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The EU/EEA Network for Official Control Authority Batch Release of Biologicals for Human Use

Catherine Milne, *Karl Heinz Buchheit* and *Jean Marc Spieser* explain the authorities' procedures for batch testing vaccines, blood and plasma derivatives.

The control of medicinal products in the EU/EEA has two main goals: the protection of public health and the free movement of products. Specifications for medicinal products are defined in the product's marketing authorisation dossier and should comply with the monographs of the *European Pharmacopoeia*. However, due to the inherent variability either in the production process or in their nature, biological medicinal products (vaccines and human blood and plasma derivatives) may require special attention prior to release on the market on a batch to batch level. This paper discusses post-licensing regulatory controls that can be applied to batches of these types of products in the EU/EEA.

Biological products attract regulatory measures on a batch by batch basis

Legal background – Official control authority batch release in the EU/EEA

As part of the regulation of biological medicinal products, according to Article 4.3 of Council Directive 89/342/EEC (vaccines for human use) and Article 4.3 of Council Directive 89/381/EEC (human blood and plasma derivatives)[1] now codified in Article 114 of Council Directive 2001/83/EC[2], Member State laboratories may, but are not required to, request samples of a batch of an immunological medicinal product or a medicinal product derived from human blood or plasma before it is marketed, and perform an examination of the product's quality and safety through appropriate additional and specific testing by competent authorities.

Official laboratories can request samples to test prior to market release of a batch...

When the results of testing are satisfactory, the Competent Authority issues a batch release certificate. This process is referred to as Official Control Authority Batch Release (OCABR) and involves analytical control and document review, which are performed in addition to the controls carried out by the manufacturer.

In order to ensure the free movement of goods, the directives also state that the Official Control Authority Batch Release procedure can only be performed if the batch in question has not already been previously examined by another Member State. Thus Member States are required to recognise Official Control Authority Batch Release carried out in any other Member State without performing additional tests or controls. This however, does not preclude any Member State from performing post-market testing on any batch as it sees fit.

...but they cannot duplicate testing already done by another Member State

In practice this means that when a manufacturer intends to place a batch of a product on the market in the EU/EEA, if Official Control Authority Batch Release is required by a Member State, the manufacturer must first send samples from the batch, along with detailed production protocols specifying the results of in-process controls, to an Official Medicines Control Laboratory (OMCL) for Official Control Authority Batch Release. The manufacturer should submit a batch to only one OMCL. The OMCL will then perform analytical tests and document controls and if the batch is acceptable, provide the manufacturer with an EU/EEA Official Control Authority Batch Release Certificate. This certificate will be recognised by all other Member States requiring OCABR. A Member State is not obliged to require Official Control Authority Batch Release for a batch of product however if they do, a pre-existing certificate of OCABR issued by another Member State must be recognised.

Network activities of official laboratories involved in control authority batch release

The batch release procedure represents an additional tool to ensure that only high quality products are placed on the market. In order for users of the system to have confidence when applying the directives quoted above, a transparent system of mutual recognition is essential. To that end, in 1992 the European Commission prepared guideline III/3589/92 for implementing the system and specific activities related to Official Control Authority Batch Release were established within the

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European network of Official Medicines Control Laboratories in 1995[3]. It should be recalled that at the request of the Commission of European Communities, the European Directorate for the Quality of Medicines (EDQM) of the Council of Europe has taken the responsibility of setting up and coordinating this network and developing and maintaining appropriate procedures and guidelines. As part of this role EDQM acts as the secretariat for OCABR network activities.

An advisory group of four MS representatives oversees OCABR operations across 17 countries

The OCABR network presently consists of 17 Member States from the EU/EEA (*see* Table 1). It is overseen by an advisory group consisting of four representatives from different Member States (two for blood and two for vaccines). Two positions in the advisory group (one each for blood and vaccines) are chosen, on a rotational basis, for re-election by the members of the network every two years. Representatives for vaccines and for human blood and plasma derivatives meet at regular intervals to elaborate common procedures and guidelines, which promote a harmonised approach to batch release in Europe and contribute to creating mutual confidence. An annual meeting is held for both vaccine and human blood and plasma derivatives to bring together all representatives for an update of yearly activities and to provide an open forum for discussion of issues concerning the network. These meetings also officially endorse all reference documents (such as procedures, guidelines and position papers).

