledge does not permit adequate prediction of 'at-risk patients. ... Until SPPS is replaced, CSL wishes to ensure that all clinicians who might use SPPS are aware of the risk of unexpected hypotension and take this risk into account when choosing therapy'.[103]

BTS Director
KB: Why did the shortage occur, do you know?
Batch failures.
KB: Pyrogens?

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[102] *gmp Code Part Two, Sterile Products - Special Provisions, Para 1000 - 1711, including Test for Pyrogens. and stipulations concerning water quality for these products.*
[103] *Dear Doctor letter of 30.4.92, CSL Blood Products Division.*

Yes, and industrial problems leading to the closing of old plant, and recently more batch failures.
KB: Are there other products where such failures have occurred?
Yes,[another albumin product] None was supplied in the week of [late 1993]. Production has been on and off. We've drawn on the national reserve, a Red Cross reserve to cover shortfalls. We have to get agreement all round the country to use it. NBTC [National Blood Transfusion Committee] created the reserve. It's been a national embarrassment for Red Cross. [The Federal Health Department representative] on the National Blood Transfusion Committee would know about it. We can't protest to anyone. CSL knows about it; we know about it; what can you do?
KB: Will things improve for you with the new plant at Broadmeadows?
We have to wait and see. There are quite often batch failures, partly because of the age of the plant, but one gets the impression it is not well organised. Broadmeadows will make a significant difference ... but there are some people at CSL ... who have entrenched views, difficulty thinking of their clients.

BTS Director
For the whole of July they failed to validate any one of the five batches of albumin, compounded by a strike over enterprise bargaining.
KB: What did you do?
We went into crisis mode and rationed.

Senior Hospital Administrator
CSL rations the supply of blood products, for example plasma volume expander. [They] give back to the States in proportion to population or donation or both. Some months ago they said there'd be none supplied at all for a while.
KB: Was there any clinical effect at the bedside?
No, because X [BTS Director] pulled a contingency plan out of his back pocket. He's brilliant.

Hospital laboratory scientist
We've been hand-to-mouth on albumin for the last year.

Factor VIII
Factor VIII is an important blood fraction product, the demand for which drives blood supply in Australia from time to time. CSL has for long worked to improve the yield and quality of factor VIII from its plant. The CSL annual report for 1978 speaks of procuring new plant to produce a freeze-dried concentrate of adequate purity and potency, and says there has been pressure to import concentrated factor VIII in the period when production was inadequate. CSL also says that plasma supply is inadequate, a common

explanation given by the company for supply problems.[104] However, the 1990 annual report of Red Cross says 'due to problems with CSL's freeze-drying plant, AHF issues for the previous year had declined, despite the fact that *input of fresh frozen plasma had increased.*'(emphasis added).

> **BTS Director**
> CSL licensed the Elstree UK process and brought it on line a few years ago; then they went after the solvent detergent process of the New York Blood Bank. The wheels came off that - it doesn't inactivate all the virus. And they were only trying to produce medium purity anyway. It was a farce. They should have gone to high purity and the recombinant factor.

> **Haemophilia Foundation Australia official**
> We've dropped behind. At one stage we got quite a way ahead of the rest of the world and we were up there with the best. But in the last five to ten years they have developed much better product overseas ... new systems, new methods and we just haven't got on with it ... here. In fact they're supposed to be trialing a new [brand] equivalent early next year... but that should have happened three and a half years ago when [the overseas company] licensed them to do it. They've sat around for three and a half years. Meanwhile we've been using an intermediate purity product ... so we've slipped way way behind.
> RS: Have you talked to CSL about why they haven't developed it?
> We talk to them constantly, every six months, every twelve months and they've always got a little bit of an excuse for one thing and another.
> KB: What did they say in that case as to why they hadn't done it?
> We're working on it, we're working on it, we're doing it, we're doing it, we're doing it, we're always doing it - but it's just not happened. Apparently they've got it to the stage where they're supposed to be starting clinical trials in April next year.
> RS: But that's another year or two down the track.
> Of course it is! Of course it is! And now with the new TGA regulations here ... which put a lot more regulations on things which are produced here ... that slows down CSL's work too, considerably.

A **BTS Director** interviewed in late 1993 reported that demand was led by the need for factor VIII starting plasma at that time and his BTS had 'dramatically increased input of plasma to CSL', aiming at two units per head per annum, a standard achieved by a number of other developed countries. He commented that he hadn't had to refuse an operation for over a year. Three months later, commenting on a transcript of his interview with the author he said factor VIII had become very short in the last few weeks, despite input of plasma to CSL being steady. He said his State could

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[104] *annual report 1978, p 27*

probably last until May but they may have to ask the government to consider alternatives, meaning the expensive recombinant product.

Another **BTS Director,** interviewed by telephone in 1994, interrupted to take an incoming call and resumed: 'That was [another State BTS] to ask if we had any factor VIII. I said no, we are already owed a large amount from [them]. They have had to cancel operations. Even if we were to distribute all we've got in [three States] we'd still be in trouble. There is no factor VIII coming in at the moment, because of complications with phasing over to the new plant.
KB: How much of the shortfall is CSL generated?
Couldn't put a figure on it. Some of the responsibility is at the coal face. Two States gave more plasma for the plant validation processes than they could really afford to give; and people have been using more than they've contributed ... the shortfall ... should have been acted on sooner ... we are close to the point where we'll have to ask government to buy some recombinant to cover the gap. However, CSL gets [a yield of] one hundred and eighty to one hundred and ninety units of factor VIII per litre, as against overseas, which gets two hundred and twenty to two hundred and forty on average. That's forty per cent less yield. You need to ask why.

The low yield of factor VIII from plasma starting material was acknowledged by CSL in interview with this author in late 1992, but only when she specifically raised the issue. Official B, the newly appointed Head of the Blood Products Division (now Bioplasma Division) stated:

> We're working very hard to develop a better methodology to improve our yields of factor VIII from each litre.

Factor IX
Factor IX is a clotting factor, also known as prothrombinex.

> **Haemophilia Foundation Australia official**
> Prothrombinex, we're very angry about that ... It's just appalling to think that they still, I've got a letter in my file in 1988 I think that says at the beginning of 1989 you will have heat treated prothrombinex the same as Factor VIII you know, they'll both be treated to eighty degrees. It's still not heat treated to eighty degrees. [ed December 1992]Well, I believe they've got it but they're still trialing it. Now that's appalling because this year up at Gosford they let those hepatitis C donations slip through the system. They got into the pool. We thought ... if it's gone to factor VIII that's not so bad because eighty degrees will kill it. But if it's gone to prothrombinex, it's going to infect people....[for] adults it's not such a bad problem ... because they would have been infected ... before 1990 when it was screened out, but if it's gone to prothrombinex and gone to children - where did it go? -[to] prothrombinex! And we know some children who probably would not have otherwise ... I said to [CSL official] what's it in and he said we're checking that out.

KB: Had CSL found out about it?
I got rung about it long after the event. It was [CSL official] and I think he rang me because it was going to break in the media that day...
KB: When he rang you, can you say what was your impression, that he knew or didn't know?
Oh, he'd known about it, yes.
KB: Do you know how long he'd known about it?
No. That's the most blatant one. ... human error does occur [referring to the mistake at Red Cross end].We need more than one protection. We're using it constantly and ... they had not heat treated the product yet [to the same degree as with the newer version under development]. Plus the fact that prothrombinex is a terrible product anyway. It's got factors two, nine and ten in it. It's not a pure nine product ... I've won the battle with the government and they're now importing a pure nine for surgery.

Commenting on new heat treatment for virus inactivation in prothrombinex, a former regulator with expertise in manufacturing and testing pointed out:

> All this product development should be done *BEFORE* the product goes on the market!

Fibrin glue
This product is used in placed of stitching to promote scar tissue growth in surgical wounds.

> **BTS Director**
> CSL stopped trying to make fibrin glue because of contamination. The marketing manager told us [late 1993] 'management aren't happy with it being marketed'.

Fibrin glue is manufactured by a clutch of biologicals companies worldwide according to the author's investigators in the United States. As seen later, the Health Department allowed importation of the product under the Special Access Scheme, in which certain patients may use products not evaluated by TGA if their treating doctor obtains their consent. One source claimed fibrin glue was being made at a large hospital in Australia. CSL listed fibrin glue under Research and Development in the 1994 CSL Sale Prospectus, saying they had 'identified a clinical need' for the product which was 'in the development stage'.[105]

Anti-D
Anti-D is an immunoglobulin to prevent disease caused by incompatible blood groups of mother and foetus.

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[105] *Prospectus p 21*

BTS Director
CSL had only half the amount of this product that they thought they had.
KB: Why?
Their reading for the measure of anti-D content in the plasma supplied was out by a factor of TWO!
KB: Did they admit this?
No! The minutes of the Directors' Subcommittee of National Blood Transfusion Committee [where CSL is represented] say only that the volume and titre [strength] of this product is declining. CSL never admitted that it was because of a new method of reading. As a result specialised donors have to be boosted and bled again ... There are many difficulties in this.

BTS Director
KB: How do you cope with CSL shortages?
We barter between divisions, on the spot, because sometimes we can't predict what the shortage will be.
KB: Will problems with pyrogens and other such difficulties disappear with the new plant?
It is said to be state of the art equipment so hopefully there will be none at all.
KB: Are you saying it is all coming from faulty equipment?
Let's say that would be an explanation. It depends not only on equipment but on people too. The new plant has new people too, so we can't judge it yet. (Laughs).

6.5.5. Recall difficulties

BTS Director
We've had stuff recalled recently for some of their toxic side effects. CSL sent out the recall notices. CSL ask us to whom we sent the batch. We give them the information overnight. They then fire off letters but don't bother to ask people to indicate when returning the product where it has come from.
KB: You couldn't actually administer the recall properly?
Yes.

BTS Director
KB Has it happened that CSL has given you back a product that was contaminated? (ie where contamination has entered in during manufacture rather than being in the starting material).
Yes, but they do have a recall ... sometimes what happens is we use the product, we see a reaction, we then alert CSL, then a recall is organised, and there may or may not be an explanation for why we got those reactions.

Other interviewees were less ambiguous, complaining of CSL's inability to trace the source of contamination or respond to requests for explanations in a

timely way. This accords with documentation obtained by the author which shows CSL's unsuccessful attempts to explain or investigate contamination of blood during manufacture, which had led to a complaint from a client.

> **BTS Director 1994**
> CSL's recall policy still stinks. Our BTS was told to recall a batch of five per cent albumin *ten days* before the hospitals got their notice.

> **Hospital Pathologist**
> To the best of my knowledge I never received a recall notice for [product]. I learned of it through Red Cross. [CSL] may have sent it to a senior hospital administrator. They may not know exactly who to send it to, but I am the person who should receive it. But my main concern is that we were not told why it was recalled, so we didn't know whether to start a 'look back' for patients who had already received it or not. We just got told 'Send it back'. We finally extracted the information from CSL. It was causing low blood pressure.
> KB: Is that serious enough to necessitate a look back?
> Depends what it had been used for... this product is used to resuscitate people. It would not be a good thing for that!

6.5.6. Difficulty developing new products

> **BTS Director**
> They keep on telling us about products that are in development, and we know that they are really products which they can't even make themselves. 'It'll be ready in February' they say. Or, 'it's just down the track', or 'just round the corner'.

> **BTS Director**
> CSL tried to produce prothrombinex HT [a clotting factor treated at high temperature to reduce contamination risk], but it is not on the market.

The product was available only under the Special Access Scheme when the author last inquired. A foreign prothrombinex is also being used.

> **BTS Director**
> You ask [CSL]: How far away are we from Antithrombin 111, for example. 'Just down the track, they say'.

This evidence was given in January 1994. Health Department records show that the agency acknowledged a notification for two clinical trials for this blood product only eight weeks before and other sources identified them as CSL products.

6.5.7. Lack of supply /wrong product

A number of officials claimed difficulty in obtaining a number of different plasma products back from CSL, despite there being no shortages known to them. One director said that for a particular product there could be a need for many bottles to meet one emergency and said 'there are only twenty-nine bottles of [product X] between us and the next disaster'. A disaster may require several dozen bottles at once.

The same Director mentioned that for one product he was seeking, when he requested it from CSL he was told to chase some up from another State. He told CSL to stop passing its responsibilities onto them. Another Director said that the lack of prediction of supply forces Directors to ration blood products and withhold them from patients.

A further incident, reported to the Therapeutic Goods Administration, concerned product of New Zealand origin being despatched to an Australian BTS. The GMP Medicinals Code stresses the need for procedures to avoid mix up of product, including at the point of issue. The Therapeutic Goods Administration reportedly did an immediate inspection of CSL to find out how the error had occurred. The outcome is not known.

6.5.8. Failure to communicate

The BTS Directors complained that they were not consulted by CSL or the Health Department about their involvement with the blood program after the planned sale of CSL. Their first feedback was from CSL at a meeting of the NBTC, which meets twice a year. As one said 'It was to our pleasant surprise that we heard the figure of fifteen years mentioned as the guaranteed time for continued involvement with the blood program. Nobody had heard that before, not even the Chairman of our Committee. [CSL official A] just dropped it in quietly with a smile. We all sat back and asked that the information be verified because it was the first we had heard of it.

KB: What sort of interpretation do you put on that?

I don't put any interpretation on it. It's just typical of their lack of communication with us ... for all they knew we may not have wanted to be tied down for fifteen years ... Absolutely nothing was discussed with us about the sale or their 1993 plant at Broadmeadows. We've been strangely dealt out of that exercise. Presumably CSL management feel that we're irrelevant. It is after all a blood products resource and we're providing the raw material but they see us like - well, I don't know how they see us but they certainly don't see us as people worthy to talk to about the plans they've got.

> **BTS Director**
> CSL will not tell us the cost per unit of producing factor VIII. Monash [a Government appointed inquiry into factor VIII supply] said the price should be known. How can we know they are cost-effective with our material? Is the price so high they are ashamed or are they just being difficult?
> KB: They'd say it's for commercial reasons.

Of course! But what's commercial about it? They don't have to relate to any other part of industry. They're unique. So there's no question of competition. One is left with a very sick feeling that they're not producing economically. If they were they'd come out and tell us. I'd love to be proven wrong. I'd be the first to shout hooray from the treetops.

BTS Director
1992: The friendship is on thin ice. Mutual trust and candour are not great. They say they didn't know they were doing wrong, but there are enough of these occasions on the record. There is now a co-ordinating committee. CSL and Red Cross are getting towards a written contract. Part of that progression is a consultative committee.
KB **1994:** Have things improved since the committee?
No; things haven't improved with CSL ... continuing problems with production and communication. When BTS Directors attempted to put them to [CSL Bioplasma Head] he just 'smiled sweetly'.

BTS Director
We [Red Cross and CSL] agreed ... that three sizes of [product X] were uneconomic and they'd delete [size B]. Their sheets for the next three months note that there will be no more [size B]. This is how they promulgate policy at CSL.

BTS Director
They should liaise with us to guarantee supply. There is no guarantee now.

BTS Director
We have been stage-managed by CSL and they have never been called to account. In the new plant they are going over from Cohn fractionation to chromatographic purification. There is some doubt about it in my mind.
KB: Do you mean doubt about its efficacy?
I don't know. No one tells me about the pure safety factor, about yield, they just never explain anything.

6.5.9 Failure to respond to complaints

The GMP Code governing the manufacture of blood products requires CSL to keep a file of all complaints having bearing on product quality,[106] whether they are made to technical staff or not. They are supposed to be investigated and resolved following a written standard operating procedure, and maintained in a form suited to reviewing.[107] The evidence here suggests this system is not working adequately and that CSL is in breach of Code requirements.

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[106] *gmp Code 1990, para 557*
[107] *gmp Code 1990, para 834-5.*

BTS Director
These instances of CSL ballsups have been documented.
KB: Were they rectified?
They were documented.
KB Like what?
[X] bottles of [a particular product] arrived broken. Four and a half months later I got a letter answering the complaint. They keep on accepting nice people to new positions who shake your hand and say 'let's have lunch' and then they disappear into the mist. When something goes wrong it takes an inordinate amount of time to get a response.
KB Are the responses adequate?
We reported to them that the plastic hangers on packs they were sending were arriving broken ... Much later we got a few pages of pseudo scientific crap about how we were the only one experiencing this trouble and it was to do with changes in ambient temperature between Melbourne and here and the bumpy ride. The reason was that no other BTS looked in the boxes to check! Forty percent of the hangers were broken - there was a break in the die. We were only telling them as a favour!

Hospital Laboratory Scientist
Their Stable Plasma Protein Solution had pyrogens [poisons contained in bacteria which cause mild to serious causing febrile reactions in the recipient] and [an agent causing hypertension] in it. SPPS is used in resuscitation. It was discontinued. We stopped [issuing it] before it was discontinued ... [but] had to go on using it for a couple of months waiting for another product. CSL's timing is very bad - putting it very very kindly - they have a lot to learn about being a big business. We didn't know the product shortages were coming. We sent some stuff off to Victoria when we had no idea of the shortage - and then *we* were short! CSL keeps on saying 'Things are improving' but they refuse to give us a date about when they'll deliver. This has forced us to be - judicious! (Laughing).
KB Have you ever thought about contacting their regulator?
If you mean [CSL employee X] - he is their front man, their nice guy up front ... Every time I see him I tell him what I need, what he should deliver - if he's really interested. He listens - then you don't hear from him. [Y] also politely listens - but he has gone - sideways.

The same witness said she wanted CSL to barcode their products 'but they won't do it.' (The GMP Code specifies that bar codes should be included on packaging where applicable).[108]

KB When did you ask them if they would do this?

[108] *gmp Code 1990 para 521.*

I have been asking for three to four years. We can't apply a simple supermarket principle that's been in since the sixties. I watch my asparagus and mushrooms being counted at the supermarket and I think 'Why can't that be my albumin!' We will think very seriously of making a bar code of our own - one that we know - just to keep track of the product.

Their inserts are hopeless. There is no facility for gathering the information that we are responsible for gathering. For example, the patient's name. You have to write it on the top of the box and rip that off and staple it onto the box. I mean, we are all imposing our own home-based mechanisms for solving the situation!

There are no batch numbers on inserts for tetanus immunoglobulin. None of the injectables have batch numbers on them. They are not on the bottle either, only on the box. But it is the insert which we ask to be returned for our audit trail. We want to know what bottle was transfused, not what box it came from! There are no expiry dates on the inserts ... it doesn't help the who-got-what process we have to go through ... and in a recall it is vital to know who got what. I tell [CSL employee X above]. I have championed my bar code and info on the insert. For three to four years I've tried. He listens. Nothing happens.

6.5.10 Possible reasons for non performance

The author questioned one informant with long experience in blood banking and a good feel for regulatory issues, to find out when CSL's performance in blood product manufacture had deteriorated, hoping to find indicators which could lead to regulatory remedies.

KB Has CSL ever been good on blood?
Informant: No.
KB Are you *sure* ?
Informant: Yes.

A number of explanations could be advanced for the concerns raised by interviewees. Of course, some might read the inventory of above complaints as mainly suggestive of a capital-starved organisation, for which the solution would be to privatise. This is based on too little analysis and differentiation. For example, in 1993, when complaints about supply were being made constantly to this author, the Blood Products Division of CSL became the second division of the company to gain a Class A rating for business performance through CSL's self regulation program, the 'internationally recognised' program MRPII (manufacturing, resources, planning) after management consultants carried out an assessment. An in-house publication says 'a major thrust of our MRPII program has been the development of

closer working relationships between the sales and production staff' and the learning of market forecasting methods.[109]

A. Poor plant

Can poor plant be blamed for the failures? Most interviewees, whether CSL, Red Cross, hospital pathologists, Health Department officials, or advocates for blood product users, were aware that the CSL production plant and laboratories are a factor in poor production.

