Official Control Authority Batch Release of Centrally Authorised Immunological Medicinal Products for Human Use and Medicinal Products Derived From Human Blood and Plasma [01/07/2010]（中央審査方式で承認された人用免疫学的医薬品及び人血液／血漿由来医薬品の EU OCABR管理手順[2010年7月1日];以下、ガイドライン2と呼ぶ）

（倫理面への配慮）

本研究では、研究対象者に対する人権擁護上の配慮、不利益・危険性の排除や説明と同意を必要とする研究、実験動物を用いる研究等、倫理面への配慮が必要な研究は行わない。

C. 結果

1）EU OCABR制度の法的根拠

EU では、医薬品は指令（Directive）2001/83/EC(一部改正、Directive 2004/27/EC)による規制を受けている。OCABR は、この指令の第 114 条（別添資料）を根拠として実施されている。第 114 条では、医薬品販売業者は、ワクチン等の免疫学的医薬品（immunological medicinal products）、及び人血液／血漿由来医薬品（medicinal products derived from human blood or human plasma）については、市場への出荷前に、ロットごとにサンプルを公的医薬品試験所（Official Medicine Control Laboratory; OMCL）に提出しなければならないことが規定されている。ただし、サンプルの提出が必要になるのは、以前に他の EU 加盟国(欧州経済領域 EEA 加盟国及びスイスを含む、以下同様)での OMCL のロットリリース試験に合格していない場合に限られている。この条文の解釈として、ガイドライン 1 では、ある一つの加盟国の規制当局が下したロットリリースの許可はすべての他の加盟国において有効であることを意味している記載されている（page 4)。さらに別の箇所では、他の加盟国においてロットリリースされたロットについては、「製造試験記録の提出を含め、(OCABR としての）追加的な試験は許されない」と釘を刺している（page 5)。このように、EU OCABR 制度においては、複数の EU 加盟国間での重複した実施について、強く戒められている。一方、それを補う意味合いがあるかとも思われるが、「市販後の試験については各国が独自に実施することが制限されていない」との記載も見られる（page 4)。

ガイドライン 1 では、OCABR において不合格との判断がされた場合には、その情報は欧州医薬品庁（European Medicines Agency; EMA）を通じて加盟国に共有されると記載されており（page 5)、その法的根拠として指令 2001/83/EC 第 123 条（別添資料）が示されている。

2）EU OCABR の手順

ガイドライン 1 では、OCABR の実施方法として、おおよそ以下のような手順が示されている（page 6 – 9)。

1. OCABR 対象製剤であることの通知と製剤別ガイドラインの制定

OCABR の対象となる製剤の市販が予定されている加盟国規制当局は、当該製剤の医薬品販売業者に OCABR の対象製剤であることを通知する。Annex I として、その通知文のひな型が示されている。

OCABR では、製剤品目ごとに制定され

ているガイドラインにしたがって審査が行われる。当該製剤に該当する適当なガイドラインがない場合には、EDQMと関係するOMCLネットワークによってガイドラインが作成され、OMCLネットワークによって採択される。

2. OMCLへのサンプル等の提出

医薬品販売業者は、OMCLに当該ロットのサンプルと製造・試験記録要約書（production and control protocols）を提出する。特定のロットについての提出先は一箇所のOMCLであるが、バックアップ等も考慮して、複数のOMCLとあらかじめコンタクトを取っておくことが推奨されている。

承認事項に変更があった場合には、医薬品販売業者はOMCLに通知しなければならない。

3. OCABRにおける審査項目

OCABRの審査は、「製造・試験記録要約書の審査」と「品目別ガイドラインに示されている試験」により行われる。

試験は、二つのフェーズよりなるとされている。通常はフェーズ1の試験のみを行うが、後述する場合にはフェーズ2の試験まで行うとされている。品目別ガイドラインに示されているのは、フェーズ1の試験項目と思われる。フェーズ2試験の内容については、ガイドラインには記載されていない。フェーズ2試験の内容は、フェーズ2試験を行う理由（フェーズ2試験の実施が求められる事例については後述する）により、ケースバイケースで設定されているのではないかと推察される。

OCABRは、サンプル等の提出を受け付けてから、一律に60日以内に終了することとされている。

さらに、OCABRは、ISO 17025にもとづく品質保証システム（外部評価が行われていることが必要）のもとで実施されなければならないとされている。ある特定のOMCLによるOCABRの結果を、EU加盟各国が受け入れる前提として、品質保証システムの運用が求められているものと思われる。

4. OCABRの結果

当該ロットがロットリリースの条件を満たしている場合には、OMCLは、OCABR証明書（OCABR Certificate）を発行する。OCABR証明書のひな型として、製剤種ごとにAnnex IIaからIIgまでの6類型が提示されている。

当該ロットが規格を満たしていない場合には、その情報は、医薬品販売業者に通知されると共に、迅速かつ機密性が確保されたシステムにより、EU OCBARネットワークの連絡官に通知される。

