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BLOOD SAFETY AND SELF-SUFFICIENCY:
AN AGENDA FOR THE EUROPEAN COMMUNITY

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DISCUSSION DOCUMENT ON
SCREENING TESTS

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1. Background

According to the report on blood safety and self-sufficiency of the Commission of the European Communities,[1] differing testing requirements in the Member States are a hindrance to the free movement of blood and blood products in the European Community and thus an impediment to its self-sufficiency. Council Resolution[2] of 2 June 1995 referred to the implementation of efficient, validated and reliable screening tests as one of the main activities that could be undertaken in working towards a Community blood strategy, reinforcing trust in the safety of the blood transfusion chain, and promoting self-sufficiency.

2. Infectious agents transmissible by blood and blood products

Since the introduction of blood transfusion and blood products administration in human therapy and prophylaxis many decades ago, the transmission of infectious agents (such as certain bacteria, parasites and viruses) by blood and blood products has always been of particular concern. Hepatitis viruses soon came to be recognized as the most significant in accounting for the infectious diseases which occasionally develop following blood transfusion or the administration of plasma-derived products (mainly coagulation factors). More recently, the dramatic experience of the AIDS epidemic and its relevance for transfusion recipients and haemophilia patients further increased the need for safer blood components and plasma-derived products.

Characterization of the causative agents, both for hepatitis (viruses A to G) and AIDS [HIV (human immunodeficiency virus) -1 and HIV-2] has considerably advanced over the last decade and the relevance of HBV (hepatitis B virus), HCV (hepatitis C virus) and HIV for the safety of blood components and plasma-derived products has been well established. More recently, HAV (hepatitis A virus) has gained prominence together with Parvovirus B19, a non-enveloped DNA virus known to be a potential blood contaminant. The possibility of infection by hepatitis G virus(es) is also cause for concern.

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[1] Communication from the Commission on Blood safety and self-sufficiency in the European Community. [COM(94) 652 final]. Brussels, 21.12.1994

[2] Council Resolution of 2 June 1995 on blood safety and self-sufficiency in the Community. (95/C 164/01). O.J. N° C 164. 30.6.95. p.1

Other viruses such as HTLV-I (human T-cell leukaemia virus type I) and the herpes viruses [e.g. cytomegalovirus (CMV)] also have aroused apprehension particularly as regards blood components.

AIDS became a worldwide tragedy at a period when many considered the threat of infectious diseases a thing of the past, amenable to control by preventive measures, vaccines and antibiotics. The extent and the reality of the AIDS epidemic have triggered the re-examination of conditions that may lead to the appearance of new diseases or to outbreaks of old ones. The concern about future threats is particularly intense among ongoing recipients of blood and plasma-derived products. Justifiably, they are concerned by the possibility that an unknown transmissible agent may cause as much devastation in the future as HIV did in the early 1980s. Table I lists some infections potentially associated with transfusion of blood and plasma-derived products. Even though the greater part of these infections mostly affect persons in the developing countries, the extended movement of people and products throughout the world gives rise to additional concerns for the European Community.

3. Required tests

The "Guide to the Preparation, use and quality assurance of blood components" of the Council of Europe,[3] recommends the following screening tests for infectious markers:

- Serological test for syphilis
- Tests for viral hepatitis:
  - HBsAg
  - anti-HCV
  - serum transaminase determination (indirect test in use in some Member States)
- Tests for AIDS
- Tests for other infectious agents:
  - anti-HTLV-I and II (used in some Member States)
- Screening methods for several other infectious diseases (i.e. malaria, Chagas diseases and bacterial diseases) are under development.

[3] Council of Europe Press. 1995. 196p.

4. Remaining risks

The possibility of infectiousness of blood components and plasma-derived products not treated with a method of virus inactivation/removal may still remain even after accurate testing. Relevant risks are presented in the "Richtlinien zur Blutgruppenbestimmung und Bluttransfusion", issued in 1992 by the Bundesgesundheitsamt in Germany. The major points of these guidelines have been taken into account in this report.

The major risk factors are human viruses, which replicate in haematopoietic cells or B- and T-lymphocytes, or come from other tissues, such as HIV, HBV, HCV and other non-A, non-B hepatitis viruses. The infections may result in life-threatening or fatal diseases.

No diagnostic/screening test can guarantee 100% detection. Therefore a small number of infectious blood donations escape detection. This is because infected donors may not have developed detectable concentrations and may not have clinical symptoms.

The cases of HIV-1-antibody-positive patients who were infected by non-inactivated blood preparations (whole blood, red cells, cryoprecipitate, frozen fresh plasma, etc.) collected from donors who were HIV-1-antibody-negative at the time of donation (in the so-called infectious window period) show that unrecognized contaminated donations have been administered in the past. The actual number of blood and plasma donations from unrecognized HIV-1 infected donors entering the supply of blood/plasma products every year cannot be stated exactly.