An executive of the Haemophilia Foundation Australia in Melbourne, who has frequent dealings with CSL, spoke in December 1992 of the plant being 'run on a rubber band because it's all crippled and run down'. The author and her research assistant asked the Head of the Bioplasma Division to show us the production facility when we visited CSL for interviews in December 1992. He replied 'Even *I* don't go down there'. The Haemophilia Foundation executive said; 'They won't show it to anybody'. A Red Cross official, interviewed in March of this year said of the plant that 'the bandaids finally fell off'. Health Department inspectors, as mentioned earlier, confirm that the plant was not up to standard. CSL annual reports over the past three decades often refer to upgrading of the facility and plans for a new one.[110]

From a regulatory viewpoint, one needs to be interested not just in the state of the plant but more so in which parties failed to prevent or correct it. The condition of manufacturing plant is a vital element in the quality and safety of products. Per the GMP Code, plant which is appropriately located, designed and constructed can ensure protection of products from contamination, can permit efficient cleaning, and maintenance and minimise the risk of manufacturing error. It must also be appropriately utilised.[111] CSL reports and other publications frequently refer to the inadequacy of the plant and laboratories. CSL is quick to blame the Federal Government for not coming to their aid with finance for a new plant which they had asked for years ago .[112]

All Red Cross Directors were asked whether the new plant could be expected to solve the problems they have experienced with supply and quality of product. A number said CSL had to be given a chance. A majority considered that problems will continue unless improvements are made amongst management and staff. A typical response was:

> [The new plant] has a chance of making a difference but it has to be managed.

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[109] *Inside CSL March 1993*
[110] *eg annual report 1977-8*
[111] *p10*
[112] *Annual Reports ; Health Department records.; official history, Brogan at p 100-102*

One BTS Director, usually very moderate and charitable in his assessments of CSL said '[Not] if CSL goes on messing it up'. A TGA source said 'I'd expect there to be problems for evermore in that company. It's part of their ethos to have problems'.

One Red Cross Director warily said there 'had been' problems but they'd get better with the new plant. Another said CSL was 'getting better'. Asked what factors were contributing to the improvement he said 'It's part of the new corporate image and TGA (Therapeutic Goods Administration) and the new plant. The problem I have is that CSL is a monopoly; you have to accept what they say and can't go to competitors.' Another said the new plant 'will make a significant difference but also there are some people at CSL who have difficulty thinking of their clients.'

As to how the defective plant was permitted to continue for so many decades, records obtained by this author show that CSL and its chief regulator, the Health Department, addressed the issue of poor plant singly and jointly on many occasions. Clearly the Federal Government was not rushing to fund a new plant, although they agreed the need was there long ago. One senior Departmental source from that time said:

> CSL never got what they wanted.
> KB Why?
> Because Governments are mean; what joy is there in government giving out money to do something they are doing anyway?

The author sought the view of CSL official A who has had long experience with CSL and the Department in relation to blood products.

> KB: What really happened in all those years between CSL and the Government over the plant? From what I hear and read I'm expecting you to tell me that the Government turned their backs continually on CSL's efforts to get the matter addressed.
> Initially it was felt you could put more money into Parkville and jazz it up.
> KB: Felt by whom?
> CSL thought that. We were short sighted, a bit myopic. Endless amounts would never have made it a twentieth century GMP plant.
> KB: How would you then assign responsibility as between yourselves and the Government for failing to upgrade the plant.
> A bit of fault on both sides.

This was the only time the author encountered a CSL official admitting CSL responsibility for any error, deficiency or less than optimum situation.

The January 1994 Plasma Fractionation Contract between CSL and the Federal Government contains a clause making it terminable by the Commonwealth if CSL allows any part of the assets, plant or equipment used for fractionation to deteriorate in such a way as to affect production of

products for the Australian community under the contract.[113] The Federal Government could have required such terms with CSL in the past and so regulated the deterioration of the old plant which resulted in poor products. For many years the statutory corporation failed, as seen earlier, to set aside monies to allow for depreciation of its plant and equipment. At the same time, in the mid eighties, CSIRO secured from the Federal Government the building of the Australian Animal Health Laboratory, a palatial and highly sophisticated facility in Geelong, at a cost of roughly one hundred and sixty million dollars.

B. Changeover from old plant

Some of the low production in recent times has been attributed to the changeover from old plant to the Broadmeadows facility. Yet, according to the company's in-house publication[114] CSL took on an extra temporary workforce especially to manage the transition. A company publication in February 1994 publication,[115] carried an article entitled 'A Healthy Future for the Plasma Business' which begins: 'With the opening of the Broadmeadows plasma processing plant and the smooth transfer of pro-coagulant to Broadmeadows, the CSL Bioplasma division is well on course for a sustainable, long term future'.

This publication was sent to interested public and media by the Commission's public relations firm handling the proposed float but it conflicts with statements by interviewees for this study. One Red Cross official went even further, saying the old plant had been closed down before the new plant was opened and asked: 'Was this done deliberately to force the hand of TGA regulators responsible for licensing the new plant?' Others said it appeared the old and new plant were used to make factor VIII in parallel, so there was twice as much in production and nothing coming out.

Another Director complained of receiving factor VIII from the new plant which had a shelf life of just five weeks. 'With the new plant, we have just discovered, it will be two years before we can get a shelf life of twelve months for that product. We constantly have to inform our clients of the changing shelf life of the product. It is a logistical nightmare. And we are still being told only after the fact.'

Health Department officials in formal interview with the author were asked in late 1993 'How is production going in the phase over period to the new plant?' to which the General Manager of the Therapeutic Goods Administration replied carefully: 'That has got commercial consequences to it'. Post-sale, the opportunities for scrutiny of CSL's manufacturing compliance will be even further reduced, but it appears that the decrepitude of the old plant and phase over to the new are not sufficient reasons for the

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[113] *Prospectus p 85*
[114] *Inside CSL March 1993 page one*
[115] *CSL 'Update' (A C N 051 588 348)*

incompetence and inefficiencies alleged from many parties having dealings with CSL.

Notably, official regulators appeared to be ignorant by and large of the practices set down in this section, or showed no interest in remedying them where they were aware.

R.18 CSL should review its complaints procedure in light of evidence presented in this report. It should conform to the Australian Standards Association complaints handling standard. Its complaints mechanism should then be audited by TGA GMP auditors whose auditing emphasis should be on outcomes rather than process.

R.19 Reports of TGA audit findings should be available on a public register accessible in Canberra and all States.

R.20 Further levels of accountability should be achieved by empowering Red Cross blood bankers to accompany TGA inspectors on inspections of the Bioplasma Division of CSL, especially when inspections are prompted by complaints from Red Cross or other clients.

R.21 The TGA inspectorate for blood banks and CSL should be required by law to submit itself to external audit by agencies such as the FDA's office of biologics, the reports to be made available to an external party such as a National Blood Commissioner, the Australian Health Minister's Advisory Council, or the Health Minister, and also to the general public.

6.6 CSL mixed plasma from different countries, including Australia.
A further questionable practice in CSL's plasma manufacturing operations came to light during the author's research. The practice was detected by Red Cross in 1985 and stopped because of Red Cross action, but had gone on for some decades according to he evidence and was not criticised in 1992, by CSL Official A in interview for this study.

More than thirty years ago, CSL began fractionating foreign plasma and returning it to the originating country for a fee. Papua New Guinea plasma was brought in first, followed by New Zealand in 1961, Hong Kong in 1980, Singapore in 1981 and Indonesia in 1982 to 1983.[116]

It is not known whether CSL consulted the Health Department before commencing this practice. Whether the compatibility of processing Australian product alongside foreign product would have required Health Department or Ministerial approval under the national interest provisions of the Act is not known, but one can easily imagine that it should have. After all, Government was concerned about the quality of domestic plasma for Australian use and funded Red Cross on that basis to screen donors, harvest blood and test it.

Plasma from foreign countries can be of different qualities and standards from Australian material. As for virus inactivation, as CSL official A said in comment on the reliability of these methods, you can never say the virus has been eliminated. In pharmaceutical manufacturing, foreign matter can lodged in cracks or moving parts of machinery and contaminate the material being processed. Mix up can occur at the point of feeding the material into the processing line or after production, as well as in packaging and despatch. GMP puts heavy emphasise on avoiding mixing materials for manufacture which are of different quality.

However, CSL deliberately mixed plasma of different origins: Australian with foreign; foreign with foreign. Thus Australian source plasma was sent overseas and foreign source plasma distributed to users here. According to this author's informants, the practice began at the same time that CSL began bringing in foreign material, in the sixties. This practice was something of a direct hit against the integrity of the Australian system. CSL did not tell Red Cross about it.

The practice was either not known or not stopped by the Board of the CSL Commission or the Health Department or the Minister, and according to the evidence, evidently ceased only because of initiatives by CSL's client and plasma supplier, Red Cross. It is interesting to note that for some of this time CSL's Board included a former Secretary of the Health Department. Since CSL thought there was nothing wrong with the practice, possibly the Board was never informed. CSL's managing director at the time Red Cross raised

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116 *Brogan p 100*

the alarm in the mid eighties certainly did know of the practice. As recently as 1992, a CSL Bioplasma Division executive interviewed for this study said there had been nothing wrong with the practice so far as CSL was concerned.

6.6.1Red Cross uncovers the practice

In 1985 a Red Cross Blood Transfusion Service Director was engaged in an accountability exercise which involved 'questioning everything'. This included asking CSL whether their albumin was true to its 'Australian' label. The answer was no. 'We were amazed at the answer, and shocked that we wouldn't have got it if we hadn't asked the question' the Red Cross official said. On further questioning CSL admitted they were not fractionating foreign blood separately from Australian material. This meant Red Cross had, for possibly more than twenty years, been unknowingly issuing foreign blood in Australia. At that time, CSL was fractionating plasma from Papua New Guinea, Indonesia, Hong Kong, New Zealand and Singapore. Papua New Guinea's plasma was recently refused for fractionation at CSL because the quality was considered to be too poor.

6.6.2 Mixing put Red Cross in breach of law

The official who tripped over this practice told the author that CSL's action put Red Cross in breach of their blood donations legislation, which requires their blood and plasma to have been collected in substantially similar conditions. Adherence to the legislation is a condition for obtaining insurance against litigation claims for bad blood.

6.6.3 Safety risk

The obvious first safety risk in mixing plasmas is that, even if they are collected in substantially similar conditions, the general health of populations may differ.

Some Blood Transfusion Service directors who discussed CSL's pooling practice with this author objected to it as a real threat to the health of blood users, as well as being a significant deception against Red Cross. The mixing was done at a time when, as one informant put it 'we didn't have sufficient procedures in place to eliminate all viruses'.

Filtration can remove moulds, bacteria and yeasts, but not viruses. Sterilisation by heating to kill bacteria must be to at least one hundred and fifteen degrees celcius for thirty minutes, which is hot enough to kill most viruses but 'cooks' the blood or plasma. Inactivation for some fractions was done by a process called the Cohn-ethanol fractionation technique. (This involved applying dry heat to a temperature of sixty degrees Celsius after treatment with ethanol, which is alcohol.) For albumin, the blood protein used in surgery and for burns, chock, trauma, dialysis and other conditions, heating was also used.

CSL officials interviewed in 1992, speaking of virus inactivation for factor IX, a blood clotting factor made from plasma, gave evidence about the sufficiency of sixty degree heat treatment for eliminating hepatitis C from clotting factors:

> Official A: [prothrombinex is] a heated product at sixty degrees for seventy two hours but sixty degrees is probably not quite sufficient treatment to inactivate hepatitis C virus.
>
> Official B: ... therefore we've tried to develop a technology whereby ... we have eradicated it - the eighty degrees heating.

Heating, or pasteurisation, was a process developed to rid milk of bacteria. It was not developed to deal with viruses. Yet the presence of the hepatitis virus in blood has been known for decades. As an adviser to this study told the author in 1987 'Despite assertions to the contrary the hepatitis bogey has not been laid to rest'.[117] Hepatitis is very resistant to heating. Neither pasteurisation nor solvent detergent process (another inactivation technique) alone are adequate to inactivate viruses that are strongly resistent to heat and organic solvents: hepatitis A and human parvovirus B19 are of particular concern because of this.[118]

A senior Red Cross official claimed that CSL would not tell Red Cross to what temperature they heated plasma and for how long it was heated, both factors being relevant in rendering it safe. The British Pharmacopoeia on which Health Department standards were based, required that product be heated to sixty degrees for ten hours. Numerous informants have given the author evidence that CSL refused to submit to the good manufacturing practice inspections which the National Biological Standard's Laboratory, TGA's predecessor, conducted of all other companies manufacturing drug and biological products in Australia. Therefore regulators could not find out what was happening at CSL. A Red Cross Blood Bank Director told the author that sixty degree heat was known to be insufficient for viruses. 'We accepted that as a risk of transfusion. If you heated it to a higher temperature it would cook and you'd have no plasma. We didn't wake up to the viral issue until HIV came along. Before that plasma was collected all over the world and mixed for fractionation. It was a marvellous way of spreading viruses around. That is why it was important to protect the Australian supply by not mixing it with plasma from other countries. The CSL representative on the National Blood Transfusion Committee assured us that the heating was done for a sufficient period to render the material safe and we had no choice but to accept his word on it.'

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[117] *Dr. Richard Pembrey, Director of the ACT Red Cross Blood Bank, personal interview*

[118] *A solvent I detergent treated, pasteurised and highly purified factor VIII concentrate, Schwinn H et al, Octopharma, Ziegelbrucke, Switzerland, February 1944, from Medline database, National Library of Medicine, Washington.*

The discovery that CSL was mixing plasma was taken up at an executive subcommittee meeting of the National Blood Transfusion Committee of Red Cross. According to a Red Cross informant in 1986, the minutes of this meeting said:

> In discussion on the processing of plasma at CSL it was learnt that in the case of factor VIII concentrates, plasma from the Australian Red Cross Services was pooled with that from New Zealand whilst for general fractionation purposes pooling of Australian plasma with that from South East Asia occurred.

The extent to which Australian plasma was mixed with foreign material was difficult to establish because of a degree of contradiction in the evidence given. CSL denied pooling Australian and South East Asian plasma, but admitted pooling with New Zealand.

6.6.4 Greater safety risk in mixing plasma for factor VIII

The significance of alleged pooling of New Zealand material for factor VIII with Australian plasma is twofold according to Red Cross officials interviewed in 1993. First, they hold that at that time New Zealand plasma had not been tested for diseases which Australian plasma is tested for, such as the potentially lethal hepatitis C, and, according to one informant, possibly for one other disease. This would make a blood audit trail impossible. Second, these products are not subjected to the same degree of heating as other blood products undergoing virus inactivation can tolerate, and thus they pose an even greater disease risk.

In an interview conducted in December 1986, six months after CSL's managing director pleaded the Commission's case for continuing to mix, a senior Red Cross blood banking official told this author of his continuing concerns that NZ plasma not tested for hepatitis C was still coming into Australia.

Finally it became public in the New Zealand lay press that testing was inadequate at least in relation to hepatitis C; indeed the Australian government approved the supply to New Zealand of some clotting factor based on Australian material while the New Zealand situation was being remedied. According to another source, in the case of the quality of New Zealand plasma, the Therapeutics Good Administration of the Health Department saw fit, this time, to specifically instruct CSL against mixing NZ material with any other plasma.

6.6.5 CSL management knew of the practice

In the course of investigations, it was found that the practice of mixing plasma from different sources was known within CSL, at least by the time Red Cross discovered it, as far up the line as the managing director. No evidence come to light of the Health Department attempting any corrective or

disciplinary action, other than echoing Red Cross' view that the practice should stop - after twenty five years.

6.6.6 CSL defends the practice

The position of the managing director on the matter may be seen from a written defence contained in correspondence to the Secretary General of Australian Red Cross Society in March of 1986, the year following Red Cross' discovery of the pooling. He stated 'we are both dismayed and perplexed' by Red Cross' request to cease pooling. He defended the practice on numerous grounds, as follow:

> 1. 'Our current batch sizes are designed to maximise both yields and throughput rates. If our non-ARCS [Australian Red Cross Society] customers - New Zealand, PNG and various Pacific and S-E Asian countries - had to be processed separately then either the interval between batches would be unacceptably long or the yield from similar batches would be reduced considerably and attended by prohibitive cost increases'.

This represents a crossing of the authority's purposes. It was obliged to a return to the Federal Government from its commercial activities but also obliged to carry out blood processing for the Australian public upon national interest lines of 'a safe and adequate supply of product'. Government reimburses CSL for its blood fractionation activities upon that basis.[119]

> 2. 'To do as you have asked would also require additional cold storage space, the keeping of additional records and the employment of extra staff, and again the cost of the fractionation program would increase significantly.'

> 3. 'For some products the ARCS is significantly indebted to NZ e.g. albumin, SPPS and hepatitis B immunoglobulin. If separate pools had to be maintained, Australia would no longer benefit from such an arrangement and we might find ourselves precipitated into both a 'repayment' to NZ and significant shortfall or extensive upgrading of the Australian program.'

> 4. 'The problem is difficult enough with relatively common products such as albumin and normal immunoglobulin for the reasons already outlined. It would seriously disadvantage our smaller customers if it were instituted for small volume products such as specific immunoglobulins, leading inevitably to product shortages which could embarrass Australian relationships with PNG etc.'

Red Cross, known for its adherence to 'neutrality', 'independence', and keeping out of public politics, could have felt threatened by this suggestion if

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[119] *personal interview with Health Department official 1993,*

they had considered it plausible. The suggestion assumes, though, that Red Cross would put public embarrassment higher than legal obligation. Surely it also assumes the pooling practice would remain secret between Red Cross and CSL. No sooner were it known to almost any of either parties' constituencies or regulators, CSL would have far more to lose than Red Cross.

In defence of the pooling practice, the managing director said:

> i) 'Albumin, SPPS and immunoglobulins prepared by the Cohn process are all regarded as safe products from the AIDS-transmission viewpoint.'

'Regarded as safe' might be good enough for a defence in court but ignores the need for donor screening and testing, both of which are indicated to safeguard the blood supply from HIV.

> ii) 'All but plasma from Indonesia and PNG are screened for absence of anti-HTLV-111.'

This means plasma from Indonesia and PNG are not screened for HTLV-III.

> iii)'All plasmas that we process have been screened for freedom from Hepatitis B surface antigen'(HBsAg).

> iv) 'Plasmas destined for clotting factor production are pooled separately, and the products derived are issued back to the particular supplying countries.'

The last statement contradicts the report of the Red Cross subcommittee which said that Australian and New Zealand plasma for factor VIII were pooled.

The managing director then said he understood that the various Acts and Ordinances covering indemnities were not uniform, and that some States neither had such legislation nor intended to pass it. 'What then are the legal implications of even pooling plasma from different States, let alone mixing them with overseas material?' He closed by saying that to implement Red Cross' request immediately would 'deny availability for many months' and suggested CSL continue 'until and unless we have sound legal opinion that this is absolutely necessary', although he did not say that CSL would seek legal advice.