規格不適合の詳細については、他の加盟国の規制当局からの要望に応じて、個別に提供されるようである。

製造業者による試験とOMCLによる試験が併行して行われ、試験不適合により医薬品販売業者が申請を取り下げた場合には、OCABR不適合とは見なさない。ただし、その場合でも、指令2001/83/EC第122条（別添資料）にもとづいて、当該ロットが不適合となった情報はOCABRネットワーク内で共有され、不適合となったロットが別のOMCLに再申請されることを防止している。

すべてのロットのOCABRの詳細な記録は、各OMCLにおいて、当該ロットの使用

期限終了10年後まで、保存される。

5. OCABR証明書の交付

OCABRに合格した場合には、OCABR証明書が医薬品販売業者に交付される。医薬品販売業者は、当該ロットを販売する予定の国の規制当局にOCABR証明書の写しと販売情報申告書(marketing information form)を提出する。これらの書類を提出後、7営業日以内に規制当局からの異議がなかった場合には、医薬品販売業者は当該ロットの市販を開始してよいことになっている。

6. フェーズ2試験を実施する場合

フェーズ2試験の実施が求められる場合として、ガイドライン1では以下の事例を挙げている(Page 9)。

- 製造工程の重大な変更
- 製造場所の変更
- 有害事象の発生
- 製造工程の著しい不整合
- 製造所による試験方法の変更
- 製造所またはOMCLで実施した品質管理試験結果の想定以上のバラツキ
- GMP査察における重大な事象

フェーズ2試験を実施する必要があると判断した機関(OMCL、規制当局、査察当局)は、迅速な通知システムにより、各OMCLに通報する。

7. OCABRデータベース

EDQMは、すべてのロットのOCABRの結果の概要を提供するデータベースを設置している。各OMCLは時宜を失せずに(例えば1週間以内に)、データベースにデータを提供する義務と責任を有するとされている。

8. 年間報告書

各OMCLは、OCABR試験の結果について要約した年間報告書を作成することとされている。

3) 中央審査方式で承認された製剤のOCABR手順

EUにおける医薬品の承認審査には、中央審査方式(Centralised Procedure)、相互承認方式(Mutual Recognition Procedure)、非中央審査方式(Decentralised Procedure)の三種類がある。中央審査方式では、医薬品販売業者からの販売承認申請はEMAに提出され、その審査結果は欧州委員会(European Commission)に報告されて行政的な決定がなされる。中央審査方式で取得された医薬品販売承認は、すべてのEU加盟国において有効になる。中央審査方式で承認された製剤に対しても基本的には、ガイドライン1により定められているOCABRの手順が適用される。ガイドライン2(別添資料)では、中央審査方式で承認された製剤に特有のOCABR手順が示されている。

1. 医薬品販売業者と特定のOMCLとの事前協議

OCABRが適用される予定の製剤に関して、医薬品販売業者は、承認後の当該製剤に対するOCABRの実施について、特定のOMCLに事前協議を申し込む。この事前協議に関する事項は、EMAの関連グループによる当該製剤の承認申請に関する事前審査会議(Pre-submission meeting)または科学的助言会議(Scientific Advice meeting)における重要事項となる。力価の測定方法などのロットリリースにおける試験方法を適切に設定するのに十分な検討時間を確保できるよう、医薬品販売業者とOMCLとの

協議は、少なくとも承認申請の 1 年前には開始することとされている。医薬品販売業者が協議を申し込んだ OMCL に関する情報は、事前審査会議の議事録に記録され、承認審査の報告者チーム（Rapporteur Team）に伝達される。EMA は、OCABR をともなう製剤の承認審査の開始時期について、随時、EDQM に情報提供する。

2. OMCL による OCABR 実施の可否の判断

医薬品販売業者から事前協議の申し込みを受けた OMCL は、EDQM 及び OCABR ネットワークからの情報を勘案して、当該製剤の OCABR を実施することができるかどうかを判断する。その際の主な検討事項は、提案されている試験を実施する技術的能力を持ち合わせているか、または、必要な時間内にそれを開発できるか、ということである。もし実施できないと判断した場合には、代替措置を講ずることができるように、できるだけ早く医薬品販売業者及び EMA に連絡する。

3. ガイドラインの準備

OCABR の実施について適格性がある OMCL は、承認審査の報告者（Rapporteur）及び副報告者（Co-rapporteur）との密接な協力を図りつつ、承認申請が行われたら直ちに、当該製剤に関連のある OCABR 起草グループ及び／または OCABR 助言グループに対して、ガイドラインの準備について連絡する。この連絡には、OCABR の過程で実施すべき試験のリスト、及び製造試験記録要約書のひな型に関連する特別な注意事項を含める。

起草／助言クループは、新しいガイドラインが必要か、それとも既存のガイドラインを改訂することで対応できるか、あるいは、既存のガイドラインですでに十分か、について判断し、適切な対応をとる。必要な場合には、一般的な OCABR における技術文書の発効手続きにしたがって、適切なガイドラインを作成する。