Table 1. Member States involved in EU/EEA Official Control Authority Batch Release

EU Member States		EEA Member States
Austria	Italy	Iceland
Belgium	Luxembourg	Norway
Denmark	Netherlands	
Finland	Portugal	
France	Spain	
Germany	Sweden	
Greece	United Kingdom	
Ireland		

Open meetings are held between manufacturers and regulators

In addition to the interaction within the network, which is held in a confidential environment, manufacturers and other interested parties are also encouraged to provide their input. An open meeting between manufacturers and the OMCL network takes place regularly whenever needed (at least once a year) and meetings on specific issues are held as required. International symposia on topics such as the evolving field of biologicals[4] and tetanus vaccines for human use[5] are examples of opportunities for exchange and interaction with the wider scientific community. All product specific guidelines (*see* below) are also reviewed by manufacturers and external experts, before finalisation by the network, thus facilitating the development of a system which addresses the needs of all its users in a transparent manner.

Administrative procedure for the network

The core document of the OCABR network is the *EC Administrative Procedure for Official Control Authority Batch Release*[6]. This document was elaborated from the basis of the previous guideline III/3589/92 published by the European Commission in 1994[3]. It was finalised by the OCABR network after external consultation and was finally adopted in September 1998 by the European Commission (Pharmaceutical Committee) and has been in force since April 1999. The document outlines the legal framework, purpose, principles and procedures related to official control authority batch release in the EU/EEA. A series of annexes provides templates for essential support documentation for both OMCLs and manufacturers for use in the batch release process. Annexes III and IV were updated and approved by the network in 2001 (*see* Table 2).

The guideline is intended for use primarily by OMCLs in Member States when implementing OCABR at a national level to facilitate them meeting the requirements of Article 4.3 of Council Directive 89/342/EEC and Article 4.3 of 89/381/EEC[1], as outlined above. It is also for use by marketing authorisation holders (MAH) and provides guidance for the communication between MAHs and OMCLs involved in batch release.

The procedure describes the steps involved in the OCABR process, which begins with a Member State making initial contact with an MAH to indicate a need for an EU OCABR certificate for a product. The manufacturer must then submit samples relevant to the batch to be released, along with production and control protocols, to an OMCL of his choice within the EU, which will then act as the testing authority.

Table 2. Annexes available in the EC Administrative Procedure for Official Control Authority Batch Release[7]

Annex	Subject
I	Template for a model letter from a competent authority to the marketing authorisation holder as regards official control authority batch release within the EU
IIA	EU official control authority batch release certificate for immunological products (template)
IIB	EU official control authority batch release certificate for medicinal products derived from human blood or plasma (template)
IIC	EU official control authority batch release certificate of approval for monovalent bulk of poliomyelitis vaccine (oral) (template)
IID	EU official control authority batch release certificate of approval for plasma pools (template)
IIE	EU administrative procedure for official control authority batch release general model for non-compliance/failure (template)
III *updated in 2001*	Contact persons for results and questions concerning EU/EEA official control authority batch release
IV *updated in 2001*	Model for manufacturers of a marketing information form (template)
V	Model format and content of annual batch release reports (template)

All OCABR procedures are clearly documented and publicly accessible

The testing laboratory will then perform a critical evaluation of the manufacturer's production and control protocols and carry out a series of analytical tests as outlined in the guideline for that product and elaborated by the network (*see* below). The analysis by the OMCL should be completed within 60 days and should be performed under a quality assurance system which moves progressively toward the International Organisation for Standardisation's standard ISO 17025. The testing laboratory may perform additional tests (referred to as phase two testing) if any of a number of criteria apply (e.g. change in manufacturing site, or unexpected variability in the results of quality control by the manufacturer); these are also listed in the procedure. All OMCLs within the network will be informed immediately through a rapid information system that phase two testing has been initiated by one of its Member States and it should consequently be carried out systematically.

If a batch is satisfactory for release, the OMCL prepares an OCABR certificate, which is issued to the manufacturer. In the case of products derived from human blood or plasma a certificate indicating approval of the plasma pool(s) used must also be issued.