After hearing from their own legal adviser Red Cross wrote back to the managing director, insisting on their original stipulation that Red Cross plasma be processed separately from all other sources. The Society also advised that they wished to take up the issue of the misleading labelling of

products which had turned out not to be derived from wholly Australian plasma. The outcome of this aspect was not known.

This author interviewed a number of CSL officials about the practice of pooling foreign with Australian plasma. The then managing director had been interviewed in early 1987. Of hepatitis C, the NZ risk he said: 'The testing for that is still uncertain, there is no definitive test or deactivation procedure; largely heat treatment is used.' He then confirmed that plasma had come in from all the countries already mentioned above. His statement that there is no definitive deactivation procedure for hepatitis reflects upon his above statement that products prepared by Cohn fractionation are regarded as safe, since the same process is used for hepatitis C and HIV.

> KB: Did you pool it?
> No, only Australian and New Zealand.
> KB: This appears to contradict Red Cross evidence where CSL admitted it.
> I think there's a confusion - if they were pooled it would only have been for products for which there was no risk of transmission of disease. The only ones with the risk of disease are the clotting factors.

The managing director's statement that the only products with the risk of disease are the clotting factors assumes that nothing ever goes wrong in manufacturing and deactivation processes, that the blood source contains no unrecognised disease which can withstand the standard inactivation process (such as CJD)[120] and also that pasteurisation at sixty degrees was adequate for known diseases. As we saw in chapter five, CJD is now known to be a disease risk in albumin products made from placental blood; the Federal Government has indemnified CSL for this.

The author then asked the managing director if he would check his records to assist her in identifying any misunderstanding. He replied: 'I'm saying to you I don't think they were pooled.[for the making of clotting factors]. I can check up. It doesn't worry me. I don't believe they have been pooled.' Later in the same interview he was reminded of his offer to check CSL's records. He replied that he would not check the records but would 'stand by' what he had said. He then went on to criticise overseas placentae trade and the French company Merieux for trying to get placental material in Australia.

6.6.7 CSL avoids public admission of mixing practice

Despite CSL's strong defence of the practice of pooling, it did not admit to it in public. The Daily Telegraph reported in 1986 that CSL was bringing foreign blood into the country, raised the possibility of pooling and mentioned Red Cross concerns. A spokesman for CSL was asked for

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[120]*Professor Fenner, Australian National University, personal interview, 1994.also Report of the Inquiry into the Use of Pituitary Derived Hormones in Australia and Creutzfeldt -Jakob Disease AGPS 1994*

comment and 'could not confirm if blood was being imported'. This comment is typical of CSL's practice of admitting as little as possible, addressed further in chapter fifteen.

In December 1992 the author interviewed Official A about the pooling practice.

> KB: It seems that in past years product was pooled ... and I wanted to ask how it happened and was rectified.
> A: It was material of a like nature in terms of its safety and test history. The services in Australian and New Zealand have pretty similar standards and test to the same standards. The reason we pooled was simply one of economy of scale ... it made sense to combine theirs with ours. That was stopped at the time of the AIDS outbreak.
> KB: Why?
> A: Because of an indemnity question that was raised, because the government would indemnify the Australian Red Cross Society but not the NZ transfusion service ... it wasn't any greater risk than the plasma collected in this country was our view...

The Federal Government has now indemnified CSL for 'products derived from blood donated by people in New Zealand which have been manufactured by CSL and supplied for use in New Zealand' in respect of AIDS-related illness, hepatitis and HIV positivity.[121]

> KB: My understanding from 1987 was that plasma from other countries was pooled as well.
> A: Not with Australian plasma .... depends what period of time you're talking about. Some countries brought them in at a certain time and we'd be careful to check that we weren't pooling stuff that was tested for HCV [hepatitis C] with stuff that wasn't.
> KB: And the country to whom you're sending material is told that it is pooled with other countries' material?
> A: Yes.
> KB: It's done with their agreement?
> A: Well, with, yes, oh that's right.

This evidence is ambiguous as to whether CSL claims not to have mixed Australian with foreign plasma, other than New Zealand's. It also seems to say that CSL continued to mix foreign with foreign and was still doing it in 1992.

6.6.8 Discussion

Given that CSL evidently believed there was nothing wrong with the mixing practice, it is relevant to ask whether they might pool plasma again. For a number of reasons, this author believes that CSL may not find it easy to obtain the increased amounts of foreign plasma they want for the new plant.

[121] *Propectus p 91*

This could possibly make them wish to pool, for the same reasons they did over several previous decades. The new plant accommodates larger batch sizes than the Parkville facility; improved efficiency will in part be linked to larger batch sizes, so if too little plasma is sent from a foreign country, CSL will be facing the same conditions as when it began mixing.[122]

The US has and will almost certainly continue to have excess plasma, particularly if the European Community persists in phasing out commercial imports and other nations or regions follow Europe's stance. America will be trying to off load its excess. Sources have told this author that much off-loaded US plasma reaches Asian countries.

If major biologicals companies get a hold on CSL through share holdings and joint agreements they could make it hard for CSL to trade in certain places. Further, other Asian-region nations may build blood fractionation plants. This is considered in international industry circles to be certain within the next five years. At the time CSL floated under the banner of its new blood fractionation plant, another plant was said to be in the planning stage in a nearby Asian nation.

However, the company should now understand that the practice would be frowned on from numerous quarters. It is not in their interests to incur the criticism of Red Cross again. There is also now a greater risk that the TGA would discover the practice and have to take action to stop it. CSL's public statements at the time the new plant was opened in March 1994 and during the sale period stressed that foreign plasma was kept separate from Australian material and returned to the originating country - which may have seemed odd to a general public who might well never have conceived of it being otherwise.

But one cannot be confident that CSL would not engage in any other similar questionable practices if the practices were not specifically prohibited by TGA and Red Cross and spelt out to CSL as a prohibited practice, or if CSL believed they could keep it from being disclosed. The TGA cannot be expected to anticipate all and any such future actions which the company might seek to undertake.

I say this because the most troubling aspect of the plasma mixing practice in regulatory terms is that CSL didn't think there was anything wrong with it. What can they have been thinking of? A Red Cross director noted that pooling of plasma from different sources was common in the international blood industry in the seventies. Did CSL, constantly wanting to enter the international market at this time, feel that international practice was acceptable to CSL, even if wasn't acceptable to Australia? For a biologicals company in Australia to believe it can follow international trends or practices and ignore local Australian standards is a recipe for disaster where blood

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[122] *see Inside CSL 75th Anniversary Edition, back page.*

products are concerned. The whole rationale for the Australian policy and regulatory system has been to maintain the integrity of a national closed system, because of the inferiority of foreign product and the need to avoid dependence on overseas markets. This, incidentally, was the whole rationale behind the establishment of the then Commonwealth Serum Laboratories in the twenties.

Even when questioned in formal interview in 1992, officials gave no indication of anyone having been cashiered, demoted or disciplined over the mixing practice, or of having 'seen the light'. Indeed, eight years after the event and in the context of a public interview, they repeated their earlier defence of the practice and said it stopped because government 'forced' them to stop it.

Again, what can CSL have been thinking of as recently as 1992 when in interview for this study, they again failed to demonstrate any disapproval of the mixing practice? CSL had earlier expressed confidence to Red Cross that the mixing of plasmas was safe because they had found no evidence of adverse reactions amongst recipients. There is no evidence that CSL ever informed clinicians or users of what to look for. Yet is acknowledged by blood bankers that most haemophiliacs have hepatitis most of the time. How did they contract it? How are we to know that it was not from various blood products containing the virus and originating from foreign material which had been mixed with Australian plasma up until the practice was stopped? How do we know that there are not other consumers of blood products in Australia who are suffering from low level undiagnosed hepatitis or other blood borne disease as a result of this long-standing practice? How do we know that users may not in the future display disease signs from either slow viruses, like CJD, or for other conditions which may have been borne in the blood supply but which may not yet be recognised by medical doctors as disease entities? Is this why CSL officials declined to criticise the mixing practice in 1992. Or does CSL still feel its obligation is to match international practice of Australian requirements? Or is there some other explanation?

R.22 There is a need for a 'mopping up exercise' by regulators and CSL itself in respect of accountability and possibly liability over the past practice of mixing plasma of difference sources.

Clearly, also, a much more transparent regulatory regime is needed to head off the possibility of such practices occurring again. It needs to be made impossible for Red Cross and TGA to not find out what is going on. Measures to achieve transparency are recommended throughout this report.

6 .7. Laboratory inspections: National Association of Testing Authorities
NATA is a non-government inspection agency financed by Federal funding and charges levied on laboratories it inspects. It operates a registration scheme for testing laboratories, using a system of peer assessment which

involves interviews with laboratory staff, and inspections of laboratories and documentation, followed by a written report to the Health Department.

If NATA finds a problem which they consider a hazard to the community, the report to the Health department will state that the laboratory does not meet a specified standard of the National Pathology Advisory Council. The laboratory is given a certain time to respond but may continue operating in the meantime. The Health Department then writes to the laboratory, discussing the response and the action to be taken. The Department may immediately revoke the laboratory's operating licence but the laboratory can obtain a stay order through the Administrative Appeals Tribunal. A NATA executive interviewed for this study was concerned about the ability of laboratories to stay in operation by this means.[123] The issue became real when NATA threatened Macquarie Pathology Services with loss of accreditation and Macquarie was able to continue operating while it appealed to the tribunal, although it had insufficient professional staff to undertake tests adequately.

In 1985 when government linked Medicare payments to NATA accreditation, laboratories had to seek accreditation. Although it's products are not within Medicare, Red Cross chose to be NATA accredited. In blood banks, NATA looks at donor assessment, interview techniques, the way bags are labelled, equipment and processing procedures. The executive interviewed for this study said that the main problems found with Red Cross centres were with accommodation and bookkeeping; everything else was described as 'excellent' and the staff were said to be 'highly trained and dedicated'.

NATA also inspects CSL's testing laboratories, but not the production facility. Inspections were said to be due every two years, but happens less frequently unless there is known to be a problem with a particular laboratory. Victoria, where CSL is based, is the only state with legislation requiring registration of pathology laboratories. CSL's Official A was asked if NATA's inspections have led to any improvement and said: 'I think it hasn't changed all that much. We have confidence in the NATA inspectorate; we're very happy with NATA accreditation. They audit to a good standard'. Red Cross Directors also expressed satisfaction with NATA.

TGA officials did not share the confidence of Red Cross and CSL in NATA's standard of audit. One informant said that officials who visited some NATA-registered testing laboratories used by blood bank collection centres were very disturbed to see many serious deficiencies, some of which had the potential to result in contaminated blood going undetected. They claimed to have found similar deficiencies in audits relating to pharmaceutical's.

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[123] *personal interview, research assistant 1992 Medical Director of NATA.*

R.23 The National Association of Testing Authorities should be required by law to submit to regular external audit for its inspection activities relating to blood testing laboratories.

6.8. Recalls

TGA has no compulsory recall powers but may delist goods immediately to avert imminent death or serious injury and with notice in lesser circumstances,[124] thus making their supply illegal and also ruling out government subsidy where the goods are on the Pharmaceutical Benefit Schedule. This is a strong financial incentive for pharmaceutical manufacturers to comply with government regulation but has little impact on blood and blood products as most of them are supplied without charge.

Manufacturers and suppliers of therapeutic goods must keep records of problems with products. The voluntary recall procedure agreed on between the Federal Government, industry and state and territory health authorities[125] is co-ordinated by the TGA and 'applied to the very letter, putting safety considerations very high on the agenda', according to an independent observer.

TGA records show CSL dominating blood product recalls. There were eleven recalls of CSL fractionated blood products between 1987 and 1994. One was for factor VIII; the rest were for two different forms of albumin, Stable Plasma Protein Solution (SPPS) and its successor, Normal Serum Albumin. These were safety related recalls, prompted by reports of adverse reactions to the product, and recalled at hospital level.

Where voluntary recall proves unsatisfactory, or other circumstances warrant mandatory recall, TGA passes the matter to the Federal Bureau of Consumer Affairs which administers product bans and recalls under the Trade Practices Act 1974. The power to require consumer safety and information standards has been within the Act since it was passed, the power to ban since 1977[126] and to recall since July 1986.[127]

6. 8.1 Safety-related recalls

If goods will or may cause harm the Minister for Consumer Affairs must be informed within forty-eight hours of recall action being taken by the supplier. The Minister may immediately ban goods posing a risk of imminent death or serious injury, making it a criminal offence to sell them, and allowing for immediate compulsory recall. There have been three mandatory recalls in the last eight years, none applying to blood products and only one to a therapeutic good. Companies are responsible for destroying condemned

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[124] *(S 30)*
[125] *Uniform Recall Procedure for Therapeutic Goods May 1989*
[126] *2d of 81 of '77*
[127] *565f.*

goods themselves, although on rare occasions the Federal Bureau of Consumer Affairs has supervised destruction.

The Minister may also publish warnings that goods are under investigation or that possible risks are associated with their use. This mechanism has been used only six times to date, none being for blood or blood products. A bureau official said it was not a preferred mechanism: 'It can do a lot of damage to markets and it is too easy to be sued'. When CSL sent a blood product to Hong Kong without Red Cross approval to export it, the company made no report of any recall to the Federal Bureau of Consumer Affairs when the blood product was found to be contaminated with hepatitis C, according to evidence from a Bureau official.

Other enforcement and investigation powers - to enter premises, inspect under a warrant, seize goods or require non-incriminating questions to be answered have not been used either, according to another FBCA official. The goods involved are normally bought in shops and tested by the Bureau, unlike blood products.

6.8.2 Compliance with recalls

TGA sources claim it has required strenuous publicity to get the pharmaceutical industry to inform them when it recalls a product, and that some smaller companies are still not complying. In early 1994 the Department began publishing a summary of safety-related recalls and information on cancellations from the TGA register.[128] This was said to be 'in the interests of patient safety' as a complement to the Uniform Recall Procedure, as it was found that notification of safety-related recalls does not always reach those who should be informed, resulting in continued use of unsafe goods. Information on consumer-level recalls has been available since 1989 in form of recorded telephone message on a free call line.[129]

The TGA newspaper for industry carried a full page article about non compliance with recall procedures in 1992,[130] saying that a small minority try to bypass or misuse the procedure and emphasising the need to report certain recalls to the Minister for Consumer Affairs. It referred to a 'common misconception that a recall will ruin the company's reputation; comments received by co-ordinators support the view that sponsors who carry out a standard recall get a higher approval rating than those who attempt to cover up'.

Some sponsors were reluctant to advise customers of a recall by letter. 'It is essential that the defect is spelt out clearly and factually in writing', TGA News said, in order to avoid confusion and to allow health workers to follow

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[128] *Monthly Recall Information Bulletin from Feb 1994, $60.*
[129] *TGA News April 1991 No 5*
[130] *TGA News 1992*

where needed. It also noted that commercial sales reps were exploiting the recall process by advising clients not to buy products under recall.

R.24 The Therapeutic Goods Act should be extended to incude recall and forfeiture powers.

CHAPTER SEVEN: REGULATING SALE, SPECIAL ACCESS AND USE IN TRIALS

7.1 Licensing of blood products for sale or issue

Under the Therapeutic Goods Act, Australian manufacturers must licence their goods by **listing** or **registration** before they may be imported, manufactured, supplied interstate or exported. The goods must also have been manufactured according to official standards( )*S14* which involves evaluation of the product and its manufacture. Manufacturing is assessed against codes of practice (which are not part of the Act), compliance with which is determined by inspections and other means. Once goods are entered on the Australian Register of Therapeutic Good, their sponsor must meet ongoing conditions, such as maintaining records of distribution and so on, to retain registration. Restrictions are also placed on the use of approved products in trials and in advertising. Many trials involve unapproved products; some involve approved products used for conditions for which the product hasn't been proven effective or safe.

Registration can be cancelled if the goods create an imminent risk of death, serious illness, or injury, or are persistently deficient in quality, safety or efficacy. Penalties of up to forty thousand dollars for a person or up to two hundred thousand dollars for a corporation for knowingly or recklessly making false or misleading statements in the course of applying for registration of goods.

7.2 Difference between listing and registration

Goods are entered on the computerised register as either **listed** or **registered.** Therapeutic goods for **registration** must undergo evaluation; these are mainly prescription-only drugs. Goods for export-only are **listable,** and are not subjected to comprehensive review of data for safety, quality or efficacy. TGA does not scrutinise all applications for listing and says the onus is on the sponsor to provide accurate information. These products still have to meet GMP code requirements. Goods for special, individual patient use, and goods already approved when the new Therapeutic Goods Act 1989 became operative in 1991, receive relatively less evaluation and vetting by the Therapeutic Goods Administration.

7.3. 1 Evaluation of therapeutic goods

Evaluation of goods before registration is by the Australian Drug Evaluation Committee, made up of practicing physicians, pharmaceutical scientists and pharmacologists who examine data supplied with an application for approval, supported by expertise within TGA.

The TGA charges companies for evaluating their products; part of the fee is due on application and part on completion provided it is within a certain

date. According to informants, evaluators are put under pressure to meet these deadlines lest the Department forfeit the balance of the fee, which itself may run into tens of thousands of dollars.

TGA also accepts drug evaluations from overseas agencies. According to one informant, these are sometimes so poor in quality they cannot be relied on; some evaluators may obtain data packages and rewrite the assays themselves in these circumstances. The FDA's regulatory program for evaluating therapeutic devices before registration has been heavily criticised for a range of deficiencies over eighteen years.[131] The report highlights FDA's excessive reliance on the credibility of corporate assurances and claims about the integrity of their data rather than conducting an independent study. It is this well-recognised phenomenon which tends to belie the plausibility of Baume's vision that Australia can 'retain its ultimate sovereign authority over the granting of marketing approvals for therapeutic substances' while extending trust to other regulatory agencies by accepting their evaluations without independent assessment. Baume wanted Australian evaluators to move faster by accepting overseas evaluation reports (amongst other measures). In the case of biological, the trust element is already high in accepting starting materials which are not standardised and cannot possibly be tested for some safety risks.

R.25 Since blood and its derivatives cannot be standardised as can chemical entities, evaluators should offset this liability by placing less weight on evaluation reports from foreign regulators than they would for pharmaceuticals, and less weight also on inspection reports by regulators of foreign plasma collection centres. This re-weighting could be achieved by, for example, supplementing study of foreign inspection reports with direct inspection by TGA of collection centres as a matter of routine, and by greater independent assessment of evaluation reports furnished by foreign countries. Even less weight should be placed on reports from regulatory authorities which or have been subject to inquiry and adverse findings pertinent the quality of their evaluation of therapeutic goods in general, or blood and blood products in particular.

In chapter one it was observed that a number of overseas blood bankers, noting that some blood products have come into widespread use without sufficient and reliable clinical evidence supporting their efficacy, have urged that clinical trials for biologicals should be even more stringent than those for chemical entities, urging at the same time a kind of fifth phase clinical trial which some have termed 'biological monitoring'.[132] This phase would seek to study (and regulate, if possible) the biological interactions between donor

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[131] *ref Report by the Subcommittee on Oversight and Investigations of the Committee on Energy and Commerce, US House of Representatives, May 1995, titled 'Less than the sum of its Parts', reviewed in the Australian Product Liability Reporter, Vol 5, No 3 June 1994 p 34 , refers to FDA inability to obtain and critically assess data, to ensure that manufacturers submit adequate data, etc.*

[132] *Vox Sang, 46 suppl 1. pp 77-80 (1984)*

and recipient, which can be unique and variable for the same reasons as starting material is variable and beyond standardisation.