OCABR ガイドラインの最終案は、医薬品販売承認が認可されるまでの間に準備されなければならない。ガイドラインは、医薬品販売承認が認可されると同時に、OMCL ネットワークによって正式に承認される。

D 考察

EU OCABR の実施手順に関するガイドラインを精査することにより、EU OCABR の内容について明らかにすることができた。EU OCABR 制度と我が国の国家検定制度を比較した結果、以下の 2 点において大きく異なっていると考えられた。

1）実施する試験におけるフェーズ 1、フェーズ 2 の区別

OCABR においては、実施する試験について、フェーズ 1、フェーズ 2 の区別をしている。我が国の国家検定においては、実施する試験項目は検定基準によって一律に定められており、このような区別はない。通常はフェーズ 1 の試験項目を実施するとされており、製剤品目ごとに定められているガイドライン（我が国の検定基準に相当するものと考えられる）にリストアップされている試験項目を指していると思われる。フェーズ 2 においてどのような試験が行われるのか、その試験項目はどのように選ばれるのかについては、ガイドラインでは触れていない。ガイドラインではフェーズ 2

試験の実施をトリガーする事象の例として、製造過程や試験方法の重大な変更、有害事象の発生、GMP 査察の結果など、7 項目が挙げられている。フェーズ 2 試験を実施する原因となる事象が様々であることから、フェーズ 2 試験において実施する試験も、それに応じて適切な項目が選択されているものと推察される。また、フェーズ 2 試験をトリガーする事例として、有害事象と GMP 査察が挙げられているが、このことは、OMCL などの OCABR を実施する機関（我が国では国立感染症研究所が相当する）と、有害事象を収集・分析する機関や GMP 査察を実施する機関（我が国では、医薬品医療機器総合機構及び厚生労働本省が相当する）との間での情報交換のルートが確保されていることを意味している。我が国の国家検定では、製造工程や試験方法の変更、有害事象の発生、GMP 査察の結果などのリスクに応じて検定における試験項目を追加する考え方はない。リスクに応じて試験内容を手厚くするフェーズ 2 試験の考え方には合理性が認められ、興味深い。

2）承認申請前の OMCL との協力による規格試験方法の検討

EU OCABR においては、適切な規格試験方法を開発するために、医薬品販売業者は、少なくとも承認申請の 1 年前から OMCL との協力を開始することとされている。規格試験方法について検定機関が検討するしくみとして、我が国においては「承認前検査」という制度がある。承認前検査と OCABR の制度を比較した場合、両者には検討開始の時期と検討期間の間に大きな違いがある。

OCABR では承認申請前に検討が開始されるのに対して、承認前検査では承認申請後に開始される。検討期間については、OCABR では「少なくとも承認申請の 1 年前」には検討を開始することとされていることから、承認審査の期間も含めれば、2 年程度の検討期間が確保されているものと思われる。一方、我が国の承認前検査は、8 カ月程度（優先審査においては 6 カ月程度）で終了することが望ましいとされており、OCABR の制度に比べるとはるかに検討期間が短い。

規格試験方法については承認申請の時点でほぼ固められており、承認前検査において改善が望ましい事項が見出された場合でも、試験方法を大きく変更することは難しい。承認前検査において見出された問題が看過できないものであり、規格試験方法を修正しなければならない事態になれば、承認の遅れの原因になり得る。規格試験方法として新規の方法が設定されている場合には、十分な検討を行うためにより長い時間が必要になる。検定機関が試験方法を導入し、習熟するための時間も必要である。このような場合に、8 カ月程度の検討期間では十分であるとは言えない。

以上のような現行の承認前検査制度に見られる幾つかの問題点は、検定機関と医薬品製造販売業者との共同による規格試験法の検討を、欧州のように、承認申請前に開始することができれば解決する。国家検定としても実施される規格試験を適切に設定することは国家検定を実施する上で重要である。国家検定制度の整備の観点、及び承認審査の円滑化の観点から、OCABR の制度を参考にして、承認前検査の実施方法について再考することには意義があると考える。

EU OCABR 制度には、我が国の国家検定制度とは異なっている点があり、一面においては優れていると考えられる点もあることから、国家検定制度を見直すにあたり、OCABR などの欧州の制度を参考とすることは有用であると考えられた。OCABR 制度の詳細については、さらに調査研究を進める必要があると思われる。

E. 結語

EU OCABR 制度について、実施手順について定めているガイドラインを精査し、その制度内容を明らかにした。我が国の国家検定制度と比較したところ、1) 試験項目をフェーズ 1 とフェーズ 2 の 2 段階で定めている点 2) 新規に承認される製剤の試験方法について、承認申請の 1 年以上前から検定機関における検討が開始されている点において大きく異なっていた。EU OCABR 制度の詳細についてさらに調査研究することは、我が国の国家検定制度の見直しに役立つと考えられた。