Certificates issued after official batch testing must be submitted to authorities in each market

The MAH must ensure a copy of the certificate is provided to the competent authority in the Member State(s) where the batch will be marketed. The OCABR certificate must also be accompanied by a marketing information form, which confirms the identity of the batch and ensures that the details of the marketing authorisation are met for the Member State in question.

In the case of non-compliance, the batch is given a certificate of non-compliance and may not be placed on the market. Ultimately a failing batch should be destroyed. On the occasion that a batch fails OCABR, all members of the OCABR network are rapidly informed contemporaneously through a specific procedure.

Information exchange

One of the keys to success of the OCABR network is the free exchange of information between Member States. Part of this involves the preparation by each Member State of an annual report of batch release activity that is distributed confidentially within the network. The annual reports should include information on batches released and rejected, specifications and methods used in evaluation of batches, summary tables, trend analyses, comparisons with manufacturer's results, discussion of any difficulties encountered with assays, technical development work and progress made in developing quality assurance systems.

Annual reports document activity of each official laboratory, although not made public

In addition to the annual reports and the various meetings mentioned above which provide an open forum for discussion, there is an emphasis on rapid communication of issues relevant to the safety and efficacy of the products, as they arise. These exchanges of information are provided for by Article 30 of Council Directive 75/319/EEC [Article 122 of Council Directive 2001/83/EC][2].

All information exchange concerning details of specific products and batches is confidential within the network. The exchanges are supported by a number of templates, including those provided as annexes to the EC procedure (*see* Table 2), which harmonise presentation and ensure that all necessary information is provided. Also included among the annexes is a list of contact details for official representatives for OCABR for vaccines and human blood and plasma derivatives for each Member State.

Development of product and method specific guidelines

In addition to the administrative procedure, a series of product specific guidelines has been elaborated by panels of experts from within the OMCL network[6]. The guidelines have been elaborated to ensure a common approach to testing in the OMCLs across the EU/EEA and thus to promote mutual recognition and confidence among the Member States. They also provide an element of transparency for all users of the system.

Official laboratory tests are selected from those in the marketing authorisation dossier

The guidelines are adopted by the OCABR network only after consultation within the network and public enquiry involving interested parties. The guidelines take into account current methodology and state-of-the-art techniques for control of biological medicinal products and are regularly updated to reflect current specifications in *European Pharmacopoeia* monographs and marketing authorisations and the most appropriate and up-to-date methodologies.

For each product type the guidelines indicate the material that should be provided by the manufacturer to the OMCL in cases where OCABR is required, and outline the tests that should be performed by the OMCL to evaluate the batch in question. The guidelines also include a model template for protocol submission by the manufacturer.

The tests performed by OMCLs as part of OCABR are chosen from among the tests performed by the manufacturer in accordance with the marketing authorisation dossier for the product. OMCLs agree on a subset of tests which are most likely to benefit from a second independent re-testing and as such provide added value in the evaluation of parameters indicating quality and safety for the batch in question.

The model template promotes a harmonised presentation of information and helps to ensure that all relevant details are included. The model comprises specifications on the identity of the batch and outlines the information concerning quality control that is required at each stage of the production process. While the guidelines provide a detailed template, including the lists of results required for thorough evaluation by the OMCL, they are considered model templates and the protocol submitted by the manufacturer for an individual product may differ in detail. They must however, contain all the relevant information demonstrating compliance with the marketing authorisation and the *European Pharmacopoeia*.

Thirty seven new and revised product or method specific guidelines are in force as of September 2001; five guidelines for human blood and plasma derivatives (*see* Table 3) and thirty two for vaccines (*see* Table 4). These guidelines are presented in a booklet[6], which is available on request from the EDQM and can also be downloaded from the EDQM website http://www.pheur.org for direct use as templates.

Product-specific guidelines aid consistency between testing laboratories...