R.26 The Health Department should seek expert advide from TGA scientists concerning the feasibility and effectiveness of requiring 'fifth phase' clinical trials for biological products.

7.3.2 'Grandfathering' - Existing goods bypass TGA evaluation

Most fractionated blood products now available in Australia were already in supply when the new legislation was introduced. Under a 'grandfathering' provision in the legislation[133] they are not subjected to full evaluation before being entered on the TGA register.

Grandfathering has particular significance for CSL's blood products which come under the scheme. Unlike the products of many pharmaceutical companies, some CSL products were never evaluated by TGA's predecessor NBSL, according to evidence given this study. If they avoid evaluation under the new system, this means they are being supplied for use without *ever* having submitted to Australian regulatory requirements for evaluation of their efficacy, purity and safety for use in humans. This is completely unsatisfactory. As Professor Braithwaite puts it:

> Regulators should acknowledge that the acceptability of grandfathering depends upon the product. It is acceptable in principle for a product such as aspirin, but unacceptable for products such as opium or cocaine. If there is a history of traditional use so long and substantial as to leave little doubt on basic safety and efficacy, then grandfathering can be accepted. Grandfathering the efficacy, purity and safety of blood products falls between the extremes of aspirin and opium, towards the opium end of the extreme - possibly even beyond it.

TGA regulators appear once again to have failed to take account of the special properties and safety risks in biologically-derived therapeutic goods under the legislation.

R.27 The TGA should develop a protocol for the application of grandfathering to blood and blood products, (preferably as part of an overall protocol on biologicals). The legislation should be amended if needed to make this protocol enforceable.

TGA extended the deadline for grandfathering applications a number of times and 'fast tracked' some applications to meet the extended deadline; processing only some of the data to the required level and leaving the remainder for review after registration. The agency newsletter TGA News

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133 *S66 of Therapeutic Goods Act 1989*

reported that 'many sponsors will need to be contacted, either because information was not supplied or was unclear'. This included 'many sponsors of imported goods' whom TGA would have to question about standards of manufacture overseas.

Compliance with grandfathering has clearly been a proble for the TGA, judging by the well-mannered nudges, hints and veiled protests in TGA News. For example in 1991 it talks of deficiencies in data supplied, including omitted declarations and certificates of product analysis, indications for use which violate the advertising code, and product labels that breach a TGA order. TGA entered these goods on the register anyway and 'urged' sponsors to 'read the relevant guide before completing the application form.[134] only a month later the agency complains that some sponsors are assuming that the product labelling is accurate simply because it has been entered on the register, even though it doesn't comply with the relevant Order. TGA says they will be 'following up'. Why should industry comply with the codes and legal provisions when TGA flouts them!

TGA finally solved its problem of unwanted responsibility for regulating this large group of grandfathered products by legislative means: the legislation was amended to clarify that the Federal Government cannot be held responsible for the quality, safety or efficacy of grandfathered goods.[135] This leaves the consumer with no protection if industry fails on quality, safety, or efficacy for grandfathered products, and one wonders how Federal Government could sustain such a provision, which contradicts the object of the legislation.[136]

R.28 Therapeutic goods which have been grandfathered under the Therapeutic Goos Act 1989 should be required by law to carry a statement that the Federal Government has (a) never or (b) not since the commencement of the Therapeutic Goods Act 1989, evaluated the goods for their quality, safety or efficacy, and this statement should be required to reach the consumer. When CPI is made a requirement it should include such statements.

The sanction against supplying false information in an application to list or register a grandfathered product is a frivolous provision making it an offence to *knowingly* supply false information, and carrying a frivolous penalty of six thousand dollars. No public prosecutor would squander money trying to prove that. Besides, TGA gives industry pointers on how a defence could be mounted, although perhaps it does not give the advice *knowingly*. A touching hypothetical from an imaginary manufacturer in TGA News runs:

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[134]*TGA News Aug 91, No 6*

[135]*Therapeutic Charges Amendment Act 1993. or part 8 of the Health and Community Services Legislation Amendment Act No 2 1993, referred to in TGA News Feb 94*

[136]*S4 Object of Act, 'to provide, as far as the Constitution permits, for ... a national system of controls relating to the quality, safety and efficacy of therapeutic goods ... '.*

> Our company records are very poor and some were destroyed when our last marketing manager was retrenched.[?!] We're concerned that we may innocently provide false information.

TGA advised the hypothetical inquirer that inadvertent supply of false information is no offence.

7.3.2 Special Access to unapproved products

In response to Baume report recommendations, the Health Department introduced a new scheme to make unapproved goods more available for patient use. Approval is for individual patient use in cases where the patient is either terminally ill or seriously ill from a life-threatening illness (category A), or who has a life-threatening condition even if not critically ill (category B), or has a serious but not life-threatening illness (category C).

A number of CSL and overseas blood products has been made available through the Special Access Scheme. The case study on UB Plasma later in this chapter shows how defective the application of the scheme was for a number of products.

TGA doesn't require individual patient data for these products before approval. Instead it conducts a post-approval random auditing of up to ten percent of applications to check that the summarised results submitted by sponsors or manufacturers accurately reflect individual case reports.

The Special Access Scheme in effect makes the medical practitioner the approving authority because she or he must be prepared to prescribe the product and obtain the patient's informed consent. Thus a patient may have to rely on the same medical practitioner for three things: whether their condition is terminal or life-threatening, whether they need an unapproved product, and what information they need about the product to give or withhold consent.

For the first category, terminal or serious illness from a life-threatening condition, medical practitioners may use unapproved drugs and notify the Department afterwards. For the other two categories, a hospital pharmacist described how the system works: 'The doctor gets an authority-to-supply form for patients seriously ill with a life-threatening condition. The scheme is run through hospital pharmacies which have to account for every dose. The Federal Government churns out the forms. Before pharmacy would handle the product they have to see the form and a summary of the information on it is sent to the Federal Government. The pharmacy relies on an informed consent form as evidence of whether informed consent was obtained.'

TGA asked companies to develop treatment protocols for each of the drugs to be approved by the delegates.[137] If a serious unidentified safety or efficacy problem comes to light, TGA may deregister the product and make a public statement that the sponsor misled the Government, or may require the sponsor to 'modify' the information with or without a public announcement. Sponsors who mislead intentionally or otherwise have to provide full individual patient data for several subsequent submissions until the TGA is satisfied of their competency and integrity.

Departmental notifications for the first category of special access usage increased by one hundred and eighty three percent between 1991 and 1992, while the next two categories increased by ninety eight percent and one hundred and eighteen percent respectively.[138]

This is a weak system of regulation which could work particularly badly in the case of foreign blood products. Even where the sponsor provided data and the data was by chance audited, the safety of source material is already difficult to control. Certification by manufacturers and suppliers has already proved inadequate. There is a real risk that a safety or efficacy problem may come to light only because the patient suffers from it, that is, when regulation has completely failed. In such cases the sanctions have no practical meaning. Nor would they in most other cases, as proving an intentional, or even reckless, misleading of TGA is so difficult.

From interviews limited to one major hospital, came evidence suggesting that patient consent under the Special Access Scheme may be defective and that hospital employees lack understanding of the legal issues involved. A hospital employee dealing with investigational drugs in the hospital pharmacy said in early 1994:

> Informed consent needs to be given but in this hospital we don't require a form. If the patient is [in a life-threatening] situation we just require the doctor to say that in his opinion the patient fits the definition. For [other categories] there is a ... hospital form, asking if the doctor has obtained informed consent. It is their business to ensure they have done it. It is the philosophy in this hospital not to require a form.
> KB Why?
> We didn't want to have to police it.
> KB Don't TGA require more than that?
> Yes, but they don't stipulate that a form must be filled in. I think they try not to get into it.

[137] *TGA News June 92, N0 10.*
[138] *Program Performance Statements 1993-4, Health Housing, Local Government and Community Services Portfolio, Budget Related Paper No 7.8A, p 103*

KB Has informed consent been an issue at this hospital? No, but it has at St.Vincents, where they have a form for all three categories. ... hospitals vary in their practices. The Austin Hospital requires a form.
KB I suppose the legal position for the hospital would have been considered when making the decision [not to get involved in patient informed consent]?
I think it probably would. It was the decision of our Drugs and Therapeutics Committee. It even has [a person from TGA] on it! He does it in his spare time - not as a TGA person. I think they would have looked at the legal stuff ... There is a good deal of concern about the scheme. ... A lot of people think it is not necessary to have this form of approval and that for category B's and C's it should only be necessary for the doctor to send off a form saying what he's doing; it would make it more accessible.

The interviewee also said the pharmacy will dispense products to out-patients of doctors employed at the hospital as VMO's and 'might make allowances for doctors outside the hospital'.

An executive in charge of clinical services at the same hospital was very clear about the hospital's responsibility:

KB What if a resident doctor or VMO didn't really obtain informed consent - the form looked as if he had but the patient really hadn't been properly informed?
The hospital is vicariously liable, if the failure was because of a failure of the hospital; this has already been established in court cases. ... If the doctor has been slack in not obtaining informed consent, the hospital would [then] hit his insurers for as much as possible.

A medical practitioner committed to accountability and effective regulation within the hospital said he believed few people were aware of the legal/constitutional framework that may exist in their area of responsibility, describing it from his point of view as 'most vague - we run essentially on the goodwill and innate common sense of people involved.'

Another hospital employee responsible for releasing a CSL blood product for administration to a patient under the Special Access Scheme expressed concerns about informed patient consent. This employee had discovered informally that the CSL product had failed to get TGA approval for general marketing, and was worried because the TGA would not tell her the grounds.

Red Cross had heard that the product was failed because of deficiencies in documentation and we told the patient this, but we don't really know why it was failed. We may have simply lulled him into a false sense of security. I specifically asked to see a document that would satisfy me that the patient had consented to the treatment

but I could not get it. All I got was a document which was TGA's form with the [Special Access Scheme] form on it. I asked through the haemophiliac clinic. They understood what I was asking for. If I was going to be responsible for giving this product to the patient, I wanted to know that someone was accountable for him having consented to it in an informed way. I wanted signatures. It is very easy for the patient just to say they'll do it because the doctor says they need it. They get overwhelmed by the hospital environment.
KB How did the clinic cope with your request?
They selectively decided that what they had sent me was what I asked for, but they didn't misunderstand me.
KB Did you rely on an assumption that if there were anything in the product that could harm the patient then the TGA or CSL would tell you?
Yes.
KB You decided to trust them?
I trusted *Red Cross!* I chose to rely on Red Cross telling me they believed the fault lay with documentation for the blood product.

Roughly twenty six thousand requests are being made annually under this scheme. Very few are made for blood products. Based on empirical and anecdotal evidence, however, blood products present a higher ratio of problems than pharmaceutical products.

The Special Access Scheme puts great responsibility into the hands of practitioners and other hospital employees without commensurate access to information they need to exercise it and without any external means for monitoring, detecting or deterring violations before they occur. Yet at a TGA seminar on the scheme in 1994 many delegates wanted the scheme further deregulated, giving practitioners greater powers to administer unapproved products.[139]

R.29 Special access for blood products should be reviewed and consideration given to restricting its applicability to patients who are terminally ill only, or for those in danger of death or seriously ill. In its present form, it should require a dialogue between a TGA officer and the ordering physician before the product can be administered. If the ordering physician elects to proceed s/he should be required to inform the patient of the dialogue and its content. Hospitals should be required to ensure that an independent second opinion is given in writing concerning the status of the patient and the soundness of administering the product in the circumstances, (taking into account available alternatives) and these written opinions should be furnished to the patient before consent is given.

[139] *Free Choice Versus Safe Choice, February 1994.*

7.4 Overseas product approvals

There are four major consequences to importing foreign commercial blood products. First, because the products are not free and are often very expensive, importation compromises the regulatory goals of affordability and equity in access.

Next, the practice takes the heat off government who should be demanding that CSL deliver a home product or attending to donor supply if that is a reason for CSL non production. In 1987 a Red Cross blood bank director told the author 'CSL is sitting on a large stockpile of raw, unprocessed immunoglobulin. Developing countries want it but Australia wants them to pay and they won't. Why is the government importing product instead of getting CSL to use theirs?'

Third, it exposes users to products which cannot be regulated for safety as readily as those made in Australia, since the TGA has no guaranteed control over how the blood is collected, and far less control than it has over Australian blood collections. Their control is even less when blood products are imported for individual patient use without full evaluation, as with Sandoglobulin in 1985, discussed later.

Finally, the practice opens the door to irrational use; commercial companies will promote hard and direct to clinicians. Who is to stop them encouraging doctors to use the products for indications which are unproven? At this point only hospitals, by refusing to pay the bill. (Immunoglobulin is such an example when used for immune diseases, according to clinicians interviewed by the author in 1987.)

In dealing with overseas product, whether plasma as starting material for further manufacture or for finished products imported for use, regulators typically have three options:

. extend the trust element;
. force manufacturers to finance regulation of their supplier, risking the supplier going out of business through lack of viability;
. form agreements with other nation states to enforce regulation themselves.

TGA's approach is a mixture of these options.[140] It is forming agreements with foreign regulatory equivalents and also requiring sponsors to finance TGA inspections of foreign manufacturing sites in countries without comparable controls to Australia. Both options imply an extension of trust, and at a time when evidence is unfolding that overseas regulators have not exercised the same degree of control over blood and blood products as required by Australian standards. TGA accepts export certification from countries including Germany, the USA, the United Kingdom and Canada, all

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[140] *TGA publication, Standard of Overseas Manufacturers 6th edition 1.7.93*

of whom buy plasma commercially and have had safety problems because of it, and from France and New Zealand, both of whom have engaged in practices unacceptable under Australian standards.

The Health department first approved a foreign fractionated blood product for patient use in early 1985. Official C, medical adviser to the TGA, was asked about the propriety of their drug evaluators approving commercial overseas blood products when State and Territory legislation prohibit sale. He replied:

> We don't bother about *State* legislation!
> KB: Why approve products if you know they can't be sold because of some other law?
> We are not subject to State legislation ... it wouldn't be our concern ... we don't police the State's legislation ... the Company has to comply with that State.

True, the Federal Government has immunity from State laws. But that is no reason for flouting the principles in State legislation, particularly if the Federal Government action in doing so flouts its own policy. As Professor Braithwaite said:

> This is a form of perverse legalism. You either show comity toward the laws of other jurisdictions in a federation, or articulate the need to change them or coordinate them. In a federation, we should struggle for inter governmental or regulatory outcomes and then work cooperatively to deliver those outcomes. Laws are just a means to the outcomes. Where they are not consistent with the consensus outcomes, parties to the consensus have a responsibility to agitate for their reform.[141]

A major reason for the importation of foreign fractionated blood products is CSL's inability to supply a home product in adequate volume or at all. Examples are blood proteins called immunoglobulins used to build up immunity and fight various diseases, and a clotting factor called prothrombinex. Recent shortages in factor VIII supply prompted calls for foreign product to be brought in as well, although it did was not needed in the end.

The policy of national self-sufficiency in unremunerated blood supply implies that where supply difficulties arise in Australia, the Department's first line in inquiry should be to ask why CSL can't deliver, not to look overseas. The decision finally to build the new fractionation plant may be an example of nationa self-sufficiency policy at work - a decade or so late. It was not clear, though, that supply issues are routinely assessed from this

[141] *Personal interview May 1994*

viewpoint. TGA officials said that CSL don't go to them if there is over or under supply.

> KB: Where would the interest in maintaining supply be represented in the Department?
> D: To the Minister through [CSL]. The Secretary would have a general role I guess.

But other evidence earlier in the same interview shows that CSL *did* come directly to TGA in the first instance on a matter of supply - 'because if we are required to have alternatives we are involved in that' as Official C put it. He added that such a matter was a public health issue yet 'in the first instance it would be determined by the expertise of TGA'. This is wrong sequence. An official dealing with CSL in the Health Department's Corporate Division said that if a foreign company applied to import a blood product being developed by CSL, he would not hear of it. 'There are Chinese walls in this Department. We don't know what TGA is doing. If they are evaluating a new product they don't come and ask us "Does [this] have financial implications for the wellbeing of CSL?"'.

R.30 In a system adhering to a policy of pursuing national self-sufficiency in blood supply from non remunerated donors, any suggestion of inadequate product or supply should be referred in the first instance to an officer responsible for having the policy implemented. The first line of inquiry should be why isn't the product available in Australia. The second line of inquiry should be how it can be made available from within the Australian system. The last should be how can we bring in a foreign version.

7. 7 Case study One - Sandoglobulin

The first foreign blood product approved for human use was a blood protein called Sandoglobulin, made by the Sandoz pharmaceutical company. CSL's product kept on producing unwanted reactions in patients. CSL Official A described these as 'usually unpleasant symptoms, flushing, nausea, back pain, tightness in the chest, palpitations ... an innate characteristic of the product as it was then made'. A former Health Department drug evaluator said the product 'did terrible things to people'.

The alternative foreign immunoglobulin was first approved for individual patient use in 1985 prior to full evaluation by the TGA. Official C believed it would have been approved on 'purely clinical grounds'. This occurred at the same time that CSL was trying to develop an acceptable substitute made under licence from a foreign biologicals company.

Quality of blood used

Sandoz obtains its starting material from Swiss Red Cross, which collects mostly Swiss donor blood but also obtains blood from other sources. A Health Department official told the author that at the time Sandoz applied for approval here there was considerable debate about the effectiveness of the HIV inactivation process for Sandoglobulin. Now the former director of Swiss Red Cross central laboratory, Alfred Hassig, is being charged with causing grievous bodily harm for allowing use of possibly infected blood clotting agents.[142] as late as May 1986. The essence of the case is that when he could have screened for HIV he chose to delay.

Extent of TGA evaluation

That Hassig delayed introducing HIV testing was known in this country from the time it happened. TGA could have known this if they had consulted even minimally. Was Sandoglobulin, as with factor VIII, also being made from blood stock untested at Swiss Red Cross level for HIV in 1985, when it was approved for individual patient use in this country? We do not know, because TGA treats all such matters as commercial-in-confidence. Nor do we know whether TGA knows.

Shortly after its approval for general marketing in 1987, the author interviewed an NBSL official involved with Sandoz' application. He said the Department had 'looked at the [virus] inactivation procedures' used by Sandoz on the product. He was asked what the Department did to verify that appropriate screening tests were done by the suppliers of the plasma or by Sandoz themselves. (These tests have to be done on individual donations before they reach the pool as testing at that point is not sensitive enough). He said 'we know that the manufacturer screens individual donor sera. ... The reliance is on the fact that screening is done and hepatitis B has never been a problem. The process separates hepatitis B out and HIV virus.'

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[142] *New York Times 23.5.94 page 1*

A spokeswoman for Sandoz in 1986 said 'The [HIV] virus does not exist in the final product'.[143] She said the company had advised every doctor using the product to monitor for signs of AIDS. 'Whether they do that I don't know, but they know it *should* be monitored ... doctors are extremely aware of the concerns with this product'. A major figure at a conference on intra venous immunolgobulins sponsored by Sandoz in 1984 said 'There is very little detailed follow up of the patients given commercial IVIG preparations around the world'.[144]

A number of interviewees for this study and in earlier research have consistently said they believe certain steps were omitted from the Department's evaluation of Sandoglobulin. Official C said the decision 'would have been made on the normal bases of quality, safety, efficacy' and added 'subject to the policy on blood products'. Asked if any trials were bypassed, he said he didn't know. Asked how the decision was consistent with the policy of national self sufficiency in non remunerated blood, official C said 'I think it was consistent with policy at the time'.

