DRAFT

BATCH RELEASE PROVISIONS OF DIRECTIVES 89/342 AND 89/381
NOTE OF A MEETING HELD AT 10.00AM ON 30 OCTOBER 1992

Present: Dr J Purves, Dr M Kavanagh, Mr R Cienciala, Mr B Dyson (MCA); Dr D Salisbury, Dr A Rejman, Mr J Canavan (DH); Dr G Schild, Dr R Stewart, Dr P Minor, Dr T Barrowcliffe, Dr M Corbel (NIBSC)

Background

The effect of Article 4.3 of EC Directives 89/342 and 89/381 is to permit batch testing of, respectively, immunologicals and medicinal products derived from blood only where another Member State has not previously examined the batch in question.

2. Mr Cienciala explained that the EC deadline for implementation of the Directives had been 1 January 1992; the UK had implemented them in stages over the course of the year. There were now only a few outstanding, unimplemented provisions, which included those concerning batch release (Article 4.3). The EC Commission had already made clear its concern over the delays in UK implementation, and MCA now had to put clear advice to Ministers as to how the batch release provisions should be implemented, or provide strongly argued reasons for deferring implementation.

European developments

3. In January 1992, EC Member States discussed procedures for the batch release of influenza vaccines. This was followed in September by the first meeting of a drafting group established by the CPMP Biotechnology Working Party to agree a European batch release procedure (EBRP). Dr Purves noted that these discussions had revealed a variety of attitudes and approaches to batch testing:

a. the UK insisted that there should be a common batch release procedure throughout the EC before Member States should be required to recognise the results of tests carried out in other Member States;

b. Germany, France, Belgium and the Netherlands were prepared to recognise the results of other Member States' batch tests;

c. Denmark did not undertake batch release;

d. the Commission felt that sufficient progress had been made for Member States to accept mutual recognition as of 1 January 1993.

Requirements for EBRP

4. It was agreed that the main elements of a common EC batch release procedure should be:

a. a common administrative process for batch release;

b. an inventory to identify products which came under the control of 89/342 and 89/381, and a set of agreed tests that should be undertaken for these products;

c. a system of accreditation for laboratories undertaking batch testing (to ensure, inter alia, that they were wholly independent of marketing interests).

5. In addition:

a. the UK should seek to insist on testing procedures which it considered essential, notwithstanding the possibility that other laboratories might be unable or unwilling to carry them out - the procedures should not simply reflect the lowest common denominator of European standards;

b. there should be a mechanism whereby, as testing procedures improved, laboratories were obliged to alter their procedures accordingly;

c. persons responsible for marketing batch-released products should be required to notify the testing authority of any other countries to which the batch was to be distributed, and the testing authority should be required to supply the appropriate national control authority (NCA) with a copy of the release certificate;

d. NCAs should have access to the results of other Member States' batch tests before the batch in question was released in their country.

6. The procedure should also be agreed with the pharmaceutical industry.

Vaccines

7. As far as vaccines were concerned, it was agreed that an EBRP was essential and that Ministers should be advised not to implement the batch testing provisions of 89/342 until such a procedure had been established. The main reasons were:

a. there was insufficient information about other Member States' batch release procedures for the UK to be able to have confidence in their effectiveness, as had been shown by the experience of attempting to agree EC tests for influenza vaccines and NIBSC's attempts to compare the UK's testing procedures with those of other Member States;

b. the significance that vaccines had for the security of public health, and the risks involved in accepting batch testing carried out in other Member States without guarantees that the safety and efficacy of the batches would be adequately proven;

c. Directive 89/342 allowed a vaccine which was licensed in the UK, but not batch released, to be sent to a laboratory elsewhere in the EC, batch released and, since licensing criteria were not dependent on batch testing criteria, re-imported and marketed in the UK.

Blood products

8. Dr Rejman argued that, as far as the need for batch testing was concerned, blood products should be considered completely separately from vaccines:

a. safety: contamination could most effectively be prevented not by batch testing, but by improvements in screening procedures;

b. efficacy: the only way of adequately testing efficacy was by means of clinical trials; batch testing could confirm potency, but not efficacy;

c. although the individual components of a pool might be different, batch-to-batch consistency was more likely in blood products than in vaccines, particularly where a product was manufactured in the same factory, using the same methodology, over a number of years.