F. 研究発表

1) 誌上発表

内藤誠之郎，ワクチン・レギュレーションの新展開－国家検定へのSLP審査制度の導入，Pharm Tech Japan 28(10): 25-29, 2012

2) 学会発表

なし

G. 知的財産権の出願・登録状況

なし

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

Official Journal L – 311, 28/11/2004, p. 67 – 128

as amended by

Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC

Official Journal L – 33, 08/02/2003, p. 30 – 40

Directive 2004/24/EC of the European Parliament and the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use

Official Journal L – 136, 30/04/2004, p. 85 – 90

Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use

Official Journal L – 136, 30/04/2004, p. 34 – 57.

This text does not contain the Annex to Directive 2001/83/EC. The Annex currently in force is laid down in Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use (*Official Journal L 159, 27/6/2003 p. 46 - 94*).

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

3. After every inspection as referred to in paragraph 1, the officials representing the competent authority shall report on whether the manufacturer complies with the principles and guidelines of good manufacturing practice laid down in Article 47 or, where appropriate, with the requirements laid down in Articles 101 to 108. The content of such reports shall be communicated to the manufacturer or marketing authorisation holder who has undergone the inspection.

4. Without prejudice to any arrangements which may have been concluded between the Community and third countries, a Member State, the Commission or the Agency may require a manufacturer established in a third country to submit to an inspection as referred to in paragraph 1.

5. Within 90 days of an inspection as referred to in paragraph 1, a certificate of good manufacturing practice shall be issued to a manufacturer if the outcome of the inspection shows that the manufacturer complies with the principles and guidelines of good manufacturing practice as provided for by Community legislation.

If inspections are performed as part of the certification procedure for the monographs of the European Pharmacopoeia, a certificate shall be drawn up.

6. Member States shall enter the certificates of good manufacturing practice which they issue in a Community database managed by the Agency on behalf of the Community.

7. If the outcome of the inspection as referred to in paragraph 1 is that the manufacturer does not comply with the principles and guidelines of good manufacturing practice as provided for by Community legislation, the information shall be entered in the Community database as referred to in paragraph 6.

Article 112

Member States shall take all appropriate measures to ensure that the holder of the marketing authorization for a medicinal product and, where appropriate, the holder of the manufacturing authorization, furnish proof of the controls carried out on the medicinal product and/or the ingredients and of the controls carried out at an intermediate stage of the manufacturing process, in accordance with the methods laid down in Article 8(3)(h).

Article 113

For the purpose of implementing Article 112, Member States may require manufacturers of immunological products to submit to a competent authority copies of all the control reports signed by the qualified person in accordance with Article 51.

Article 114

1. Where it considers it necessary in the interests of public health, a Member State may require the holder of an authorization for marketing:

- live vaccines,

- immunological medicinal products used in the primary immunization of infants or of other groups at risk,

- immunological medicinal products used in public health immunization programmes,

- new immunological medicinal products or immunological medicinal products manufactured using new or altered kinds of technology or new for a particular manufacturer, during a transitional period normally specified in the marketing authorization,

to submit samples from each batch of the bulk and/or the medicinal product for examination by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose before release on to the market unless, in the case of a batch manufactured in another Member State, the competent authority

of that Member State has previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

2. Where, in the interests of public health, the laws of a Member State so provide, the competent authorities may require the marketing authorization holder for medicinal products derived from human blood or human plasma to submit samples from each batch of the bulk and/or the medicinal product for testing by an Official Medicines Control Laboratory or a laboratory that a Member State has designated for that purpose before being released into free circulation, unless the competent authorities of another Member State have previously examined the batch in question and declared it to be in conformity with the approved specifications. Member States shall ensure that any such examination is completed within 60 days of the receipt of the samples.

Article 115

Member States shall take all necessary measures to ensure that the manufacturing and purifying processes used in the preparation of medicinal products derived from human blood or human plasma are properly validated, attain batch-to-batch consistency and guarantee, insofar as the state of technology permits, the absence of specific viral contamination. To this end manufacturers shall notify the competent authorities of the method used to reduce or eliminate pathogenic viruses liable to be transmitted by medicinal products derived from human blood or human plasma. The competent authority may submit samples of the bulk and/or the medicinal product for testing by a State laboratory or a laboratory designated for that purpose, either during the examination of the application pursuant to Article 19, or after a marketing authorization has been granted.

Article 116

The competent authorities shall suspend, revoke, withdraw or vary a marketing authorisation if the view is taken that the product is harmful under normal conditions of use, or that it lacks therapeutic efficacy, or that the risk-benefit balance is not positive under the normal conditions of use, or that its qualitative and quantitative composition is not as declared. Therapeutic efficacy is lacking when it is concluded that therapeutic results cannot be obtained from the medicinal product.