TGA evaluators of Sandoz product never consulted Australian Red Cross.[145] They accepted Sandoz' perspective that it was in competition with the voluntary agency. According to CSL, they were not consulted either. CSL's official A said 'I don't think that the Department before they put through the evaluation of the registration application ever bothered to ask CSL if we had an equivalent product or whether we were proposing to produce an equivalent product'.[146] An official with the company who licensed CSL to make the alternative product to Sandoglobulin reportedly claimed that at the time of the company granting the licence he urged CSL to take two scientists along with the recipe, to ensure its speedy production, but CSL would not.

Why did the Health Department not send NBSL inspectors in to find out why CSL wasn't getting its own product up? Probably because the TGA never told its own department of the Sandoz application in the first place. There was no evidence of any interest within the Department in finding out what it would cost to speed up production in the Federally-owned plant or comparing that with the costs of a foreign blood product costing hundreds of dollars a treatment and affordable by only a few. (Sales are slight now because CSL's successful alternative is free of charge).

Sandoglobulin went on to receive general marketing approval in 1987 with CSL's product still not on the market, though it followed soon after. Sandoz celebrated by flying a string of haematologists out to the Yulara desert resort and promoting immunoglobulin use to them. Australian clinician Professor

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[143] *Sandoz, Dr Ruth Bailey, by telephone, 1976*
[144] *Conference on Intravenous Immunoglobulins, published*
[145] *personal interviews with the author, 1987*
[146] *personal interview Dec 1992.*

John Dwyer, who Sandoz described as their most experienced user, said the product was 'a bench mark product, the best.' Red Cross and some clinicians were incensed. A practicing clinical haematologist told the author 'Australia's blood supply should be encouraged in its aim and realisation of self-sufficiency, not eroded.' CSL protested too, at the 'importation of an intravenous gammaglobulin preparation which is processed in Europe from blood/plasma collected under circumstances different from those characterising the Australian Red Cross Blood Transfusion Service'.[147] At the same time they took on distribution of the product for Sandoz. Health Department official C told the author at the time that Australia has had a firm policy against trading in blood since 1966. Health Minister Blewett's office concurred.[148]

CSL's failure with its earlier product was clearly a factor in the Health Department's decision to import. An official interviewed in 1987 said there was 'very strong pressure from medical scientists to get it on [including] gammaglobulin immune people and sundry allergy people'. Their delays in working up a replacement version under licence may have been a factor too. But the Department had other options before granting general marketing approval. They could have left Sandoz' product on the special access scheme and put GMP inspectors in to straighten out CSL's delays with developing the licensed product, a course that had been followed before in the case of vaccines.

A major failure in this case was that the decision to consider the application in the first place was made by drug evaluators, not blood policy officers. However, there is no evidence there were any such people on the job at that time, nor that anyone in the Health Department reliably answers to that description now.

Legal basis for approval

A number of parties, such as Red Cross, some Health Department officials, and an industry person, wondered aloud how Sandoz' product obtained general marketing approval. Official C told the author in 1992 that the decision 'would have been made on the normal basis of quality, safety and efficacy' and added 'subject to the policy on blood products'. Asked whether a legal opinion was sought on the matter he replied: '[I] don't see why a legal opinion would have been taken' and said he did not recall one.

At the same time a Health Department legal officer told the author that in 1985 the head of TGA had sought advice on the importation of immunoglobulin 'which was banned from being able to be sold under State law'. This officer looked at one of these laws and gave comment on the 1975 World Health Organisation resolution urging national self-sufficiency in blood, to which Australia is a signatory. He advised that it had no force

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[147] *CSL annual report 1987 p 7 Chairman's Report*
[148] *personal interview 1987*

unless enacted in domestic legislation. This officer said that blood products had not been included in any schedule prohibiting their import under customs legislation.[149] This legal opinion was then taken by other Health Department officials as meaning there is no blanket prohibition on imported blood.[150]

Thus the fact that all States and territories have legislation prohibiting the sale of blood hasn't stopped foreign blood coming in for sale. Some States, such as Queensland, exempted immunoglobulins by an Order under the legislation; others appear to have simply allowed them to be sold without the necessary legislative power. When State Health officials were asked during this study whether the product had been sold in their State some had not heard of the product, and were surprised to learn of it being available for sale. One informant maintained that the Federal Government, far from being unconcerned with the issue of how Sandoglobulin could be sold in the States and territories, actually attended a meeting at which ways of amending State legislation to allow the sale of Sandoglobulin were discussed.

Bases for approval by TGA

Clinician demand for the particular brand was probably also a factor in Sandoz' success. The company promoted hard to certain clinicians who praised the product openly. But Professor Dwyer pointed out that another foreign company had an immunoglobulin which would win in a price war with Sandoz. Yet another Health Department official said of the decision in 1987 'it was a mistake; it should not have happened. It will not happen again.'(It did). The product could have been disapproved by the Health Department once CSL got their version on the market.

A Sandoz employee told the author in 1992 that the company was not promoting the product. They were only leaving it on the market because 'if CSL runs into trouble again' they would have to supply their product to all the chronic ITP cases in Australia, otherwise they might die. 'We are an ethical company' he explained. CSL is clearly content with that too. CSL official A told the author there was 'no sense trying to get it removed', and that CSL was having difficulty meeting demands for its own product. Health Department in 1994 records show a clinical trial notification for immunoglobulin acknolwedged by the Department in December 1991. Others said Sandoz has been trialing their product here. The trials are believed to be for extended indications: the product has been promoted for conditions like chronic fatigue syndrome.

7.7 Case study Two - UB plasma

[149] *Customs (Prohibited Imports) Regulations in force under the Customs Act 1901, reprinted 1.11.92 Schedule 8.*

[150] *eg National Control Requirements for Blood Products in Australia, a paper by an NBSL official given at a CSL IABS symposium in Melbourne in 1986.*

The German UB Plasma incident is a second example of trouble arising from the importation of fractionated blood products. In 1993 HIV cases in Germany were traced to products from the UB Plasma company which had omitted certain HIV tests on individual donations to save money, testing only on the pooled product. Australians viewed the UB scandal with horror and were thankful again that our closed system protects us from such things. Then a radio report mentioned that the Immuno company had dealt with UB Plasma.[151] CSL had told the research assistant to this study that Immuno company was importing fibrin glue, a blood product used to seal surgical wounds.

A hospital clinician who is also a Red Cross blood banker confirmed that foreign fibrin glue is in use here - 'very little but not zero'. He had not been aware of the Immuno/ UB Plasma connexion and said he would inform national headquarters of the Red Cross.

For goods listed or registered in Australia, TGA must be notified of any product recall overseas which could affect the goods distributed here.[152] The author asked the company handling Immuno's imports what they were doing to ensure the product was not derived from untested UB Plasma. 'That's a matter for the Health Department and us' the representative said, aggressively interrogating the author about her identity. He became extremely excited and claimed the virus inactivation process, called steam heat vaporising, was 'absolutely guaranteed ... there have never been any indications of problems with the product'. He claimed the method was 'recognised by leading Australian experts and world leaders in this field' but repeatedly refused to say who they were. The author told him that other company representatives she had interviewed were always keen to send her scientific papers backing up their product claims. He turned to interrogating her about which companies she had interviewed but wouldn't back up his claims.

Asked why Immuno's fibrin glue was not being sold in the United States he eventually admitted it was not approved by the FDA but said he did not know why. He referred the author to the Therapeutic Goods Administration, in whom he had 'absolute faith ... diligent operation that they are'. He then sermonised on the French blood scandal, as proof of 'what happens to voluntary bloodbankers', something we must 'NEVER FORGET'.[153]

The author then told a number of journalists that Immuno's fibrin glue was coming into Australia. This was partly to test their role as potential players in the regulatory process: would they go beyond the usual treatment of is-it-AIDS-infected-or-not? TGA told one of these reporters they had been able to establish that the fibrin glue imported into Australia had not been derived

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[151] *ABC Radio 2CN , 9.30 am 8.11.93.*
[152] *ref The Pink Book p 26*
[153] *Telephone interview 9.11.93*

from untested plasma and nor had another Immuno product, a globulin. However, a third Immuno product, factor IX for haemophilia, was under investigation. All three products were available on the Special Access Scheme, discussed above. Because of this TGA had very little data to assist its audit trail.

The Sydney Morning Herald carried a page one report of Official D saying that two batches of a blood product linked to UB Plasma had entered Australia and that TGA had every reason to believe the two virus inactivation methods used on the products would inactivate HIV virus, but he was 'unable to reveal at this stage' when the batches had entered the country.[154] He also expressed concern in this report and elsewhere [155] about the government's acceptance of the Special Access Scheme which allows people to have 'unauthorised' drugs, including blood products, under special conditions.[156]

The author then asked Officials C and D how they had gone about establishing the validity of a manufacturer's claims concerning virus inactivation methods. They replied that they 'get information from every possible source', but would not elaborate. Asked about the United States Food and Drug Administration (FDA) Official C said they had no access there.

It is important in assessing the worth of licensing procedures for foreign drugs that the agency have such access. The Baume report[157] recommended that less thorough drug evaluations be carried out by the Australian Drug Evaluation Committee, but instead overseas evaluations should be obtained.

According to TGA News in April 1994, TGA was exchanging evaluation reports on products accepted for marketing with fifteen European countries, Canada and South Africa. US and Canadian evaluation reports on therapeutic devices were first obtained by TGA in 1992 to 1993. For 'accelerated evaluations' the TGA relies on reports from the US, the UK, Canada, Sweden and the Netherlands.[158] Successful 'harmonisation' of international regulatory efforts is crucial for the safety of foreign imports. Harmonisation runs like a mantra throughout TGA's publications as the rationale behind discarding the more thorough Australian system in place before Baume. The Special Access Scheme is an ideal avenue for market entry. For TGA to allow products to be used before obtaining overseas data seesm rather close to allowing a form of experimentation.

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[154] *Sydney Morning Herald 11.11.93*
[155] *ABC World Today 10.11:93*
[156] *SMH 11.11.93 p 1*
[157] *A Question of Balance; Report on the Future of Drug Evaluation in Australia, commissioned for the Minister for Aged, Family and Health Services, Hon. Peter Staples, by the Hon. Professor Peter Baume, AGPS July 1991., see p 16 and onwards*
[158] *TGA News Sept 92, no 11.*

In this case access to overseas data was particularly relevant. In 1992 this author was told by a US informant that fibrin glue licensing applications had been rejected by the FDA on the basis of the virus inactivation process. In December 1993, fibrin glue applications from a clutch of companies were further claimed to be stalled in December 1993.

In 1991 TGA published that sponsors are required to notify TGA of overseas rejections when lodging an application for evaluation, or afterwards if applicable.[159] However, this requirement does not apply to products under the Special Access Scheme.

Safety from virus

CSL's official A told the author that while he believed the virus inactivation method of steam heat vaporisation was perfectly adequate for HIV 'a large amount of virus let in at the beginning may overwhelm the inactivation; [virus inactivation] is a belt and braces approach ... you never say never'. This seems to be saying that steam heat vaporisation is *not* perfectly adequate for HIV. A scientific expert with long experience evaluating company claims and data relating to the safety of products told the author that companies 'commonly do not understand the principles behind what they do to render products safe.' He would 'need a great deal of data to be able to understand and assess the validity of steam heat vaporisation' in this case as he could not see how it could be either workable or effective for inactivating viruses such as HIV.[160]

The inactivation technique used for these products may or may not be guaranteed for HIV, but there have been reports of hepatitis C surviving inactivation.[161] There is a window period of twelve months before this disease is detectable. Official D, the Manager of the Therapeutic Goods Administration, made no reference to the products' safety for hepatitis in media reports viewed by the author.

The German UB Plasma company sold to numerous intermediaries. Some of them omitted their own HIV tests and relied on UB certificates; some of these were unsigned.[162] Allegedly, a worker at the company told German officials in 1987 that the company was distributing questionable blood products, but regulators took no action.[163]

Some German companies buy plasma from countries like South Africa and Latin America, the science editor for Die Speigel claimed.[164] Trading in blood is illegal in South Africa but the government didn't prevent blood being flown from the 'homelands' across South African airspace and out through

[159] *TGA News Sept 91, No 7 p 2.*
[160] *personal interview with the author 1994*
[161] *CSL official A, telephone interview 16.12.93*
[162] *Time. 15.11.93 p 26*
[163] *Time p 27*
[164] *ABC Radio National 8.12.93*

Durban, according to research by the author in 1986. International law and regulation is currently not equal to the task of controlling the global trade in blood. How then can TGA place its trust in foreign certifications of blood safety and quality or the product approvals of regulatory agencies who cannot control the industry? According to an Australian media report[165] the German government which was supposed to regulate the companies involved in the UB Plasma scandal, will pay about one hundred and fifty victims of the AIDS-tainted blood the sum of $22.7 million a year for three years.

[165] *Canberra Times*, 13.11.93

Patient consent under Special Access Scheme

The Therapeutic Goods Act, as well as hospital authorities where clinicians use these products, rely on the doctor to obtain the informed consent of the patient. How much doctors tell patients is up to them, and also depends on how much they know. Do Australian clinicians who order these foreign blood products know or tell their patients about these overseas regulatory and manufacturing calamities and their implications for product safety? Or do they just tell the patient the good things the product will do for them and leave them to trust the doctor and the 'health authorities'? Why should doctors be expected to bear the responsibility for obtaining informed consent when they have not been informed by TGA of relevant facts about the blood product?

The author asked Health Department official D if the TGA investigation into these products had involved trying to find out whether the clinicians had fully warned patients of the possible risk in using foreign product which was not fully evaluated. He responded that the matter was being investigated and gave no further information.

If informed consent is to be a goal of blood product regulation, regulators need to stop conveying the sense, by statements or omitted statements, that virus inactivation for blood products is guaranteed or almost certain[166] to work. Where patients are to give informed consent, an enforcement mechanism is needed to ensure that clinicians who prescribe them have enough information to pass on and to ensure that they actually do obtain consent. Nor can there be a right to consent if there is no remedy when consent fails. Recommendations to achieve these conditions are contained in chapter eight.

Some hospitals have established committees to regulate blood usage within the hospital. Such a committee relying on its persuasive powers could very effectively educate clinicians on this issue. A majority of hospitals still do not have such structures but the trend is growing. If prices for blood are introduced, many more can be expected as hospital boards and their accountants move to contain costs.

Role of media

If journalists had not learned of the Australian connexion to UB Plasma, presumably Australians would never have been told that such products are coming in. Not that media reports are an adequate substitute for timely and thorough information. This author's minor piece of action research confirmed that the media still see blood mainly in terms of HIV only, and tend to be reactive rather than inquiring. Once a government official reassures them the HIV virus isn't there, the story tends to die. Journalists have said over the years that their editors have told them to follow the HIV angle, that the 'story won't get in the paper unless we do it as an AIDS story'. Other diseases are of

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[166] *Canberra Times 10.11.93*

no or peripheral interest, despite the fact that death or severe suffering may follow from their transmission. Hepatitis has been a serious risk to the blood supply for decades, including nonA-nonB (recently named hepatitis C). It is only now that the disease is unmistakably epidemic that it has become fashionable to acknowledge its seriousness, three years after testing was introduced.[167].'

Media in this country have little information base with which to asess claims about blood products. Few are permitted the time or resources to research, reflect or identify issues. Before AIDS the media had been told nothing about the blood supply anyway, apart from reassurances as to its superiority. When AIDS emerged into public consciousness there was a powerful, concerted and effective effort by some clinicians, Red Cross and certain government agencies to steer journalists off inquiries about blood and disease transmission which might involve debate about the blood supply. This author encountered the effects of this campaign when, working as an investigative journalist in 1987, she asked clinicians how viruses were entering the at-risk cohorts in the first place. No one wanted to talk about it. One high-profile clinician became enraged, accusing her of irresponsibility for even asking such questions. 'Next you'll be telling us that the CIA did it!' he proclaimed, demanding to know who her editor was so he could have her stopped. This sort of encounter helped form her view that the subject was worth pursuing.

The belief that our Australian system has always been closed off from the international industry is probably another reason why the media have not been very effective as watchdogs. The general public and the media received no indication that the closed system had been breached, and had little knowledge of overseas systems in order to recognise the significance of those breaches. Further barriers to media involvement are the technical nature of the subject and the fact that the technologies and systems of blood supply are constantly changing.

Role of TGA

The above case studies on UB Plasma and Sandoglobulin also show that the regulators of our blood supply have an inadequate information base themselves. The Health Department and most State Health Departments interviewed for this study thought it was not their role to develop expertise on blood and blood products. They preferred to leave it to Red Cross. The TGA cannot hope to rival agencies such as the FDA in data acquisition and expertise, though it will acquire more of both in time. But the case of fractionated blood products, knowledge of the source material is vital.

TGA's legal position

[167] *Canberra Times 23.8.94 'The Federal Government has set up an urgent task force to develop a national strategy to tackle Australia's fastest-growing communicable disease, hepatitis C*

It may be time for government to consider its legal position in allowing blood products under the Special Access Scheme. It cannot take the view that all the responsibility rests with the clinician. The Federal Government's commitment to national self-sufficiency in unremunerated blood donation, and its commitment to safety, purity and efficacy, means it must take responsibility for its part in choosing to deregulate the usage of blood products under this scheme.

As cases mount of overseas companies and foreign regulators acting recklessly or negligently, a question arises about TGA's authority to rely on foreign assurances and certification. Is it enough? Are the public placing their trust in the TGA and are they assuming TGA has more control over the quality of foreign imports than they can or do have? Would patients use these products if they knew of TGA's lack of real control?

The US Bureau of Biologics attracted legal action over a faulty vaccine it had approved. The German government, which licensed the UB Plasma company which omitted HIV tests, is paying out millions of dollars following the scandal. TGA cannot have control without responsibility, and cannot assume responsibility without necessary information. If they cannot get enough information about foreign products, of if the information cannot be trusted, TGA should say so to clinicians and patients.

R.31 There is a case for reviewing the use of blood products under special access schemes with a view to restricting their use unless and until more evaluation data can be tapped from other countries. Alternatively, the Secretary of the Health Department should require, under the Therapeutic Goods Act, that the TGA be responsible for monitoring patient consent much more closely. This could take the form of occasional random follow-up interviews of patients to check that informed consent was properly obtained. If it was not, the TGA could make a submission to the appropriate medical board alleging irresponsible medical practice on the part of the relevant clinician. The hospitals in which most of these blood products are administered could also be deemed to be the body treating the patient, making monitoring and regulation much easier.

R.32 For foreign blood products from countries with whom TGA has data exchanging arrangements, where these products are allowed under the Special Access Scheme, the Secretary should instruct TGA to obtain relevant data on overseas applications which have failed or not been approved because of safety considerations. The administering clinician should be required by hospitals to inform the patient that approval has been refused on safety grounds, after receiving the relevant data from TGA (with data identifying the manufacturer excised).

R.33 The same recommendation above should apply for local products.

(The Secretary is already empowered under the legislation to require and release information which is necessary to ensure the safe use of particular therapeutic goods). ( ) *S 61(7)*

R.34 Written evidence of the patient's understanding on this point should be obtained by the clinician from the patient or a patient representative before administering the product, and should be furnished to the hospital and TGA before or at the time the product is administered.