Among the various types of hepatitis transmitted by these viruses, it is hepatitis-Non-A-Non-B that is most frequently observed post-transfusion. The actual risk of hepatitis-Non-A-Non-B transmission by transfusion is not known precisely not withstanding the introduction of anti-HCV testing as part of donation screening.

The majority of hepatitis-Non-A-Non-B cases is caused by the hepatitis C virus. According to estimates made in 1991, HCV caused 60 % to more than 90 % of the post-transfusion cases detected in the USA, Europe and Japan prior to the introduction of anti-HCV testing.

For the aforementioned reasons, it appears desirable to further improve the donor selection process. A complementary approach is represented by the implementation of other measures such as quarantine and virus inactivation methods.

5. New tests

The desire to narrow the infectious window (diagnostic gap) has given rise to considerations of adding to blood donor screening programmes assays for the direct detection of HIV p24 antigen or HIV nucleic acid (DNA and RNA) and HCV nucleic acid (RNA). Additional testing for p24 antigen was recommended as an *ad interim* measure by the Food and Drug Administration (FDA) of the United States in 1995, but has not been followed by the European Community. The projected cost of p24 antigen screening in the USA has been estimated at USD 75 to 100 million per year with the expected annual result of perhaps the prevention of infection of 10 recipients. This translates into nearly USD 10 million per HIV transmission prevented[4].

Genomic amplification techniques [(GAT), e.g. Polymerase Chain Reaction (PCR)], appear to have exceptional sensitivity and specificity for the detection of viral nucleic acids even though they have not yet been fully standardised for diagnostic use. The remaining risk to blood transfusion and blood product recipients could possibly be reduced by this method and adoption of these techniques in blood-donor screening programmes has been recently considered in the Community. In the USA, although GAT tests could narrow the window in the case of HIV infection to a slightly greater extent than p24 antigen, these assays are not yet considered practical for large scale screening. For blood products, where valid removal/inactivation steps are absent, nucleic acid amplification tests for HCV RNA in plasma pools (European Community) or in finished products (USA) have been requested, both by the FDA, and the CPMP for intramuscular immunoglobulins not subjected to a viral inactivation step.

[4] M.P. Busch and P. Alter. Transfusion 1995, 35.536

6. Current licensing situation

Licensing procedures for diagnostic kits for viral markers in blood and blood products needs to take into account three major factors:

(i) screening of viral markers greatly contributes to the viral safety of blood and blood products, which is an essential and undisputable requirement for such products. Therefore, sensitivity, specificity and reproducibility of the test are essential in this respect;

(ii) wide variance in the methodologies which can be used for such screening - some tests are intended to be true screening tests, others are suggested for use as confirmatory tests; and

(iii) rapid obsolescence since scientific progress in the field results in a continuous improvement of the existing kits grouped in sequences of first, second, third, etc. generation tests.

These factors are all inter-related and pose a number of serious difficulties for the screening of blood, plasma and blood products. Strict attention, therefore, needs to be given to the particular problems associated with diagnostic kits used for this purpose. Negotiations on a relevant European Community directive on *in vitro* diagnostics[5] are underway but implementation is unlikely before 1998 at the earliest.

The present situation with respect to licensing and selection of screening kits in the European Community, which is summarised in Table II, shows that different evaluation procedures for test kits, ranging from no control to batch release testing, are in place in the different Member States. Moreover, this diversity is accentuated by the fact that plasma and plasma-

[5] Proposal for a European Parliament and Council Directive on *in vitro* diagnostic medical devices. (95/C 172/02) O.J. N° C 172, 7.7.95, p.21.

derived products are imported from the USA where different evaluation procedures may be used.

7. Information on test kits used

A requirement for information on test kits is in place only for medicinal products derived from blood and plasma and is set out in the "Contribution to Part II of the Structure of the Dossier for Application for Marketing Authorizations: Control of Starting Materials for the Production of Blood Derivatives". Moreover, the Biotechnology Working Party (BWP) of the Committee for Proprietary Medicinal Products (CPMP) of the European Medicines Evaluation Agency (EMEA) has recognized the need for a revision of the guidelines on "Medicinal Products derived from Human Blood and Plasma" to include the information required on test kits.

8. Introduction of new test kits

Currently, when a new test kit is introduced, the manufacturer will provide its own evaluation of the kit's performance. An independent laboratory from a Member State may perform its own assessment. The end users may carry out further studies and may run the test in parallel with another before its wider introduction.

For plasma intended to be used for fractionation, it is important that the introduction of improved state-of-the-art tests is not impeded by the regulatory process for Variations to Marketing Authorizations. Introduction of new tests should be dealt with as a notification rather than a variation where the test kit has been independently evaluated to the satisfaction of the national authority in the country where the blood/plasma is collected.