An authorisation shall also be suspended, revoked, withdrawn or varied where the particulars supporting the application as provided for in Article 8 or Articles 10, 10a, 10b, 10c and 11 are incorrect or have not been amended in accordance with Article 23, or where the controls referred to in Article 112 have not been carried out.

Article 117

1. Without prejudice to the measures provided for in Article 116, Member States shall take all appropriate steps to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market, if the view is taken that:

(a) the medicinal product is harmful under normal conditions of use; or

(b) it lacks therapeutic efficacy; or

(c) the risk-benefit balance is not favourable under the authorised conditions of use; or

(d) its qualitative and quantitative composition is not as declared; or

(e) the controls on the medicinal product and/or on the ingredients and the controls at an intermediate stage of the manufacturing process have not been carried out or if some other requirement or obligation relating to the grant of the manufacturing authorisation has not been fulfilled.

2. The competent authority may limit the prohibition to supply the product, or its withdrawal from the market, to those batches which are the subject of dispute.

Article 118

1. The competent authority shall suspend or revoke the marketing authorization for a category of preparations or all preparations where any one of the requirements laid down in Article 41 is no longer met.

2. In addition to the measures specified in Article 117, the competent authority may suspend manufacture or imports of medicinal products coming from third countries, or suspend or revoke the manufacturing authorization for a category of preparations or all preparations where Articles 42, 46, 51 and 112 are not complied with.

Article 119

The provisions of this Title shall apply to homeopathic medicinal products.

TITLE XII

STANDING COMMITTEE

Article 120

Any changes which are necessary in order to adapt Annex I to take account of scientific and technical progress shall be adopted in accordance with the procedure referred to in Article 121(2).

Article 121

1. The Commission shall be assisted by the Standing Committee on Medicinal Products for Human Use, hereinafter called "the Standing Committee", in the task of adapting to technical progress the directives on the removal of technical barriers to trade in the medicinal products sector.

2. Where reference is made to this paragraph, Articles 5 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 5(6) of Decision 1999/468/EC shall be set at three months.

3. Where reference is made to this paragraph, Articles 4 and 7 of Decision 1999/468/EC shall apply, having regard to the provisions of Article 8 thereof.

The period laid down in Article 4(3) of Decision 1999/468/EC shall be set at one month.

4. The Standing Committee shall adopt its own rules of procedure which shall be made public.

TITLE XIII

GENERAL PROVISIONS

Article 122

1. Member States shall take all appropriate measures to ensure that the competent authorities concerned communicate to each other such information as is appropriate to guarantee that the requirements placed on the authorisations referred to in Articles 40 and 77, on the certificates referred to in Article 111(5) or on the marketing authorisations are fulfilled.

2. Upon reasoned request, Member States shall forthwith communicate the reports referred to in Article 111(3) to the competent authorities of another Member State.

3. The conclusions reached in accordance with Article 111(1) shall be valid throughout the Community.

However, in exceptional cases, if a Member State is unable, for reasons relating to public health, to accept the conclusions reached following an inspection under Article 111(1), that Member State shall forthwith inform the Commission and the Agency. The Agency shall inform the Member States concerned.

When the Commission is informed of these divergences of opinion, it may, after consulting the Member States concerned, ask the inspector who performed the original inspection to

perform a new inspection; the inspector may be accompanied by two other inspectors from Member States which are not parties to the disagreement.

Article 123

1. Each Member State shall take all the appropriate measures to ensure that decisions authorizing marketing, refusing or revoking a marketing authorization, cancelling a decision refusing or revoking a marketing authorization, prohibiting supply, or withdrawing a product from the market, together with the reasons on which such decisions are based, are brought to the attention of the Agency forthwith.

2. The marketing authorization holder shall be obliged to notify the Member States concerned forthwith of any action taken by him to suspend the marketing of a medicinal product or to withdraw a medicinal product from the market, together with the reasons for such action if the latter concerns the efficacy of the medicinal product or the protection of public health. Member States shall ensure that this information is brought to the attention of the Agency.

3. Member States shall ensure that appropriate information about action taken pursuant to paragraphs 1 and 2 which may affect the protection of public health in third countries is forthwith brought to the attention of the World Health Organization, with a copy to the Agency.

4. The Commission shall publish annually a list of the medicinal products which are prohibited in the Community.

Article 124

Member States shall communicate to each other all the information necessary to guarantee the quality and safety of homeopathic medicinal products manufactured and marketed within the Community, and in particular the information referred to in Articles 122 and 123.

Article 125

Every decision referred to in this Directive which is taken by the competent authority of a Member State shall state in detail the reasons on which it is based.

Such decision shall be notified to the party concerned, together with information as to the redress available to him under the laws in force and of the time-limit allowed for access to such redress.

Decisions to grant or revoke a marketing authorisation shall be made publicly available.

Article 126

An authorization to market a medicinal product shall not be refused, suspended or revoked except on the grounds set out in this Directive.