There is also the issue of CSL's role as a supplier of Australian equivalents for these products, and the Health Department's diligence in assessing the new for foreign product. All three blood products involved in the above two case studies on regulation of imported blood are products CSL has attempted or is attempting. Efforts to develop fibrin glue have been going on in some fashion for a number of years. CSL official A said in late 1992 that they 'hadn't quite sorted it out'. Recently, a CSL official reportedly stated that management were not happy to market the product yet. They hope to make it in the new fractionation plant. One BTS Director interviewed for this study mentioned that a local hospital is producing its own fibrin glue.

The UB Plasma case study show that national regulators were unable to determine the quality of the starting material for blood products from external sources. It is also an example of the forsaken role of CSL as a home brand producer and bulwark between Australian users and international blood products.

R.35 The Federal Government should not passively permit TGA to bring in blood products on the basis of 'clinical need' as this criterion is insufficient for making decisions about products derived from blood. Decisions must also take account of the cost to the user or hospitals of these products compared to Australian products, the impact of importation on local supply dynamics and the special challenges which foreign blood products pose for regulators in respect of safety.

R.36 The Federal Government should make its purchase of CSL's existing range of blood products conditional upon CSL also producing other products for which a clear clinical need has been established, thus offering the national fractionator a financial incentive to develop home products while permitting the Federal Government to stay true to the national policy of pursuing a closed self-sufficient system of unremunerated blood supply for Australia.

If overseas products must be considered in the meantime, the TGA needs to consult more fully before deciding whether to approve them. Health Department officials told the author they wouldn't consult Red Cross expertise if a company applies to have a product licensed, 'because [the companies] are in competition with Red Cross'. This is an extreme

perversion of the public interest, wherein the Health Department is positioning itself on the side of commercial companies seeking to break down the national policy of self-sufficiency in unpaid blood donation. In doing so, the Health Department is working against the very agency which it funds to carry out the national policy for government on behalf of the Australian people, and on whom it has dumped much of its own responsibility for the national blood supply.

Where resort to overseas products is genuinely needed in special cases, foreign companies should have to account for the quality of their product. Secret reassurances about the quality of a blood product, made by its manufacturer to one agency, the TGA, do not constitute accountability in a democracy. This is true in principle, and its truth is borne out in practice by the handling of foreign blood product applications by TGA and its predecessors in the same agency.

TGA policy of not consulting beyond itself is also foolish in that it ignores the Red Cross and other blood banking experts as potential sources of information on blood products derived from overseas plasma sources, a matter on which Red Cross officials have considerable knowledge because of their international connections with the global haematology community. The Sandoglobulin case study shows how TGA secretiveness and failure to consult with available experts on the quality and safety of blood products may jeopardise the process of evaluation. One Red Cross informant suggested that some TGA officials consult them unofficially, but there was no evidence the practice is uniform. In any case, it should not be done on the judgement of individual officers as this places too much responsibility on them without the commensurate authority.

Recombinant factor VIII

Another foreign blood import will enter Australia along with recombinant factor VIII. Recombinant actor VIII has human serum albumin mixed with it shortly after manufacturing to stabilise it, so human blood risks come back in that form - (As to its safety aside from the albumin content, CSL's official A said it *should* be safer but that won't be known for three to five years.

BTS Directors often said that a properly funded plasmapheresis program could supply enough factor VIII for our needs, including for prophylactic use at home. CSL has for long worked to improve the yield and quality of factor VIII from its plant, according to evidence given the author. Yet now, if government can be persuaded by the Haemophilia Foundation and others to fund it, CSL will import the recombinant version for commercial distribution alongside the 'free' product derived from Red Cross plasma. The recombinant product is expensive. Official B told the author that the two companies marketing it spent over two hundred and fifty million dollars in research and development and will be looking to recover the majority of their costs in the next ten to fifteen years - by which time gene therapy for haemophiliacs might have emerged.

Conclusion
The above cases taken together demonstrate that failure to regulate CSL in the direction of meeting national need for home-sourced product has opened the door to the international blood industry, which has brought with it a range of questionable products and a corresponding range of serious regulatory challenges. Currently these challenges do not appear to have been confronted adequately . Certainly they are not being adequately addressed.

Advertising
Blood products may be ordered on prescription. Advertising for prescription and non-prescription drugs is regulated by voluntary industry codes.[168] The Department has an observer on the code committee who is nominated by the Secretary. The author was told she 'didn't need to know who it was'. Official D, the General Manager of TGA, was asked how the code was working and said that industry keeps the TGA informed and they were happy with the way it worked.

In the past, CSL has had representatives on National Health and Medical Research Council Committees concerned with determining appropriate usage of CSL products such as vaccines. A Health Department official said that they would not be eligible for such memberships now the company has been sold. CSL will be on an equal footing with pharmaceutical companies who let medical practitioners know about their prescription products through medical journals, trials, symposia and visits from sales representatives.

7. 8 Regulation of trials
There are two schemes for regulating trials of therapeutic goods that are not fully approved, known as Clinical Trial Exemption and Clinical Trial Notification schemes. (The names suggest the opposite of what the schemes mean). TGA's Drug Evaluation Branch is responsible for regulating them.

Under the first scheme, CTX, TGA evaluates summaries of data in a submission modelled on UK lines, emphasising safety ahead of efficacy. Data on fatal or life-threatening events must be included in submissions under the scheme. If an objection arises the trial must wait on its resolution. TGA may stop a trial if it is not proceeding according to requirements or for any other urgent reason.

The second scheme is a radical departure from previous regulatory controls. Under CTN, a trial may proceed *before* information relating to it has been reviewed by the TGA, as long as written approval from the ethics committee of the institution conducting the trial has been submitted to TGA and the

[168] *Australian Pharmaceutical Manufacturers Association for prescription drugs; Proprietary Medicine Assoc of Australia for non-prescription.*

ethics committee is operating standardly.[169] It is up to the trial sponsor to decide if a review of the data by TGA prior to the conduct of the trial is desirable, possibly after discussion with the ethics committee.

Trials must be conducted in accordance with the National Health and Medical Research Council Statement on Human Experimentation. These say that trial investigators are responsible for giving trial subjects sufficient information about the risks of participating in the trial.

The reason given for deregulating trials in this way was the Health Department had become too involved in shaping sponsors trial proposals for them. 'We had become clerks for the drug companies; they knew we had the expertise to make their proposals shipshape so they sent them in any old form' said one source. According to TGA News, 'queries were raised' at the outset of the scheme as to whether it afforded adequate protection for the trial population and it was introduced subject to review. The secretary of the Health Department has the power to stop a CTN trial in the public interest, as with the CTX scheme. An informant said that many CTN trials are not a risk because they are pre-marketing trials usually backed by prior overseas trials.

The CTN scheme is clearly achieving the goal of increasing trials, which was sought by the Baume. CTN notifications increased from three in 1990 to six hundred and forty four in 1993.

Trial schemes reviewed

After the new CTN scheme came in, TGA said that adverse reactions occurring on the trial had to be reported, and then they required 'appropriate background data' on the trials. A review of the CTN scheme was called in 1992.[170] It was conducted by three medical doctors, one being a TGA Official. The review team said urgent attention should be paid to making advice on toxicology available and educating trial investigators and ethics committees in order to 'maintain the viability' of the scheme. Then it addressed how to relieve ethics committees of liability for their involvement in trials, relying on representations that this liability was impeding medical research. There was no evidence of legal action in Australia resulting from clinical trials in Australia, and 'very little overseas' but industry, ethics committees and trial investigators were extremely worried about the issue and considered it the main obstacle to the conduct and expansion of trials. It recommended that when TGA was notified of a trial, the form submitted should bear the approval of a person authorised by the institution conducting the trial. This

[169] *in line with the current Statement of Human experimentation and Supplementary Notes issued by the National Health and Medical Research Council.*

[170] *Report to the National Manager of the Therapeutic Goods Administration on the Review of the Clinical Trial Notification Scheme, May 1993*

was to make sure that 'legal' responsibility for the trial 'clearly rests' with the institution, not the ethics committee.[171]

So if the trial sponsor was the same body undertaking the trial, the responsibility for approving *and* undertaking such trials would lie with the same party, a clear conflict of interests. Besides, the responsibility of the Ethics Committee should not be caste away in this manner. As Professor Braithwaite said in comment on this recommendation:' Either the Ethics Committee is independent of the promoter of the trial, and accountable for the ethics of its decision, or the promoter is accountable for the ethics of the decision. If the latter is the case, the Ethics Committee is not a locus of independent judgment; it is a 'Cypher Committee'. If this recommendation were implemented, it is doubtful that it would achieve the intention behind it, since ethics committees would still have the same duty of care caste on them by common law as before and can be liable under normal principles of negligence. Further, such a legal provision would in effect take away the right of action of individuals aggrieved by the action of an ethics committee. The Therapeutic Goods Act would have to authorise legislation to that effect, before it could be enacted.

R.37 Where more discretion is sought in trials systems, there should be assurance of independence of judgment, dialogue, and clear accountability for the discretion.

The review also recommended that **biological products at an early stage of development 'where a virology review is considered desireable' should go under the more stringent CTX trial scheme rather than the CTN scheme.**[172] This is a sound suggestion and should be pursued. For biological products a full virology review and all toxicology data should be viewed also.

R.38 Biological products at an early stage of development, where a virology review is considered desireable, should go under the more stringent CTX trial rather than the CTN scheme. (This recommendation comes from a Health Department Report).

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[171] *TGA News Nov 93 No 15 ; see also Report to the National Manager of the Therapeutic Goods Administration on the Review of the Clinical Trial Notification (CTN) Scheme, May 1993*

[172] *(op cit, Rec 14, p vi)*

Application of trials schemes
This study did not extend to studying regulation for trials of current blood products. The Department was informed in 1991 of a recombinant factor VIII trial to be conducted under the older CTX scheme, which sources said was for the product CSL has licensed from the Baxter Biologicals company. Under the less regelated CTN scheme, the Department had acknowledged notifications of a clinical trial for an immunoglobulin in 1991, which sources said was Sandoglobulin, the Sandoz product which rivals CSL's version, two trials for a blood product called Antithrombin 111 which sources said was a CSL product, and two others.

Recent evidence of the regulatory effectiveness of the TGA trials systems came not from blood products but from other trials of pharmaceuticals on women. In one case the evidence shows that the system broke down and TGA was extremely slack as a regulator once that came to light. Female journalists in the print media played a part in exposing the regulatory failure; still the Department was slack. Strong Ministerial intervention was evident, even while the first questionable trial was itself on trial through the media. In the second case, the trial deficiencies were detected by diligence from within the Health Department but there was internal resistence to taking action from the middle executive level.

Abortion drug trial
The first trial was conducted by Family Planning Victoria for a drug that can induce abortion from the time of conception. TGA had asked for guidance from the Minister for Family Services in the event of an application for marketing approval for this controversial drug and were told to keep the Minister fully informed. The company did not seek general marketing approval. When questions were raised in the Parliament about the possibility of trails, the former Health Minister gave an undertaking that the drug would not be imported for this purpose without prior reference to him. Family Planning Victoria notified TGA of their trial under the CTN scheme. TGA cleared the drug for import without any reference to the Minister, putting him in breach of his parliamentary undertaking.

TGA told the Catholic Bishops they would 'withhold consent' about a trial notification if they had 'unresolved concerns'. According to Margot Kingston in the Canberra Times, TGA had already denied to an estimates committee having any such discretion. Besides, as the trial was notified under the CTN scheme, which doesn't require data to be submitted to TGA, they had no documentation on the questionable aspects of the trial to even allow them to form doubts.

When Family Planning Victoria's consent forms and trial monitoring were found deficient, TGA denied all responsibility, reported Kingston. She said senior Health Department officials played 'silly word games' with her inquiries. TGA said the trials were in the hands of private ethics committees complying with strict guidelines. When it was known that the religious

representative on the ethics committee had received papers for meetings but not attended them, TGA said that didn't matter, as the representative only had to be on the committee; he didn't have to contribute anything. As Kingston put it:

> An edifice designed to assure the public that concerned lay people are keeping doctors honest was thus exposed as a sham.[173]

Then the new Health Minister, Carmen Laurence, learned that the gynaecologist heading the abortion drug trial had supported discredited pituitary hormone trials in the eighties after the risks were known in medical circles, and Family Planning Victoria's Dr Anna Lavelle could see nothing wrong with Healy heading the trial. Laurence said this link was very worrying and ordered an immediate investigation by the Department. FPV agreed to government requests for an independent review, then reneged, then agreed again as the trials ceased under Ministerial threat of using the Secretary's power to ban them in the public interest. An independent review of institutional ethics committees was ordered by the new Minister in August 1994, to be conducted by the Australian Health Ethics Committee. It is also reviewing the NHMRC Statement on Human Experimentation.

If the Department did have concerns about the safety of the CTN scheme as it says,[174] are there timely briefings to the Minister or other relevant quarters to show it? Surely, TGA officials are not taking the attitude that they will simply wait for the damage to show rather than agitating for reform if the scheme is based on unsound principles. What is the point of having a statutory power in the Secretary to terminate a trial in the public interest if the Department ignores evidence relevant to the Secretary exercising that power?

Kingston says the Minister bent over backwards to give Family Planning Victoria the chance to save its credibility. Simultaneously the Health Department had the same opportunity to demonstrate that they understood their duty to step in smartly if the body to whom responsibility had been delegated under the new CTN guidelines was getting it wrong. The evidence suggests relevant officials neglected that duty and only began to act decisively once the Minister was at their shoulders. This is worse than what Braithwaite calls the regulatory 'benign big gun'; it suggests, for this area of TGA's activity at least, that the gun wasn't even in the holster, and when it did fire, only blanks were used until the chief sheriff started positively *hollering* for a result.

A Departmental informant believed the committee was 'suggesting' to the truant religious representative on the committee that he resign. Sources said these committees vary greatly in their performance, however the vast

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[173] *Canberra Times 10.8.94*
[174] *TGA News Dec 92, no. 12*

these committees vary greatly in their performance, however the vast majority were worthy of trust. This suggests that a backstop watchdog role is needed within the TGA to identify the minority who err.

R.39 As a standing acitvity, a random audit of ethics committee deliberations, or an auditing role when negative indicators come to light, should be undertaken to augment the CTN scheme, and the reports should be public. The audit need not be done by the TGA but could be undertaken by an external body approved by the TGA and paid for by the sponsors of the trial. The external body should consist of people experienced with Ethics Committees, so that it functions as a peer review scheme.

Alternatively, TGA could tighten the approval process again, and charge sponsors for their expertise in assessing proposals, to avoid a return to the previous practice of companies exploiting Health Department resources. This idea was suggested in a limited form by the 1992 review team, but appears not to have gone forward. Indeed, it could have been adopted at the outset, without deregulating the trial scheme at all.

Newcastle breast cancer drug trial

By contrast with the Family Planning Victoria case study, deficiencies in a trial for a drug designed to prevent breast cancer in women were picked up in 1994 by diligent study from within the TGA. The Australian Drug Evaluation Committee demanded changes to the Newcastle section of the Australia-wide trials because the subjects were not adequately informed that the drug posed a risk of causing uterine cancer.[175]

The only TGA impediment in this case, according to this author's research, was that the discovery of the trial irregularity was not made by the scheme's regulators incidental to the routine monitoring of the drug trial system, but came adventitiously from a particularly conscientious and well-informed area of TGA, while middle level executives attempted to ignore it.

Both case studies presented here suggest the need for improvement in the system of regulating trials of therapeutic goods. The CTN scheme is attracting more review and criticism than many schemes.

R.40 Before long the Health Department should undertake a cost-of-deregulation impact study of its trials approval and notification schemes, and should not keep shoring up the system if the costs outweigh the benefits.

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[175] *Margot Kingston, Canberra Times 29.8.94*

CHAPTER EIGHT: REGULATING SUPPLY, DEMAND, USAGE AND USER CONSENT

Regulation of supply, demand and usage and of user consent can affect for good or ill a majority of the eight desirable goals for blood and blood products, including encouraging unpaid blood supply, use of Australia source material rather than foreign material, use for clinical purposes only, minimisation of harm to users, equity in access, and user consent.

8.1 Supply, demand and usage

Demand and **usage** may be determined or influenced by a hotchpotch of factors: fashions in prescribing, TGA licensing, new technology, the outbreak of war, the needs of peacekeeping missions overseas, the quality of a corporation's products and manufacturing expertise, changing rates of surgery, the advent of new medical conditions for which blood products may have a role, and increasing rates of organ transplants or other surgical procedures using a lot of blood. For example, in October 1989 three liver transplants were conducted in Sydney, each requiring fifty units, which resulted in the entire O+ blood stock being used in one weekend.[176] Conversely, because of greater understanding of the disease risks in blood, many Australian surgeons are abandoning the use of blood transfusion during hysterectomy unless it is absolutely needed and freeing up significant amounts of blood for other procedures. One Blood Transfusion Director stressed the need for policy and regulation of demand and usage:

> Should blood and blood products be given on a first come, first served basis; should we ration? What about private hospitals who do liver transplants on wealthy people who come from [other countries] just for the operation? I don't know what the answer is to this issue of usage but ... it is important to try.

Supply also can be affected by many and diverse factors, such as adequacy of funding, promotional expertise, the attitude of media towards blood donation, technological developments in harvesting, employer attitudes towards workers giving blood, changes in population health status, and even factors such as the state of the economy - high unemployment results in fewer donors and a less healthy population to draw upon. Red Cross maintains that media reports in Australia of overseas blood scandals also harm voluntary donations, even when the scandals reported involve the commercial sector. Donors in this country do not necessarily distinguish between the different causes of failure in blood services, nor between the different conditions prevailing in Australia and overseas.

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[176] *Organ Transplants: The Need for Community Debate; An Information Paper by the Health Issues Centre and the Association of District Health Councils of Victoria. p 17*

Demand and supply also inter relate in important ways. A strong demand for one blood fraction leads to surfeits in others. This can prompt industrialists to promote new uses for the excess fractions, including medical indications for which they are of dubious or unproven effect.

R.41 State and Federal governments should fund research to establish from whom the general public and donors would best receive information about the importance of unpaid blood donation and the effects of commercialisation, and should fund appropriate information programs designed to improve supply and maintain public confidence in unpaid blood donation.

8.1.1 Connexions between yield, demand & commercialisation

A Health Department official, responsible for regulating CSL post-sale via the Plasma Performance Contract, said in 1994 that the Department had never reviewed CSL for its performance in blood product manufacture, including its yield of product from Red Cross starting material. He thought the ability of CSL to make more product was 'apparently linked to Red Cross supply' of starting material. He was aware that CSL was constantly trying to improve its yield but did not know why the CSL factor VIII was lower than the yield achieved by overseas manufacturers. (His figure was thirty percent less; a senior Red Cross official maintained the shortfall was up to forty percent). The purpose of the new TGA is said to include ensuring the 'timely availability' of therapeutic goods,[177] but in practice the Health Department takes little direct interest in the availability of appropriate blood products.

