



The European Agency for the Evaluation of Medicinal Products
Inspections

London, 18 December 2002

Doc. Ref: EMEA/MRA/CH/84/02/Final

**MUTUAL RECOGNITION AGREEMENTS
EC - SWITZERLAND**

Questions and Answers

**Covering Interpretation of Chapter
15, Explanatory Notes, Annex 16 and
Notice to Applicants**

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 95
E-mail: mail@emea.eu.int <http://www.emea.eu.int>

INTRODUCTION

The Mutual Recognition Agreement (MRA) between the European Community and Switzerland entered into force on 1 June 2002. The Chapter 15 on Medicinal Products GMP inspections and batch certification is of great interest to the pharmaceutical industry both in the European Union and Switzerland.

In order to ensure a proper and uniform implementation and application of Chapter 15 and to allow industry to make the necessary arrangements, an Explanatory Note complements the MRA text. This note represents the Commission's and the Swiss Authorities' common interpretation of Chapter 15.

However in the practical application further and more detailed interpretation of the Chapter 15 has been requested by industry. Questions were raised in the context not only of the MRA with Switzerland, but also the other MRAs the European Community and Switzerland have signed. In particular issues on territorial application and batch release arrangements required further guidance.

This document has been compiled from questions received by both industry and regulators and the answers have been discussed and agreed by the Regulatory Authorities of both the European Communities and Switzerland. The answers take into account the legislative, regulatory and administrative provisions existing in the EC and Switzerland in June 2002. They do not make reference to further provision by individual Member States.

It is hoped, that this document will assist both industry and regulators in their application of the Chapter 15. However it may not cover all issues arising in the future, when new legislation will be in force (e.g. investigational medicinal products and active pharmaceutical ingredients).

SECTION 1

Scope

Question 1:

What is the scope of this MRA?

It covers all medicinal products which are industrially manufactured in Switzerland or the European Community, and to which Good Manufacturing Practice (GMP) requirements apply.

This is further elaborated by the following text:

“Medicinal Products” means all products regulated by pharmaceutical legislation in the European Community and Switzerland as listed in Section I of Chapter 15. The definition of medicinal products includes all human and veterinary products, such as chemical and biological pharmaceuticals, immunologicals, radio-pharmaceuticals, stable medicinal products derived from human blood or human plasma, pre-mixes for the preparation veterinary medicated feeding-stuffs, and, where appropriate, vitamins, minerals, herbal remedies and homeopathic medicinal products.

Since medicinal gases are considered as medicinal products, they are also included.

Question 2:

Does the MRA only apply for products to which GMP requirements are set out according to the legal framework of both parties?

No.

“With respect to medicinal products covered by the legislation of one party but not the other, the manufacturing company can request an inspection be made by the locally competent inspection service for the purpose of this agreement. This provision shall apply inter alia to the manufacture of active pharmaceutical ingredients, intermediate products and investigational medicinal products, as well as to the pre-marketing inspections.”

In those cases the locally competent authority should inspect against its own GMP requirements, or in absence of specific requirements, against the applicable GMP requirements of the importing party.

Question 2a:

Are there specific provisions in the case of investigational medicinal products?

Yes (see answer to question 2 above).

Investigational medicinal products shall be treated similarly as finished products. However, there are currently no legally binding GMP requirements in the EU until May 2004 when the Directive 2001/20/EC will come into force. In any case no re-control at import into EU/EEA is required according to Article 51 of Directive 2001/83/EC (Article 55 of Directive 2001/82/EC for Veterinary Medicinal Products) and Directive 2001/20/EC.

In addition:

There are currently different national regulations for investigational products in the EU Member States. For example in some Member States importers of investigational medicinal products already need a manufacturing authorisation. After May 2004 any importer of investigational medicinal products will need a manufacturing authorisation in the EU.

Question 2b:***How do you handle active pharmaceutical ingredients (active substances) and starting materials under the MRA?***

In general there are no legally binding GMP requirements for starting materials and APIs in the EU. Normally answer No.2 would apply.

For biological medicinal products, such as immunological medicinal products and medicinal products derived from human blood or plasma, Annex I Part 2C 2 of the Directives 2001/83/EC and 2001/82/EC include specific provisions. Supplementary GMP requirements for these products – including starting materials are provided in Annex 2 and Annex 14 of Volume 4 of the Rules Governing Medicinal Products in the EU.

In addition: There are currently different national regulations for APIs in the EU Member States.

SECTION 2

Territorial Application

Question 1:

Importation into the EU of finished medicinal products manufactured partially outside Switzerland and the EU?

- a) *active ingredients* from a third country, other starting materials from EU, product manufactured in CH – is the origin of the product then Switzerland?*
 - b) *packaging material of the finished product manufactured in third country*
 - c) *intermediates of the finished product (bulk product) manufactured in a third country*
-
- a) Yes, the origin would be CH. The MRA applies; no re-control of the finished product in the EU is required. (*For biological medicinal products, such as immunological medicinal products and medicinal products derived from human blood or plasma, see Section 1, question 2b.)
 - b) The MRA applies; no re-control of the finished product in the EU is required
 - c) The MRA does not apply; re-control of the finished product is required

Question 2:

Are we talking about import into the EU or into the EEA?