No decision concerning suspension of manufacture or of importation of medicinal products coming from third countries, prohibition of supply or withdrawal from the market of a medicinal product may be taken except on the grounds set out in Articles 117 and 118.

Article 126a

1. In the absence of a marketing authorisation or of a pending application for a medicinal product authorised in another Member State in accordance with this Directive, a Member State may for justified public health reasons authorise the placing on the market of the said medicinal product.

2. When a Member State avails itself of this possibility, it shall adopt the necessary measures in order to ensure that the requirements of this Directive are complied with, in particular those referred to in Titles V, VI, VIII, IX and XI.

3. Before granting such an authorisation a Member State shall:

(a) notify the marketing authorisation holder, in the Member State in which the medicinal

EU Official Control Authority Batch Release

Human Vaccine and Blood Derived Medicinal Products

EU Administrative Procedure for Official Control Authority Batch Release

This version in force from 01/07/2012
Replacing version in force from 01/01/2012

European Commission

edqm European Directorate for the Quality of Medicines & HealthCare

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Custodian organisation	The present document was elaborated by the EDQM in the OMCL network and finalised under PA/PH/OMCL (12) 62 DEF

CONTENTS

EU ADMINISTRATIVE PROCEDURE FOR OFFICIAL CONTROL AUTHORITY BATCH RELEASE

Guideline for the administrative procedure to be followed by the competent OMCL authorities for the implementation of Directive 2001/83/EC Article 114 as amended by Directive 2004/27/EC.

Legal Framework

For the purposes of this guideline all reference to the European Union shall be taken as all European Union Member States and the States, which have signed the European Economic Area agreement, namely Norway, Iceland and Liechtenstein.

Article 114 of the codified 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 and the amending Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004, allows but does not require a Member State laboratory to test a batch of an immunological medicinal product or a medicinal product derived from human blood or plasma before it can be marketed. The competent authorities issue a Batch Release Certificate when the results are satisfactory. This is known as "Official Control Authority Batch Release" (OCABR) within the meaning of the above-cited Directives and consists of analytical controls and document review which are additional to the batch release that must be carried out by the manufacturer for a given batch in accordance with Article 51 of the said Directives.

The list of Official Medicines Control Laboratories (OMCLs), in the European Union, currently carrying out "Official Control Authority Batch Release" is available from the European Directorate for the Quality of Medicines and HealthCare (EDQM), Department of Biological Standardisation, OMCL Networks and HealthCare (DBO), OCABR Section of the Council of Europe and it is regularly updated (see www.edqm.eu). Each of these laboratories corresponds to the "Official Medicines Control Laboratory" cited in Article 1, paragraph 78 of Directive 2004/27/EC which amends Article 114 of Directive 2001/83/EC.

The Directives require Member States to recognise Official Control Authority Batch Release carried out in any other Member State, (while taking into account the next paragraph). This means that once a batch is released by the competent authority of one Member State, then that Official Control Authority Batch Release, if required, is valid for all other Member States, (while taking into account the next paragraph). The "European Union Official Control Authority Batch Release Certificate" delivered by a National competent authority is the document used by a Member State to indicate that "Official Control Authority Batch Release" has taken place. Although the Directive specifically precludes any Member State from carrying out OCABR testing of a batch already released by another Member State, nevertheless post marketing testing of this batch by any Member State, e.g. as part of post-marketing surveillance, is not precluded.

The wording of paragraph 1 (immunological medicinal products) and the wording of paragraph 2 (blood and plasma derivatives) of Article 114 of Directive 2001/83/EC, as amended by Directive 2004/27/EC are almost identical, the only difference being the mention, in paragraph 1 only, of the phrase: *'in the case of a batch manufactured in another Member State'*. The practical significance of this statement and the consequence for immunological medicinal products is that, when a batch of an immunological medicinal product is marketed in the Member State where it was manufactured and that Member State requires Official Control Authority Batch Release, then the OMCL in that Member State would normally carry out Official Control Authority Batch Release of that particular batch. The Member State of manufacture may, however, decide to recognise Official Control Authority Batch Release of that particular batch carried out by another Member State. Furthermore, when the batch of an immunological medicinal product is marketed in the Member State where it was manufactured and that Member State does not require Official Control Authority Batch Release, then the OMCL in any other Member State may be the testing authority for the purpose of Official Control Authority Batch Release within the European Union of that particular batch.

For a batch of either an immunological medicinal product or a medicinal product derived from human blood or plasma, which has already undergone Official Control Authority Batch Release in another Member State, Article 114 of Directive 2001/83/EC as amended by Directive 2004/27/EC does not permit any additional or renewed material control, for example, requiring further information concerning the batch, such as the protocol.

In the case of Centrally Authorised Immunological Medicinal Products or Medicinal Products Derived from Human Blood or Plasma the situation is similar. A specific Procedure for Official Control Authority Batch Release of Centrally Authorised Immunological Medicinal Products for Human Use and Medicinal Products Derived From Human Blood and Plasma agreed upon by the European Commission, the EMA, EDQM and the OMCL network is available and should be applied.