Table 3. Product Specific Guidelines for Humn Blood and Plasma Derivatives, EU

Guideline for Official Control Authority Batch Release of:	Status as of 2001
Clotting factor concentrates, plasma inhibitor concentrates and fibrin sealants	Revised
Human albumin	Revised
Human immunoglobulin	Revised
Solvent-detergent (SD) plasma	New
Validation of nucleic acid amplification technology (NAT) for the detection of hepatitis C virus (HCV) in plasma pools	Unchanged

Table 4. Product Specific Guidelines for Vaccines, EU

Guideline for Official Control Authority Batch Release of:	Status as of 2001
BCG vaccine	Revised
Diphtheria and tetanus vaccine (adsorbed)	New
Diphtheria, tetanus and hepatitis B (rDNA) combined vaccine (adsorbed)	New
Diphtheria, tetanus and pertussis (acellular component) combined vaccine (adsorbed)	New
Diphtheria, tetanus and pertussis (whole cell) combined vaccine (adsorbed)	Revised
Diphtheria, tetanus and poliomyelitis (inactivated) combined vaccine (adsorbed)	New
Diphtheria, tetanus, pertussis (acellular component) and haemophilus type b conjugate combined vaccine (adsorbed)	New
Diphtheria, tetanus, pertussis (acellular component) and hepatitis B (rDNA) combined vaccine (adsorbed)	New
Diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated) and haemophilus type b conjugate combined vaccine (adsorbed)	New
Diphtheria, tetanus , pertussis (acellular component), poliomyelitis (inactivated) combined vaccine (adsorbed)	New
Diphtheria, tetanus, pertussis (whole cell) and poliomyelitis (inactivated) combined vaccine (adsorbed)	New
Diphtheria, tetanus, pertussis (whole cell), poliomyelitis (inactivated) and haemophilus type b conjugate combined vaccine (adsorbed)	New
Haemophilus type b conjugate and hepatitis B (rDNA) combined vaccine	New
Haemophilus type b conjugate vaccine	Revised
Hepatitis A (inactivated) and hepatitis B (rDNA) combined vaccine (adsorbed)	Revised
Hepatitis A (inactivated) and typhoid polysaccharide combined vaccine (adsorbed)	New
Hepatitis A vaccine (inactivated, adsorbed)	Revised
Hepatitis A (virosomal) vaccine	New
Hepatitis B (rDNA) vaccine	Revised
Influenza vaccine	Revised
Measles, mumps and/or rubella component combined vaccine	Revised
Measles vaccine	Revised
Meningococcal polysaccharide vaccine	Revised
Mumps vaccine	Revised
Pertussis vaccine (acellular component, adsorbed)	Revised
Pneumococcal polysaccharide vaccine	Revised
Poliomyelitis vaccine (inactivated)	Revised
Rabies vaccine	Revised
Rubella vaccine	Revised
Tick-borne encephalitis (TBE) vaccine	New
Typhoid polysaccharide vaccine	Revised
Typhoid vaccine (live - strain ty21a, oral)	New

...and are updated frequently to keep pace with new techniques

Technical competence and traceability

The quality standards under which OMCLs perform Official Control Authority Batch Release are specified in the EC administrative procedure. A Quality Assurance (QA) system has been implemented as part of a support system for the network, in an intensified effort to further improve mutual confidence and assure an excellent level of technical competence and traceability within the network in general. The programme, run under the aegis of the EDQM, is based on peer review, thus allowing a sharing of workload and costs. Participation is voluntary. The programme consists of two levels of evaluation: mutual joint visits (MJV) and mutual joint audits (MJA). Both are performed by trained auditors, selected from a panel within the network, who volunteer their time. The objective of MJVs is to give advice and to help OMCLs build a sound QA system based on the standard ISO 17025 (and previously European Norm EN 45001). They are limited to a total of one or two visits per OMCL after which the OMCL will enter into the MJA program. MJAs are for laboratories with a QA system in place and involve a full audit including follow up of corrective actions where appropriate. The QA programme began in 1999 and has been very well received, with the number of participating laboratories increasing every year.

Participation by official laboratories in the QA programme is voluntary

As another means to ensure technical competence within the network, OMCLs participate regularly in Proficiency Testing Studies (PTS). A series of PTSs on basic methods of analysis are organised by Division IV of the EDQM every year in order to help OMCLs evaluate their technical competence. OMCL participation is voluntary and the programme has been well received. Recent subjects for Proficiency Testing Studies include molecular size distribution for haemophilus type b conjugate vaccine and analysis of hepatitis A immunoglobulin using ELISA. A series of two PTSs per year evaluating the detection of hepatitis C virus content in plasma pools by Nucleic Acid Amplification Techniques (NAT) have also proved successful.