For these reasons, Dr Rejman argued that the more effective way of ensuring the safety and efficacy of blood products would be to carry out tests as part of the product licensing process and apply 'spot checks' thereafter (product monitoring). This would also be more cost-effective - the Directive required that Member States which wished to apply batch testing examine each batch produced.

9. HC(M) would not be opposed in principle to an EBRP for blood products, if it incorporated the elements set out above (see paras.4-6). However, other EC countries were unconvinced by the need for batch release of blood products. In view of the above considerations, the UK should not therefore press for a European-wide requirement.

10. Furthermore, the Benelux countries and France were considering pressing for amendments to EC legislation to ban Member States from importing blood products (whether from other Member States or third countries), which would make Article 4.3 of 89/381 redundant.

11. NIBSC argued that there was a good case for batch release of blood products, on the following grounds:

a. there was not necessarily greater batch-to-batch consistency in blood products because:

i. manufacturers started with entirely heterogeneous starting materials;

ii. new infectious agents were emerging all the time;

b. the risk of viral contamination in blood products (Factor VIII has recently been shown to have transmitted Hepatitis A in four EC countries);

c. the inadequacy of selective product monitoring in terms of gaining expertise and being able to examine trends over a number of years;

d. the contribution made by NIBSC's current procedures in terms of deterring manufacturers from cutting corners;

e. evidence that EC countries without batch release (eg Denmark) became dumping grounds for products unlikely to be released elsewhere;

f. the difficulties associated with withdrawing batches from the market where contaminants were discovered in the course of product monitoring;

g. the significant financial advantages of carrying out potency assays on batches.

Given these arguments for batch testing blood products, there was then a strong case (comparable to that for vaccines) for not recognising other Member States' batch testing. In particular, there were safety risks other than contamination by HIV or Hepatitis that were not adequately checked for by other Member States.

12. Dr Kavanagh suggested that, for <u>some</u> blood products, there was little to be achieved by batch testing; and said that MCA would like the medicines testing scheme (product monitoring) extended to blood products. The UK should, however, seek to apply batch release to blood products for which there was strong evidence of batch-to-batch variation.

<u>Product monitoring</u>

13. Dr Purves raised the subject of products for which the UK would not be permitted to apply batch testing under EC law, but for which some form of (post-marketing) product monitoring might be needed, eg insulin, hormones etc (in particular, products which could vary according to the manufacturing process and for which it was difficult to write a pharmacopeia monograph).

14. It was agreed that there should be a separate meeting to consider what products should be subject to product monitoring and how product monitoring might operate.

15. In this context, Dr Schild pointed out that the EC system of classification was often unhelpful: although a hormone might be made in the same way as a vaccine, one was subject to batch testing and the other was not. The UK should raise this issue at the CPMP Biotechnology Working Party.

Conclusion

16. Vaccines - it was agreed that Ministers should be advised not to implement Article 4.3 of 89/342 in view of the possible risks to public health and safety.

17. Blood products - NIBSC agreed to provide:

i. a list of those blood products for which it considered batch release essential;

ii. information about which tests should be applied, and how often;

iii. instances of where batch release per se had revealed shortcomings in the safety or efficacy of a blood product which would have otherwise been marketed.

18. MCA would prepare a submission to Ministers. In order to convince senior officials and Ministers, this would have to explain:

i. why the UK was alone in having concerns over Article 4.3 (NB: virtually all vaccines licensed in France and the Netherlands were manufactured domestically - it was therefore academic whether or not they recognised other Member States' batch tests);

ii. why the UK had agreed to Article 4.3 when it was negotiated in 1988 and why advice not to implement it was being put to Ministers at such a late stage (ie details of UK's persistent attempts to press for an EBRP);

iii. the harm likely to be caused by implementation of Article 4.3, and its likely extent (giving examples);

iv. the likelihood of the Commission bringing successful infraction proceedings against the UK;

v. the likelihood of a company challenging the UK for requiring it to submit batches tested elsewhere in the EC;

vi. at what point the UK would be able to implement Article 4.3 (when EBRP agreed? when other Member States applying it satisfactorily?).