Article 123 of Directive 2001/83/EC requires that whenever a Member State takes the decision to prohibit the supply of a medicinal product this Member State must bring this decision to the attention of the EMA forthwith. It is, therefore, in line with these legal provisions and it is, moreover, in the interest of public health that a mechanism be in place for the exchange of information concerning non-compliance of a batch of an immunological medicinal product or a medicinal product derived from human blood or plasma, which has been examined as provided for in Directive 2001/83/EC and amending Directive 2004/27/EC and in accordance with this guideline on Official Control Authority Batch Release.

Purpose

Directive 2001/83/EC as amended by Directive 2004/27/EC requires Member States to recognise OCABR carried out by any other Member State. This guideline outlines the administrative procedure for Official Control Authority Batch Release within the European Economic Area including the European Union.

As additional safeguards for the protection of public health, this guideline outlines a system for the exchange of information, amongst all the competent authorities and the marketing authorisation holders concerned, on batches that do not comply with OCABR testing by a European Union Authority. Furthermore, it provides a format for the OMCLs annual reports on OCABR testing.

This guideline is for use firstly by the OMCLs in the Member States, to facilitate them in meeting the requirements of Directive 2001/83/EC as amended by Directive 2004/27/EC and to recognise Official Control Authority's Batch Release within the European Union and its validity. Formats for Official Control Authority Batch Release Certificates for the European Union Member States are included.

Secondly, it is also for use by marketing authorisation holders. Guidance is provided for the documents used for communications, concerning Official Control Authority Batch Release, between the marketing authorisation holder and the competent authorities in the Member States.

Principles

For batches of a medicinal product to be marketed in a Member State requiring Official Control Authority Batch Release, there shall be an Official Control Authority Batch Release Certificate common to all Member States. This shall show that the batch of medicinal product has been examined and tested by an OMCL within the European Union in accordance this procedure and with Official Control Authority Batch Release guidelines pertaining to the medicinal product within the European Union and is in compliance with the approved specifications laid down in the relevant monographs of the European Pharmacopoeia (Ph. Eur.) and in the relevant marketing authorisation. The current version of this procedure and product specific guidelines are available on the EDQM website www.edqm.eu.

Procedure

1. Where appropriate, the Member State where the product is to be marketed informs the marketing authorisation holder that the product is to be subjected to the Official Control Authority Batch Release procedure applicable within European Union; the model letter presented in Annex I shall be used. Such a letter shall identify, for the marketing authorisation holder, the contact person in the Member State to whom the European Union Official Control Authority Batch Release Certificate (see Annexes II) and the marketing information form (see Annex IV) must be sent.

   If one does not already exist, an appropriate product specific guideline is elaborated by EDQM and the concerned OMCL network for OCABR and adopted by the OMCL network for OCABR according to the relevant procedures.

   The Procedure for Official Control Authority Batch Release of Centrally Authorised Immunological Medicinal Products for Human Use and Medicinal Products Derived From Human Blood and Plasma as approved by the European Commission, the EMA, EDQM and the OMCL network for OCABR, replaces the paragraph above for Centrally Authorised Medicinal Products.

2. The marketing authorisation holder shall submit samples relevant to the batch to be released together with production and control protocols to an OMCL[1] within the European Union, which then acts as the testing authority for the purpose of release of that particular batch.

   The releasing OMCL should be notified by the MAH of any new approved variations that have an impact on product specifications or on data supplied in section 3 of the manufacturer's OCABR batch release protocol and relevant for the OMCL in the releasing Member State. The MAH should indicate from when the variation(s) will be applied (indicate 1st batch that is affected)[2].

3. Official Control Authority Batch Release procedure within the European Union consists of:

   a) a critical evaluation of the manufacturer's production and control protocol, and

   b) testing of samples submitted by the manufacturer as specified in the relevant guidelines, which may consist of two phases. Normally OCABR consists only of Phase 1 testing. However, Phase 2 testing may be appropriate in cases as described in 6, as a transitory measure; Information concerning phase 2 testing and other important technical issues is transmitted to the network using the model template in annex VI.

   c) testing for viral markers of all plasma pools used in the production of medicinal products derived from human blood and plasma, as prescribed in product specific guidelines.

   Within the European Union, Official Control Authority Batch Release shall be completed by the OMCL within 60 days of receipt of the complete set which consists of the protocol and samples and the fees, where required.

   Furthermore it should be ensured that Official Control Authority Batch Release is performed under a quality assurance system, which undergoes regular external assessment based on the international standard ISO 17025.

4. If a batch is satisfactory for release, the OMCL shall prepare an Official Control Authority Batch Release Certificate, giving the details shown in the model certificate presented in Annexes II a and II b.