Regulators - and government purchasers - need to concern themselves with matters such as the yield CSL gets from starting material. Neglect of this factor can compromise the goals of adequacy in blood supply and the maintenance of a closed system based on unpaid blood, as the following example shows. CSL's Canadian counterpart, the Connaught Laboratory, was, like CSL, given the exclusive right to produce factor VIII from local blood, in order to increase national self-sufficiency. Connaught's yield of factor VIII from local starting material was half that of the commercial Cutter Laboratories of California. Because of this gross inefficiency in yield together with poor government management, Canada in the eighties was driven to importing American blood from paid donors which was heavily contaminated with HIV.[178]

8.1.2 Regulating supply

Supply, as well as yield, must be regulated in order to proof Australia from the international blood industry. A number of Red Cross interviewees consistently said that with adequate resources they could run plasmapheresis

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[177] *The Pink Book 'entitled 'What you Need to Know About the Regulatory Requirements for the Manufacture and Supply of Medical Products In, or From Australia, TGA November 1992, p 2.*

[178] *Kate Dunn, in the Canadian Medical Association Journal, February 15 1993, 148(4), pp 609 - 612*

programs which would significantly boost supply. A number of Red Cross and other interviewees spoke of expensive plasmapheresis machines lying idle around Australia for want of the funds to buy plastic plasma collection bags. As seen above, some blood banks claimed they diverted resources intended for blood collection into paying for improvements needed to satisfy GMP codes.

R.42 The potential of Australian plasmapheresis programs to meet demand for blood products should be reviewed to establish whether their funding and development can increase supply and reduce the need for foreign imports.

8.1.3 Who should determine what CSL produces?

As to what CSL could and should be making in the way of blood products, the same Health Official quoted above said that was 'up to red Cross. It is difficult for us in the Commonwealth to get a good feel for what the system needs'. This reveals a peculiarly lax attitude towards regulating the demand and supply of a medical product derived from scarce material and supplied by government free of charge in the national interest.

Evidently the Federal Government does not care to make use of its funding power over Red Cross to inform itself on supply and demand for human blood. As seen in this report, Red Cross has had little success in getting CSL to perform adequately, either for the existing range or for new blood products, and hasn't enough authority for the task. The laxity of Federal Government regulators in this sphere also leaves ordering clinicians with too much influence over the use of blood, especially given that most hospitals do not regulate usage adequately and many not at all, according to evidence given this inquiry.

When the Health Department determines the facts about Australia's capacity to supply starting material for factor VIII now and into the future, it must stop unquestioningly accepting CSL's line that the only problem is lack of enough plasma. CSL can be expected to push this line as it creates a market for their recombinant product. The Head of the Bioplasma Division told the author and her research assistant in 1992 that the 'excess of demand over supply was a standard problem in the world of fractionation.'

> RS How does it get solved?
> B It's never been solved, not in my lifetime. Since we were able to isolate antihaemophilic factor we have never been in balance on a world basis, which means that the haemophiliacs suffer the greatest, they don't get the supplies they require; it's been the same for thirty years ... no solution other than recombinant.

CSL's regulators must get close enough to the company to see what it is doing with its plasma and should realise that with recombinant factor VIII now on

the market, the company could have an interest in talking down the Australian product.

R.43 The Health Department should determine an acceptable clinical level of haemophiliac treatment within the context of its health budget allowing for equity in access for other needy groups. Then it should compare the cost of local production for that level with the cost of recombinant. If recombinant is cheaper, it should not allow infrastructure for plasma derived factor VIII to be run down, because the safety of the recombinant will not be known for some time. If local production is cheaper, the Federal Government and State governments should discourage the use of recombinant factor VIII by adjustments in government funding and should educate clinicians accordingly.

8.1.4 Hospitals neglect regulation

In 1994 a senior scientist in a hospital laboratory which, in regulatory compliance, is ahead of most counterparts in Australian hospitals, reported having to be 'constantly on the tails of doctors ordering blood and blood products'. The same hospital is one of few with a committee attempting to control the use of blood and blood products through peer review and education.

> One thing came out of HIV - people were rational about usage for a while. Now we've almost become complacent again, on the basis that 'we test for everything'. This enables is to say 'it is as safe as the state of the technology'. ... Very few hospitals have peer review. ... Very few are doing anything much about usage.

The availability and use of blood products is influenced considerably by clinician pressure on TGA to approve them for special access or general marketing. It is somewhat influenced by the few hospitals introducing blood usage, and by the Red Cross, who assist in preparing and disseminating voluntary guidelines on appropriate usage. Red Cross also generates and seizes upon opportunities to persuade and educate clinicians, hospitals and other users.

Regulation at hospital level is likely to have the most effect in controlling wastage and inappropriate usage. The need to control budgets, the proximity to clinical practice, and the opportunities for education and peer review suit hospitals for this role. The senior scientist interviewed above, who has had long experience with hospital-based regulation, said that education of clinicians was without doubt the key factor in successful control of blood and blood products:

> The challenge is educational, not regulatory. You couldn't regulate this area with a gun.

8.1.5 Health Department lack of interest

TGA approves blood product information, which includes indications for use. However, they don't prevent medical practitioners from going beyond these indications. 'The Commonwealth doesn't want to stop actual clinical practice', said Official C. When asked if the Federal Government had any concern about wastage or use of blood products he said 'No specific brief, but the Commonwealth funds forty percent of Red Cross Blood Transfusion Services and have an interest in maintaining efficiency. I know from attending meetings that Red Cross works at this'.[179] In other words, the agency leaves it to Red Cross, another case of the Health Department giving away rather than delegating its responsibilities.

8.1.6 Red Cross' efforts to regulate demand and usage

Some Red Cross BTS's will refuse to release blood or blood products for uses they find clinically unsound. The latter practice, while it is well-motivated and responsible on Red Cross' part, can open the door to fighting between clinicians, hospital personnel and Red Cross. The Head of a Haematology Department in a large hospital gave evidence that hospital staff, when ordering products from the blood bank, do not accept Red Cross' right to restrict their access. This witness said they tell Red Cross whatever Red Cross wants to hear about the use to which the product will be put and then use it according to their own judgment.

8.1.7 Need for national co-ordination

The national government should not to desert this area on the basis that intervention is tantamount to regulating clinical practice. The National Health and Medical Research Council recently issued a statement condemning the clinical practice of administering a back pain drug by epidural route. Besides, blood is a finite, scarce resource supplied by gift in the public interest; it is not a chemical entity which may be synthesised in any amount to meet demand. Clinicians, hospital boards and government have a responsibility to account for its appropriate usage.

The Federal Government should also address usage and wastage with their State counterparts, from policy and regulatory viewpoints. There is nothing to stop Health agencies endorsing guidelines for rational use of blood products from other bodies, such as the Australian Society of Blood Transfusion. Governments have ample leverage over hospitals and clinicians through funding of medical benefits, and hospital funding. The Commonwealth has similarly useful leverage over CSL. The leverage is even greater now that CSL wants to provide recombinant factor VIII, because the Federal Government can refuse CSL's brand.

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[179] *telephone interview 12 Oct. 1992*

R.44 There is a clear need for governments, led at the national level, to pursue compliance with guidelines on the appropriate use of blood and blood products.

R.45 Federal and State Health Departments should co-operatively and in consultation with Australian Red Cross Society and other relevant parties determine the effects of current policy, regulation and funding levels on supply and demand, and make recommendations for changes as needed.

8.1.8 Reporting problems in use

It is a condition of registration or listing on the register that adverse reactions to products be reported. Printouts of clinical details of reports are available to sponsoring companies and are included in a Departmental publication called the Adverse Drug Reactions Bulletin, which is distributed free to medical practitioners, dentists and pharmacists. Circulars reporting problems with therapeutic goods may be distributed if needed, according to the Department.[180] The agency can also reach the general public by publishing in journals which lay media may pick up.[181] In 1993 the ADRAC Bulletin reported on severe hypersensitivity reactions to a plasma volume expander called Haemaccel.[182] There are numerous papers dealing with serious reactions to plasma volume expanders made from human plasma, however lack of reporting makes it difficult to establish the actual cause or assess whether the incidence is untoward. One paper mentions twenty one reactions in a twelve year period and adds 'Most authorities believe the true rate is considerably higher than the reported rate'.[183]

A senior Red Cross blood banker told the author in 1992 that reporting of adverse reactions to blood and blood products prior to the new legislation had been neglected; nor had it been encouraged by the Health Department. During 1992 to 1993, one hundred and twenty four drug problem reports were received by the Department and referred for investigation, a decrease of twenty four percent on the previous year.[184]

TGA's Therapeutic Devices branch produced a video called Report the Problem, which was launched on the high rating ABC consumer program The Investigators and resulted in 'many calls' to the TGA's hotline about device problems. The same sort of initiative could be used to educate the general public about blood and blood products.

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[180] *The Pink Book November 1992 p 26*

[181] *eg August 1994, warning on antibiotic flucloxacillin, possibility of inappropriate prescribing eg Canberra Times 26.8.94*

[182] *Vol 12, No. 3 Aug. 93*

[183] *Adverse Effects of Plasma Volume Expanders, Isbister, J.P. & Fisher M. McD. in Anaesthesia and Intensive Care, Vol 8, No 2, 1980 p 147*

[184] *Program Performance Statements 1993-4, Health Housing, Local Government and Community Services Portfolio, Budget Related Paper No 7.8A, sub program 1.5 p 111*

R.46 The Health Department should actively promote the importance of clinicians, manufacturers and users reporting problems with blood products to the Department. This promotion should be done at least through the Adverse Drug Reactions Bulletin and the Australian Prescriber, in order to reach all specialist and general medical practitioners and pharmacists. The Department should investigate reported problems and publish summaries of reports and the findings in ADRB, the Australian Prescriber and to blood banks, hospital and clinics using blood products. Investigations should be extended, where multiple adverse reaction reports are received for one product, to studies designed to determine the nature and extent of risk for that blood product.

R.47 As with pharmaceuticals on the pharmaceutical benefit schedule, the Health Department should implement a consumer education program designed to show consumers how to recognise and assist in the reporting of adverse reactions. This information should be distributed to consumers through hospital pharmacies, treatment clinics for blood clotting disorders, and organisations such as the Haemophilia Foundation.

8.2 User consent

The implementation of effective measures for ensuring informed consent is of paramount importance in the case of biologically-derived therapeutic goods. No amount of regulatory control can negate the potential for harm when humans use biological matter which cannot, by definition, be fully standardised. As a former NBSL regulator put it: biologicals are only as good as the people they come from. Further, since these products are often referred to as drugs or therapeutic substances, there is a greater need to explain to patients that they are different in significant ways relating to safety.

Even assuming the effective application of a full range of regulatory measures, from strong legislation, to conscientious self-regulation backed by external controls and by responsible, accountable clinical practice, patients must still be brought to a full understanding of the nature of the products if the system of supplying blood and blood products is to work. Not to ensure patient consent is to invalidate the right of patients to chose what goes into their bodies, and opens the door to product liability suits which cannot be afforded by insurance companies, manufacturers, clinicians, government, or the community.

Since the High Court ruling in Rogers and Whittaker and a clutch of other cases concerning adequacy of care, it is clear in common law that it is no longer enough for a doctor to claim that the course taken in informing or not informing patients of the nature and risks of medical treatment was accepted practice. The Court must not be denied the role of deciding for itself what is adequate on objective grounds, taking into account the evidence and the expectations of the patient. These decisions may have a moderating effect on doctors who would decide what is best to tell the patient. Whether they are

having that affect was not gauged in this study. But empirical evidence over seven years shows that while legal liability considerations have caused many doctors to reduce usage, there was little sign of doctors specifically informing patients of the risks in these products in the course of obtaining consent. One senior hospital employee with long experience in releasing blood and blood products said that clinicians were still reluctant to adequately inform patients about products: 'They won't give up their power. Any proposal that looks like it would disenfranchise them at all, they play a very rearguard action'.

A showcase prosecution on informed consent could fix practitioners' attention on this issue, after which they would likely be more receptive to educational initiatives and regulatory requirements. The public interest fund administered by legal aid could be used to finance a test case on informed consent for blood products.

In 1993 the National Health and Medical Research Council published General Guidelines for Medical Practitioners Providing Information to Patients. The guidelines have status in courts of law hearing cases alleging negligence. The NHMRC intended them to be widely disseminated and observed in medical practice. During consultations over consumer product information, however, a committee found that very few practitioners, even the chairman of an ethics committee at a major, prestigious metropolitan hospital, knew of their existence. Few who did know of them were aware of the legal status, according to the informal feedback received.[185]

The Baume report recommended provision of consumer product information, but some levels of the Health Department have became legalistic over the issue and tried to walk away from effective measures to ensure that information reached the consumer, by limiting therapeutic goods act regulations concerning the supply of patient information to the sponsor alone. The General Manager of TGA stated in 1994 that 'TGA is attracted to the concept of self-regulation' for consumer product information.[186]

R.48 Blood and blood products should be considered to have the same status as prescription pharmaceuticals for the purpose of legislation governing the supply of patient information: regulations applying to consent should apply to both therapeutic groups.

R.49 Legislation should be framed to ensure that all relevant health professionals involved in ordering or administering blood and blood products provide appropriate patient information, and carry out their common law duties to obtain informed consent.

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[185] *PHARM, a multi disciplinary, multi sectoral Committee on quality use of medicines, which acts as a bridge between the Health Department & all other sectors.*

[186] *Report and Action Plans from PHARM Meeting on Consumer Product Information 6-7 April Canberra1994, p 85*

R.50 The National Health and Medical Research Guidelines for Medical Practitioners Providing Information to Consumers should be disseminated to all health professionals involved in ordering and administering blood and blood products; the guidelines could state that they apply where blood and blood products are given.

R.51 The Health Department and National Health and Medical Research Council should continue in its recent form of acknowledging in public that biologically-derived products cannot be fully standardised and carry innate risks. Drawing on appropriate scientific and legal expertise they should then draw up a protocol for general patient information on blood products derived from Australian plasma and a separate protocol for foreign products, which sets out:

1. the general nature of biological products and how this sets them apart from pharmaceutical products;

2 their potential for harm from disease, other contamination and individual patient 'allergic' reactions;

3. the relative safety of paid versus unpaid donation;

4. the limits of testing to assure screening for known and unrecognised disease;

5. the limitations on regulators in assuring quality and safety, including whether the product is grandfathered or made available under the Special Access Scheme;

6 The obligation of TGA to inform practitioners if the status of an overseas regulatory body on whom the TGA relies to certify products, or of an overseas supplier, becomes questionable; (see earlier recommendations)

7 the statuary and common law duties of clinicians to inform patients of these factors when obtaining consent;

8. The importance of practitioners not degrading the status of information intended to assist the patient in giving or withholding consent on informed grounds, by adding their own opinion of the data given or overriding it with generalised reassurances not borne out by the facts available to the patient;

9. The elements involved in the process between the medical practitioner and the patient of actually obtaining informed consent, including the need to ensure by questioning and two-way communications that the patient, irrespective of any language, ethnic

or other barriers, are brought by the practitioner to a state of understanding before giving their written consent; provision of written patient data is not sufficient for obtaining informed consent.

10. The need to document the process and outcome of obtaining informed consent and to obtain the patient's declaration that the process was carried out and informed consent was given.

These protocols should be disseminated on all lines currently used for pharmaceuticals and to specialist groups involved with the supply of blood and blood products, including under the Special Access Scheme, and should be given to the patient in written form at the same time as specific product information.

R.52 Patient information should be consistent with and not contain less data than product information.

R.53 The protocols should then be backed by Federal rather than States legislation, either under the Therapeutic Goods Act or as part of future law relating to requirements for informed patient consent, and included also in the National Health and Medical Research Council 'General Guidelines for Medical Practitioners on Providing Information to Patients'.

R.54 Responsibility for seeing that patient information for blood and blood products aligns with relevant regulations and product information, and actually reaches the patient and is understood by them, should not under any circumstances be left to the sponsor alone, since the sponsor alone is not capable of discharging this responsibility. The responsibility must be recognised in policy, law and practice as a mutual obligation between Federal and State governments who subsidise and regulate blood and blood products in the public interest, manufacturers, hospitals and other suppliers, accident and emergency departments, medical practitioners, nurses and ambulance paramedics, and learned intermediaries involved in their delivery to the patient, such as pharmacists.

R.55 Clinicians, nurses and others involved in delivery of these products to patients should be educated to ensure compliance with consumer product information. The cost of these programs should be born by the practitioners and other health professionals, since the programs assist them in discharging their existing legal and ethical duties to inform patients and obtain their consent.

Pending protocols and legislation, the practice in some hospitals of medical practitioners being permitted to state they have obtained consent without written declarations from themselves and the patient that consent was actually obtained needs immediate address.

R.56 Federal and State Health Departments, hospital boards, medical associations and consumer groups with a stake in the safe, appropriate use of blood and blood products, especially the Australian Red Cross Society, the Haemophilia Foundation and health consumer groups, should individually and co-operatively declare that practitioners must obtain written evidence that informed consent has been obtained as proof that they have met their common law obligations. The TGA must recognise its responsibilities to provide relevant information concerning blood products to permit this process.

R.57 Consumer groups should be empowered to take part in the development of consumer patient information on blood and blood products as they are the principal stakeholder.

In this report we saw that two hundred and fifty million dollars has reportedly been spent in development by the two companies marketing the new recombinant factor VIII. This may seem a lot, but compared with the estimated costs of collecting and processing plasma based products worldwide, including product liability payouts, it is not. Yet there is little benefit in replacing one blood product with a synthetic version if blood banks still need to collect blood in order to produce the other products. There is a need for development of alternatives.

R.58 The Federal Government should favour research aimed at developing alternatives to human blood and urge its progress in appropriate international circles.

CHAPTER NINE: EFFECTIVENESS OF THERAPEUTIC GOODS ADMINISTRATION AS REGULATOR

9.1 Compliance

For 1992 to 1993, two hundred and forty nine manufacturers of medicines and devices were inspected for compliance with GMP codes to determine their eligibility for licensing ; twenty two percent were unacceptable. This figure reduces to seventeen percent if blood collection centres are excluded. The average time between inspections was seventeen months. Of thirty nine overseas manufacturers inspected, eighteen percent did not comply satisfactorily with GMP practice. Twenty eight plant master files from overseas manufacturers were evaluated; sixty two percent of these were found to be unacceptable in demonstrating compliance with good manufacturing practice. Of one hundred and sixty reports provided by sponsors of therapeutic goods obtained through arrangements with overseas countries, thirteen percent indicated unacceptable standards.[187]

The Therapeutic Goods Administration has a compliance branch which contains the GMP audit and licensing functions as well as a Surveillance Unit, staffed by three people. This section monitors compliance with the legislation, investigates possible offences under the Act with Australian Federal Police assistance in the more serious cases, and prepares cases for prosecution by the Director of Public Prosecutions.

The Surveillance Unit received three hundred and forty five referrals of information concerning offences in its first year;[188] none concerned blood or blood products. TGA News cited the Department and industry as the most valuable sources of information about legislative breaches. Unannounced compliance inspections are carried out but yield less evidence. The Unit issues warning letters to sponsors identified as breaching the legislation, unless the breaches are too serious to warrant a warning and should be prosecuted. Two hundred were sent over one twelve month period reported and the response in a majority of cases was considered acceptable.