It is the intention of the BWP to establish a list of currently licensed tests and tests that have been withdrawn in Member States. This will be an internal list for the use of national regulatory authorities when reviewing information provided in relation to Marketing Authorizations for plasma-derived products. The EMEA has proposed to the Food and Drug Administration (FDA) an exchange of such information. It is difficult in some cases to

identify identical test kits because of differences in their brand names on different markets. The EMEA has sought the assistance of the European Diagnostic Manufacturers Association (EDMA) in compiling a list of test kits; identifying in which countries of the European Community and the USA they are marketed, indicating the brand name used in each market; and introducing a unique identification code for identical kits regardless of brand name.

A similar approach should be agreed for the test kits used for the screening of blood donations intended for blood and blood component transfusions.

9. Problems or difficulties with test kits

Currently, decisions on the suitability of test kits are taken at national levels with no common source for collating or referring to relevant information. As a consequence, the CPMP - BWP is compiling a list of licensed tests and those that have been withdrawn. A Community-wide classification system clearly identifying test kits is required. Such a system should require a unique code for each test kit and for any one that is modified by the manufacturer in a way that affects its performance characteristics.

10. Working standards for use with test kits

The level of reactivity of "positive control" samples supplied with test kits varies considerably. Criteria for scoring a sample as positive also vary from kit to kit. The Blood Transfusion Service of the United Kingdom identified the need for working standards relevant to the testing of donations that could be used with any test kit to ensure that an adequate level of sensitivity is being achieved with each series of tests. Responding to this need, the National Institute for Biological Standards and Control (NIBSC) prepared a British Working Standard for HBsAg for use in the UK Blood Transfusion Service. This material, which contains 0.5 IU/ml HBsAg, serves as a "go/no-go" standard with all laboratories required to detect this material in each test for it to be considered valid. The inclusion of this material, and a lower level monitor sample, gives added assurance that assays are of a maximum level of sensitivity. NIBSC is developing similar standards for anti-HCV and anti-HIV. Development

of such working standards will give added assurance that assays are performing satisfactorily on a routine basis in the hands of the testing laboratories.

11. Testing required when a kit is modified

Modifications to a test kit can affect the performance of the tests. Unfortunately, test kit manufacturers do not always inform users of such modifications. The *in vitro* devices directive, however, will require, if adopted, that where modifications affect performance beyond certain levels, the manufacturer will have to bring this to the attention of the notified body for review. The directive, therefore, will tighten up conditions prevailing in this area.

In the meantime, manufacturers should be required to inform users when kits have been modified. There might also be a need to provide guidance on what testing is necessary when test kits are modified to check that performance has not been adversely affected.

12. The proposed directive on *in vitro* diagnostic medical devices

The BWP is currently discussing appropriate criteria for the evaluation of test kits for the screening of blood donors who are providing material intended for fractionation. The following issues have been identified:

- There is a need to ensure that only tests of suitable sensitivity and specificity are used. This is compatible with the new approach directive that is proposed;

- There is a need for a scientific meeting of European Community experts in the field to discuss appropriate criteria for the evaluation of these kits;

- Any examination of appropriate criteria for the evaluation of test kits needs to consider the following:

  (i) The need for and feasibility of establishing standard sample sets of sera including sera which are difficult to identify and samples which show evidence of seroconversion;

  (ii) The need to establish standard criteria that a new test kit must meet to be considered suitable for its intended purpose;

  (iii) The importance of regular re-evaluation of test kits;

  (iv) Whether batch testing of kits by an independent body is necessary; and

  (v) The evaluation needed when a test kit is modified.

13. Conclusions and recommendations

(i) To ensure the safety of blood and plasma-derived products, tests used to screen blood/plasma donations for markers of viral infection must be reliable i.e. sensitive, specific and of good batch to batch consistency. It is critical that these tests are of the highest available standard because they are used on a single occasion to identify and reject virally contaminated donations. Any failure in these tests is a serious public health issue.

(ii) Many European Community Member States have independent evaluation systems for these test kits because of their importance to public health. These are national systems which differ in their legal basis and detailed operation but have many elements in common.

(iii) A harmonized European Community evaluation system for these kits based on sound scientific principles is desirable on grounds of safety and self-sufficiency. It is

essential that any new system combines best practices for current evaluation systems and that there is no reduction in safety standards in this highly sensitive area.

(iv) The key elements of a harmonised evaluation system and control should include:

- A thorough, independent, objective evaluation, including testing;
- A system that does not cause undue delays to the entry of improved products on to the market;
- Agreed standard criteria for the evaluation of new and modified test kits;
- Evaluation of performance against sample sets of sera that have sero converted;
- Evaluation of suitability of tests in the in-use situation;
- Independent batch release of kits;
- Monitoring of performance of test kits in-use, including a "vigilance" information network and a rapid alert system; and
- Regular re-evaluation of performance of test kits at intervals appropriate to the speed of changes in the technology.

(v) Kits used to test blood/plasma donations for viral markers will fall within Annex 2 of the proposed directive on "*In Vitro* Diagnostic Medical Devices". It is essential that the future legal framework for the control of these test kits provides an independent, scientific robust evaluation for the protection of public health.