   For the specific case of monovalent bulk of Poliomyelitis vaccines (oral), plasma pools, ancillary medicinal products derived from human blood and plasma to be used in medical devices and when special arrangements are required for pneumococcal polysaccharide bulk conjugates as determined by the network, a certificate of approval shall be issued according to the model presented in the relevant Annexes II c, II d, II f and IIg, respectively.

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[1] A given batch should be submitted to only one OMCL for the purpose of OCABR however it is recommended that the MAH make arrangements to interact regularly with more than one OMCL for OCABR of a given product in order to help ensure adequate coverage and back-up capacity where necessary.

[2] If an 'overlap' period with batches using the previously approved MA is expected the MAH should inform the OMCL at this time.

The certificate may be written in the national language of the country of the OMCL and should be accompanied, if relevant, by a translation into English.

Should a batch be found not to comply with the specifications, this information shall be provided to the marketing authorisation holder and, by a rapid, confidential, information exchange mechanism, to specified contact persons in the EU OCABR network (including OMCLs, competent authorities, EMA, the EU Commission, EDQM, DBO, Batch Release Section and any OCABR network observer approved through a specific network procedure) for use in the context of control of medicines by the relevant authorities. The list of specified contact persons is given in Annex III. A model notice of non-compliance/failure is presented in Annex II e.

Technical details of the non-compliance shall be made available to other Member States, on request. The same applies for manufacturer withdrawal or method deficiencies after being informed using the appropriate annexes noted below.

In the specific case where an arrangement has been made between the testing OMCL and the manufacturer to perform batch testing in parallel, any batches failing tests and subsequently withdrawn by the manufacturer before completion of the OCABR procedure may not be formally considered as non-compliance. Information of the withdrawal shall, nevertheless, be circulated within the OCABR network (Annex III contacts) whenever this occurs in order to avoid the possibility of these batches being submitted for official batch release to another OMCL. The model template in Annex VII is provided for this purpose. These exchanges of information take place in accordance with Article 122 of Directive 2001/83/EC as amended by Directive 2004/27/EC.

For the sake of public health, detailed documentation on all batches of the medicinal product should be kept by the OMCLs for 10 years after their expiry date, to be made available for examination by the competent authorities upon request.

5. The Official Control Authority Batch Release Certificate within the European Union shall be issued to the marketing authorisation holder. The marketing authorisation holder of the batch of the medicinal product concerned must ensure that a copy of this certificate is provided to the competent authorities of the Member States where the batch will be marketed. A copy of the certificate and the corresponding "marketing information form" must be sent by the marketing authorisation holder to the competent authority in the Member State(s) wherever the batch or any portion of the batch of the medicinal product is to be marketed. A model of "marketing information form" is presented in Annex IV. After sending these documents, the marketing authorisation holder could market the batch in the Member State where the batch is to be marketed if, within seven working days, the competent authority in that Member State has not raised any objection.

   Without delaying placing a given batch on the market, further exchange of information and documentation may take place between OMCLs.

The OCABR certificate provided to the MAH for a given batch cannot be recalled once issued however if confirmed quality or safety issues arise which result in the recall of a batch from the market, the OMCL may issue a 'Nullification Notice' as presented in annex VIII to indicate that the original certificate should no longer be used for distribution of the batch.

6. Official Control Authority Batch Release within European Union: Phase 2 testing.

More extensive testing may need to be performed by an OMCL. Examples of events that might trigger Phase 2 testing include:
- a significant change in the manufacturing process;
- a change in the manufacturing site;
- adverse events;
- marked inconsistencies in the manufacturing process;
- changes in the manufacturer's test procedures;
- unexpected variability in the results of quality control tests performed by the manufacturer or the OMCL;
- a critical inspection report from the medicines inspectorate.

Through the rapid information system (Annex VI), the institution (OMCL, competent authorities and/or inspectorate) requiring Phase 2 testing must advise the OMCLs performing OCABR that Phase 2 testing should be initiated for the product concerned, by informing the specified contact persons (in Annex III) and indicating the specific reasons. Phase 2 testing represents a set of additional testing measures that are only valid for a transitory period, unless otherwise specified and agreed; the latter case will then imply an appropriate revision of the product specific guideline concerned.

OCABR Database

A database is set up at EDQM to provide a current overview of the outcome of all batches of final products, plasma pools and bulks eligible for OCABR and submitted to the OCABR procedure. Each OMCL has the obligation and responsibility to contribute their own data in a timely manner (eg. within 1 week). Access to the database is restricted to OMCLs and authorities recognised as part of the OCABR network and any network observer approved through a specific network procedure.

Annual report

Each OMCL shall produce an annual report summarising the OCABR testing it has undertaken. A model format for the annual report is presented in Annex V. Exchange of annual reports shall be dealt with on the basis of strict confidence and be accessible only to the CA/OMCLs of the OCABR network, the EDQM, the EMA and the European Commission and any network observer approved through a specific network procedure. The EMA and the European Commission shall be informed by EDQM of any relevant major issues.