Benefits

Smooth operation of OCABR system is due to high level of interaction between MSs

The Official Control Authority Batch Release network has steadily evolved over the ten years since its inception and has reached a level of maturity that is reflected in the extent of cooperation and mutual trust between Member States. Member States can rely on the support and experience of their colleagues across the EU/EEA when addressing the challenges that inevitably arise in dealing with the control of biological medicinal products. The resources available to each OMCL are multiplied by grace of the interaction with their peers in the network, resulting in a richness that would be difficult to achieve individually. The experience and information acquired through the system allows the network to influence future developments of technical control activities by identifying the need for harmonised common standards and methods, especially for new products and new technologies.

Manufacturers also benefit from the network. Not only does the system enhance mutual recognition and thus reinforce the free flow of goods in the EU/EEA, as evidenced by the decrease in the number of disputes encountered since the system has been in place, they can also be assured that evaluation of their products is being performed with a high level of technical competence. In addition when problems or issues of concern do arise, they can address themselves to a single, unified group which will then work together to find a common solution acceptable to all parties concerned.

Recognition outside the EU/EEA

The strength of the OCABR network of the EU/EEA has not gone unnoticed in the global arena. Countries outside of the EU/EEA such as Australia, India, Japan and a number of CADREAC countries have also begun to use the EU/EEA system in some instances. (CADREAC is the Collaboration Agreement between Drug Regulatory Authorities in European Union Associated Countries. Signatories include Bulgaria, Cyprus, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovak Republic, Slovenia and Turkey). Examples include acceptance of EU OCABR certificates for products on a case by case basis by some non-EU/EEA countries and for others, integration of EU-style criteria and testing for national controls. The transparency of the system allows these countries to be fully aware of the criteria used to judge each product and the support infrastructure of the network assures that the evaluation is being performed at a suitable level of competence.

Switzerland and EU will mutually recognise OCABR results from 1 June 2002

It should also be noted that as of 1 June 2002 when the Mutual Recognition Agreement between the EU and Switzerland comes in to force, the automatic mutual recognition of OCABR will be accepted between these two parties[8].

Future prospects

The network for Official Control Authority Batch Release is not a static one. Thanks to the initiative of its members it will continue to evolve and improve so that it can cover the needs involved in the control of biological medicinal products in the EU/EEA in the best possible manner. The increase in the number of biological medicinal products to be controlled and the advances in technology for monitoring their quality and efficacy presents a significant challenge for the future that OMCLs can best solve by working together, building on the firm foundations which have now been established.

References

1. The Rules Governing Medicinal Products in Europe, Volume 1 Pharmaceutical Legislation: medicinal products for human use, European Commission DG III – Industry pharmaceuticals and cosmetics, 1998
2. Council Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, 2001, *OJ*, **L311**, 67-128
3. European Commission, CPMP, Control Authority Batch Release of Vaccines, December 1994 and European Commission, Inventory of Provisions Relating to Medicinal Products Derived from Human Blood or Plasma, March 1995
4. International Conference, Biologicals Beyond 2000: Challenge for quality standards in an evolving field, Proceedings of the Conference, *Pharmeuropa Special Issue*, April 2000
5. International Symposium, Tetanus Vaccines for Human Use, Proceedings of the Symposium, *Pharmeuropa Special Issue*, October 2000
6. EDQM, Biological Substances Submitted to Official Control Authority Batch Release: Compilation of relevant documentation in relation to official control authority batch release for biologicals concerned by the procedure in EU/EEA Member States, 2001
7. The EC procedure including annexes is available in a booklet upon request from EDQM and can be downloaded from the EDQM website http://www.pheur.org for direct use
8. Agreement between the European Community and the Swiss Confederation on mutual recognition in relation to conformity assessment - Final Act - Joint Declarations - Information relating to the entry into force of the seven Agreements with the Swiss Confederation in the sectors free movement of persons, air and land transport, public procurement, scientific and technological cooperation, mutual recognition in relation to conformity assessment, and trade in agricultural products, 2002, *OJ*, **L114,** 369-429