Unlicensed manufacture under substandard conditions, counterfeiting of legitimate products; supply, import and export of products not included on the TGA register; fraud involving ingredient substitution, alteration of labels and falsification of documentation; and promotion and display of unlisted goods at trade displays, were some of the breaches detected.[189]

9.2 Adverse Publicity

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[187] *Program Performance Statements 1993-4, Health Housing, Local Government and Community Services Portfolio, Budget Related Paper No 7.8A, p 108*

[188] *Program Performance Statements 1993-4, Health Housing, Local Government and Community Services Portfolio, Budget Related Paper No 7.8A, sub program 1.5 p 109*

[189] *TGA News Nov 93 No 15*

TGA informants and their predecessors varied in their opinions concerning the effectiveness of adverse publicity as an incentive to compliance. The idea of publishing a list of blood banks that failed inspection was said to be 'counterproductive to the relationships we have established'. Many officials preferred to deal in private with the companies and entities they regulate, believing they would lose their co-operation if they went public. Few had thought beyond their anxiety at industry's likely initial reaction to such disclosures, to consider how disclosure might benefit all sides in the game or how sponsors and manufacturers would subsequently respond if presented with no choice.

9.3 Prosecutions

TGA is required to refer all its prosecution briefs to the DPP, who has the final say on whether to proceed. According to Braithwaite and Grabosky, agencies whose regulatory activity is limited to a single industry resort to prosecution about one-fifth as often as regulatory bodies which oversee a diverse variety of industry sectors.[190] Sources said that there were no prosecutions at all under the previous therapeutic goods legislation.

Prosecutions began under the new Act only after a Surveillance Unit was established within the Therapeutic Goods Administration. The unit is pitifully inadequately resourced but very effective within those constraints and the constraints of the legislation. All fourteen prosecutions resulted in conviction. There have been no prosecutions for offences relating to blood or blood products.

The first prosecution was in 1993 against a defendant for illegally importing and supplying collagen injected to reduce the appearance of scars and wrinkles.[191] A number of other cases against an individual, a company and directors in four other companies were successfully prosecuted, involving offences such as illegal import, unlicensed manufacture, and export of products not on the TGA register.

One individual identified by TGA's surveillance unit was making an arthritis poultice from Bovril and exporting it to India. The preparation was putrid and contained pathogenic bacteria. Recommended for sporting injuries, its application could have led to gangrene. Another was 'making millions' out of veterinary steroids which he was supplying for human use. These cases show the extremes to which people will go to make money from therapeutic substances. There is no reason why such criminal impulses should not be directed towards blood and blood product manufacture; what makes the eventuality less likely is the relative difficulty of obtaining biological starting material as opposed to synthesising or obtaining chemical compounds.

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[190] *Braithwaite and Grabosky Of Manners Gentle p207*

[191] *TGA News April 93, no 13.*

After the first conviction the General Manager said in TGA News, the agency's newsletter directed to the industry: 'People who deliberately try to circumvent the law are not only showing a complete disregard for public safety, they are inviting substantial penalties' and added that further prosecutions could be expected soon. The cases received substantial media coverage.

However, the General Manager's warning about substantial penalties is not borne out in the cases to date. All defendants pleaded guilty, which meant their offences were heard by a magistrate's court. The penalties were far less than the legislated amounts of up to a hundred and twenty thousand dollars where cases are indicted in a higher court. The penalties were further reduced in the magistrate's court on grounds the defendants were first offenders.

Informants in a number of agencies were aware that the requirement to show that offences were committed knowingly or recklessly is a major obstacle. Nor does the Act provide for imprisonment, despite containing criminal offences. A number of observers said that laxities in the legislation, a general dislike by TGA officials of confronting criminal or unlawful conduct, and an attitude of reluctance to interfere with commerce, especially after government accepted the Baume report recommendations, were combining to invite a 'major criminal element' into the area of therapeutic goods. 'The criminals are laughing at the TGA. People can make as much money from these goods as from hard drugs and without the risk of going to prison. They get off with a three thousand dollar fine and TGA can't stop them going back into business or destroy their goods. One, who appeared to have his assets overseas, boasted after his conviction that he had won the lottery against the TGA.' Another informant put it this way:

> If you were a criminal making money from drugs why would you chose illicit drugs and pit yourself against the combined police forces of Australia as against one or two investigators from the TGA?

The legislation does not providce for forfeiture of goods for any of the indictable offences.[192] When illicit drug manufacturers and traffickers are convicted of their crimes, the police don't give them back their heroin and amphetamines.

If the Act were amended to include forfeiture on conviction, and remove the requirement to prove the offence was done knowingly or recklessly, cases could be moved swiftly through magistrates' courts with maximum penalties applying and disposal of the goods. A convicted offender who later applied for a manufacturing license under the legislation could be turned down on grounds they had been convicted under the Act.[193]

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[192] *S54*

[193] *s 38 and S 38 (1) (f)*

R.59 The Therapeutic Goods Act should provide for recall of therapeutic goods and forfeiture of goods on conviction of an offence.

R.60 Legislators should appreciate that improper manufacture and supply of goods under the legislation can cause as much harm as manufacture and supply of the same goods supplied 'illicitly'. In terms of deterring criminal supply, the distinction between an illicit manufacturer and a lawful or licensed manufacture is not relevant when framing offences under the legislation.

R.61 Provisions in the Therapeutic Goods Act relating to intention in committing indictable offences and to penalties should be reviewed and brought into line with legislative sanctions for criminal and unlawful activities relating to the supply of 'illicit' drugs, all of which fall within the definition of therapeutic goods.

9.4 Deterrence

The best of external regulatory systems is never superior to the best of self-regulation, but external systems can have two general good effects. One is a direct effect, by preventing harm through product licensing and inspections. The second is by functioning as an incentive to the corporation to self-regulate, on threat of regulatory escalation.

The capacity of an agency like the TGA to achieve constructive compliance towards the eight goals posited for blood and blood supply is far higher than, say, the random forces of changeable markets or the threat of product liability suits. This study showed that especially where external and self-regulation is weak or non existent, the fear of liability suits can have a random and undesired effect on the behaviour of blood product manufacturers, sometimes causing only short term reform and all too often breeding a harmful pre-occupation with meeting the perceived requirements of the law, irrespective of whether that may result in greater product safety and quality. Where manufacturers were already meeting external or internal regulatory requirements, they tended to be less fearful of legal suits.

One informant with long experience of TGA and its predecessor said he believed TGA was not now particularly effective as a mechanism for direct regulation. He felt its really effective period was in the sixties, the early days when 'any old bag merchant could buy a drum of starting material and make it into pills. After good manufacturing practice codes were introduced it was in industry's interests to regulate themselves.' Now, he claimed, the TGA only 'spots the odd problem'.

This ignores the fact that outrageous practices of pharmaceutical manufacturers in the sixties were stopped in large part by the presence and activity of the agency. Besides, compliance officials do still detect outright villains and gross negligence, as shown above.

TGA claims their prosecutions resulted in cessation of the illegal behaviour, and that in most cases sponsors faced with prosecution applied to have their products listed on the register.

More importantly, however, TGA has great potential as a threatening presence to deter lapses, and to use its powers as what Braithwaite calls the 'bargaining chips' in the day-to-day business of achieving compliance with self-regulation. If most companies have gone on from the primitive days of the sixties to realise the benefits of self-regulation, that is as it should be, but one cannot deny the role of NBSL, TGA's predecessor, in helping to set up the preconditions for these realisations. It does not mean that TGA should pack up and go home, rather that it should work with manufacturers in more refined and creative ways to achieve the goals of regulation while minimising unnecessary intervention or schemes for which the benefits outweigh the costs.Part of this would include increasing penalties and sentencing in tandem with surveillance of the field until empirical data show that the right threshhold has been reached for the threat of prosecution alone to act as a deterrant, and then maintaining that threshhold with selected head-on-a-pike or showcase prosecutions on one hand, and more refined financial and other incentives to compliance on the other: the message should be that obeying laws and complying with regulation is good for business. In the current climate of internationalisation of business, consumers have an even greater need for uniform standards and co-operative regulation globally. The realisation of a uniform national system is a necessary step for each country and a natural mission for an agency like the Therapeutic Goods Administration.

R.62 The Therapeutic Goods Administration should use its authority as regulators of therapeutic goods and its commitment to maintaining a closed national system of blood supply to assist the latest international movement towards uniform standards and regulatory schemes for blood and blood products based upon non-remunerated blood supply. To assist it in this, it should first actively inform itself of the nature of the international blood industry and its effects upon safety, efficacy, appropriate use and equity in access.

As for CSL, it must be remembered that the national fractionator operated until very recently outside the reach of NBSL and the TGA. CSL is only now entering the same phase of external and self-regulatory control as was accepted by the multinational pharmaceutical companies or impressed upon the bag merchants three decades ago. As regulated bodies go, it is still very much a baby - and with an immediate past life that needs to be solidly forgotten. CSL can only be expected to gain from a strong TGA presence, and is reported to be displaying a predictably co-operative attitude.

9.5 Licensing power

One senior informant in TGA said that the power to refuse a license is without doubt the TGA 'big stick' in these early years of the new Act, and that compliance with the Codes is taken seriously. The initial refusal to grant licences to blood banks was successful in achieving compliance with the Code. This accords with all evidence from blood banks taken by this author. Some Red Cross officials objected to the mode of implementation and the costs, but none believed the principles governing manufacture were unnecessary or counter-productive.

9.6 Resources

This study found that resources amongst TGA various activities were not spread appropriately and were inadequate for some functions.

R.63 All TGA's consumer safety activities must be adequately staffed and resourced. In particular, there should be no shortages in surveillance and inspection resources as against product evaluations and approvals as this can invalidate the purpose of approving goods for therapeutic use and can contribute to increases in crime and unlawful behaviour.

9.7 Conflicts of interest, corruption and capture

There appeared to be lack of uniformity in addressing these matters throughout the Health Department. Some managers and committees have discretion in making and applying rules.[194] Rules varied from one section to the next, not necessarily in keeping with the degree of threat of capture, corruption or conflicting interest arising out of officers' contact with potentially compromising players.

TGA committees include external representation and expertise; members must declare any conflict of interest in writing. If a conflict of interest arises the member does not participate in discussions and does not vote. It is left to the Member concerned and the Committee chairman to determine whether the member should absent themselves.

There is potential for conflicting interests in the government's policy of 'user-pays', which results in considerable fees being charged by TGA for almost every activity it undertakes. Evaluation of information supplied with an application for marketing approval can cost up to ninety dollars a page; data packages can run into thousands of pages. As one official said: 'Since we started charging the companies fees, they think they own us'. Conversely, individuals and voluntary consumer groups who cannot afford the costs of TGA publications can be frozen out. This was tried by one official on this author, who undertook the study with minimal resources and no income. He told her a list of major documents she should digest and sent her a price list, which ran into hundreds of dollars.

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[194] *ref for example TGA regs on disclosure of interests.*

Some Administration officials are forbidden to work in industry for some years after leaving TGA. There was no requirement to report job offers from industry. An inspector or evaluator could be flattered and softened by intimations or offers of employment with the applicant company, which are easy to make as they need not be sincere to be effective. One observer said: 'Most public servants are unaware when they are being compromised; there are good crooks who do it very well. A sponsor can send the public servant hampers and gifts, take them out to lunch, create a nice warm client relationship and the public servant doesn't realise the dangers. The time comes when the sponsor wants to get their application processed quickly, or have inspectors softened and the public servant doesn't see it as compromise to move the application up the queue or tell the inspectors that the sponsor is really a nice guy who wouldn't do anything wrong.' One source said gifts given to TGA staff are not returned but may be put on display. Another said a cash bribe was offered to one officer to fix something for the company.

Some officials are rotated to avoid unduly close contact with the same manufacturer or corporation, as a measure against capture. There is arguably a unique risk of capture for TGA in relation to CSL, arising out of the unusual closeness between the two which began with CSL as part of the Health Department in the twenties. As seen earlier, in CSL's long period as a statutory authority from 1961 to 1994, some Health Department officials were reluctant to intervene because CSL was seen as 'part of the family' and beyond scrutiny, while yet others were highly critical of CSL. Lenience is less likely now, but after the sale, a TGA informant spoke of another potential problem:

> We are starting to get into bed with CSL of course.
> KB What do you mean?
> Well, they are starting to admit that some of the things they did at Parkville [the old production plant] were wrong and they have asked TGAL to help them.
> KB Isn't that a good thing?
> Yes, but I am not sure we have the expertise to help them, with some of things they are asking. I mean, we may not have the clout to get them to do the necessary research to make the changes. I am worried that we could get sucked into another one of their problems.

There is another potential for bias by regulators in dealing with CSL. The company is still the monopoly fractionator of plasma for Australian use. This factor could lead to lenience for fear of 'being responsible'(that is, blamed) for interfering with supplies of a vital product, a consideration which was voiced by some interviewees as having influence on their decisions.

R.63 The Health Department should formulate and enforce uniform principles governing conflicts of interest, corruption and capture. From these agency-wide principles, further detailed guidelines should be

extrapolated for the Therapeutic Goods Administration in respect of its dealings with industry regarding blood and blood products. These guidelines should be available to the public without the need to apply for access under the Freedom of Information Act.

R.64 Anti-corruption compliance systems should be introduced to the Health Department, involving duties to report ethical concerns followed by review and discussion, and resolution of the concerns in writing.

R.65 TGA officials and consultants should disclose on a register all their pecuniary and other relevant interests in corporations and other organisations involved with the manufacture, trialing and supply of blood or blood products or pharmaceuticals and any past interests that could be perceived as a conflict with their current activities, including substantial periods of employment with CSL. The register should be available to the public without charge and without the need to apply for access under Freedom of Information legislation.

9.8 T G A secrecy versus disclosure

Provisions for the disclosure of information by TGA are patchy. The agency is unduly weighted in favour of secrecy and lack of access to information where blood and blood products are concerned.

Inspection reports on blood collections and manufacture are confidential between TGA and the manufacturer. So is information contained in foreign or commercial applications for blood products, and the names of parties sponsoring clinical trials involving drugs that already have general marketing approval. Even the existence of an application for licensing or registration, the reasons for decisions to list or not list, and the fact of disapprovals, are secret. The Secretary may release inspection reports or evaluation findings to various government bodies in Australia and overseas, but not to individuals using the products or their practitioners.

NATA reports to the Health Department are confidential. This became of concern to health consumers and doctors relying on test results from Macquarie Pathology Services when the Canberra Times revealed that Macquarie had gone on practicing while appealing against NATA's report recommending they lose their accreditation due to inadequate staffing.[195] After the media disclosures, Health Minister Laurence asked the department to see if the process could be made more transparent.[196]

9.9 Information charges

Much of the information TGA does release carries a charge, or is obtained by paid subscription. Release of information from the ARTG (Australian Register

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[195] eg *Canberra Times 17.8.94*
[196] *Canberra Times 11.8.94*

of Therapeutic Goods) is subject to fees calculated on same lines as if the request for information were made under the FOIA, unless the request is from sponsors asking about their own products, from other government agencies or deemed to be in the 'public interest'.[197]

9.10Attitude towards external scrutiny

As mentioned in the section on study process, the author spent many months obtaining interviews. She was not permitted to tape what was said when interviewing Official C and said that she felt this compromised her ability to report accurately on matters in discussion, particularly where they were highly technical, as was the case much of the time. Nor was she permitted to interview other officials to elicit their reactions to questions about the effectiveness of the regulations they administer. Lack of time was the constant reason given. Relations with official C were strained for much of the time. However, after official access was denied, the author found the agency's back door open. Numerous officials helped her build an understanding of TGA's complex operations although there is no denying that lack of official access makes the study of TGA's role incomplete. Officials in agencies who deal with the Health Department also gave valuable insights and information about how the agency works, the limits of the therapeutic goods legislation and similar matters.

9.11 Commercial confidentiality versus public interest

Secrecy and denial of access is a severe restriction on public and parliamentary accountability for the principle regulatory mechanisms governing a statutory authority making blood products in the national interest. As far as the author could establish, this secrecy commenced when CSL began processing plasma commercially for foreign countries. The Health Department seems to have then adopted the habit of treating all CSL information as secret. Then Baume criticised the Department for hostility towards industry and told TGA to get along with them. However, there is a world of difference between getting along with industry and taking or deferring to industry's viewpoint on disclosure. The concept of secrecy held by some manufacturers is so extreme that they have tried to prevent the Health Department having access to its own files on prior drug approvals! And Baume didn't acknowledge that some in industry will only get along with government officials while they're getting what they want.

Little evidence came to light during this study of any real attempt to weigh the public interest against commercial confidentiality in considering blood and blood products, despite the public interest rationale behind the policy on national self-sufficiency in blood and the fact that CSL has always had a monopoly on manufacture of Australian blood products. Some officials were unable to speak with reason about the rights of 'non commercial' stakeholders

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[197]*TGA News June 92, no 10.*

and especially about the public interest, a term they have virtually eliminated from their vocabulary.

Documents created by the Therapeutic Goods Administration or in its possession are subject to the Freedom Of Information Act 1982. A request which could affect a third party must be referred to the agency for its consideration under the 'reverse FOI' mechanism. The final decision rests with the Health Department and must take the public interest into account when deciding on disclosure. Given the current mentality of construing the commercial exemption widely and dismissing or ignoring the public interest, requests for blood product manufacturing inspection reports could easily fail in the hands of key senior officers of the Administration.

TGA's attitude to secrecy in this field is untenable. When the Department first began to sit down with a highly secretive pharmaceutical industry three decades ago, the guarantee of secrecy might have been a sensible tactic to allay companies' deep fears about data passing to their competitors. But twelve years after the Freedom of Information Act 1982, when transparency is the government catchcry and the extension of freedom of information to the private sector is under consideration,[198] the TGA's undifferentiating, attitude towards the paramount importance of commercial secrecy in the field of blood products, only serves to intensify the impression that they have been captured by the industry they are supposed to be regulating.

Reports on nursing homes and nursing home pharmacies are not only accessible under the Freedom of Information Act but must be displayed at the entrance of each facility.[199] Red Cross interviewees for this study were quite open with the author about the findings of their own TGA inspections under the Blood Code, warts and all. The Trade Practices Commission has a public register which displays the findings of government inspections. Even nuclear power plants exchange inspection reports with each other internationally. The apparent barrier of commercial secrecy can be easily overcome by deleting material which truly falls within this category. If TGA can't tell the difference, an independent opinion can be taken, without the need to slog it out before the Administrative Appeals Tribunal or in the Federal Court. An independent committee could be appointed for this purpose.

Finally the administration's secrecy is foolish for TGA itself. It stops regulators thinking creatively about solutions to situations that arise, inhibits discussion and communication and contributes to a sense of detachment from the community whose interests it is there to serve. It also gives the Administration such a low profile that personnel receive no public credit for

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198 *Administrative Review Council/Australian Law Reform Commission Review 1994*

199 *per recommendations 26 - 28 in Raising the Standard: Resident Centred Nursing Home Regulation in Australia, Braithwaite, J., Makkai, T., Braithwaite V. and Gibson D.; Department of Health, Housing, Local Government and Community Services, Aged and Community Care Division, No 10, January 1993 AGPS, Canberra*

their work, with consequent morale problems. A secretive Administration cannot demonstrate public accountability nor answer unfair attack. Its low profile can make it virtually invisible to Treasury, Ministers, or parliamentary committees from whom it needs recognition in order to maintain or expand its powers and budget and from the public and consumers who may assist it by reporting breaches of the legislation and in many other ways.

A former TGA official said the Administration's stance towards CSL is to regard them as 'just another manufacturer - though with a public interest component'. If TGA treats CSL as equal with other manufacturers this will be a good thing in regulatory terms and certainly an improvement on the former approach of going gently because CSL was part of the family.

Whether TGA's regulatory powers are enough to safeguard the public interest component, particularly in relation to blood products once they go off the manufacturing site, and especially for materials coming or going from overseas, is doubtful.