EEA includes the EU and Norway, Iceland and Liechtenstein.

Article 4, 2 of the MRA EC-CH states that in the event that products are also covered by agreements of mutual recognition in relation to conformity assessment between Switzerland and Member States of both EFTA and the EEA, the MRA EC-CH also covers products of those EFTA Member States.

EFTA Member States are Switzerland, Iceland, Norway and Liechtenstein. The EFTA Convention, Annex I, Appendix 1, Chapter 15 covers medicinal products. Therefore importation from CH into EEA falls under the Scope of the MRA EC-CH.

Example:

Investigational products (bulk tablets) manufactured in a third country, shipped to CH, packaged, labelled and released by RP in CH. Clinical trial in EU – Is the MRA applicable?

No.

The product was not industrially manufactured in CH/EC – The MRA does not apply.

SECTION 3

Responsibilities of Qualified Persons

Question 1:

Can a Q.P. certify a batch without physically receiving any part of the batch?

Yes.

There is no legally binding obligation in EU law that the product must be located at the site at which the Q.P. operates. With regard to the duties of a Q.P. see Annex 16 to the GMP guidelines.

Question 2:

Does a batch need to be physically imported before Batch Release into the EU/EEA?

Yes.

According to Paragraph 7.1 of Annex 16 to the EU Guide to GMP the Q.P. may certify the batch when he/she is satisfied with the manufacturer's confirmation that the batch has been made and tested in accordance with its marketing authorisation, the GMP requirements of the third country, and that the batch has been transported under the required conditions, and has been received and stored in the EU by an importer.

Question 3:

*Does each part of the batch need to be imported at the same time and to the same site?
Does each part of the batch need to be located at the site of the "Official Importer" in the EU responsible for Batch Release into the EU/EEA when it is released?*

No.

It is possible that physical import of subsequent parts of a single batch may take place at different times and at different importing sites within the EU/EEA, provided that each importer has a manufacturing authorisation, and that an effective system for recording and controlling the destination of each part of the batch is in place and communicated to the Q.P. of the "Official Importer".

The Q.P. of the "Official Importer" must certify that each part of the bulk batch meets the requirements of Article 51 of Council Directive 2001/83EC or Article 55 of Council Directive 2001/82/EC (for Veterinary Medicinal Products) before it can be released for sale at the other importing sites in the EU/EEA.

SECTION 4

Contract Manufacture and Analysis

Question 1:

Can a certification of the conformity of a batch issued by a laboratory authorised in Switzerland for the analysis and control of medicinal products (other than the manufacturer of the batch) be accepted under the MRA? Are laboratories authorised for the analysis and control of medicinal products included in the MRA?

Yes.

The agreement specifically mentions contract laboratories and these are required to be mentioned in the certificates of GMP compliance to be issued by the competent authorities.

“The certificates shall also identify the site(s) of manufacture (and contract quality control laboratories, if any).”

Question 2:

Where should samples be taken and stored?

Samples of each batch of finished products shall be retained for at least one year after the expiry date and shall be maintained at the disposal of the competent authority (Article 11 (4) of Directive 91/356/EEC and Directive 91/412/EEC).

A new guideline is currently under internal discussion .

Question 3:

Does the MRA exclude the possibility of re-control after import into the EU?

No.

According to the scope of MRA EC-CH Chapter 15, the manufacturer’s certification of the conformity of each batch to its specifications shall be recognised by the other Party without re-control at import.

The Q.P. may rely on the confirmation of the manufacturer or certification of other Q.P.s. However in exceptional cases the Q.P. can repeat the testing if he/she deems it to be necessary.

Question 4:

Is it required that the manufacturing licence of the manufacturer (or importer), which is responsible for batch release into EU/EEA, includes the dosage form of the imported product in question? If not, how can it be ensured that the Q.P. of this manufacturer has the adequate and up-to-date knowledge to certificate the batches?

One of the requirements an applicant for a manufacturing authorisation is requested to meet in order to obtain a manufacturing / import authorisation according to EU law is to specify the medicinal products and pharmaceutical forms which are to be manufactured or imported and also the place where they are to be manufactured and/or controlled (Article 41 of Directive 2001/83/EC and Article 45 of Directive 2001/82/EC).

Question 5:

Who is responsible for the verification of the packaging (outer packaging and immediate container) and of the patient leaflet, for conformity with the national requirements of the different EU member states where the batch will be distributed?

The Q.P. in the EU is responsible for ensuring the quality of imported medicinal products in accordance with the requirements of the marketing authorisation and therefore would be responsible for verification of the packaging and labelling contents.

He may rely on the written confirmation of the manufacturer. In this case the responsibilities should be ensured by a written agreement .

Question 6:

How many Q.P.s does an importer need in the EU? Only one Q.P. with overall responsibility supported by national Q.P.s or do you need only the national Q.P.s?

There must be at least one Q.P. who has the overall responsibility for the finished product batch. If a marketing authorisation holder imports a batch directly from Switzerland into different member states each importer needs a manufacturing authorisation and a Q.P.. The responsibilities of the different Q.P.s should be ensured by a written agreement within a quality system. An effective system for recording and controlling the destination of each part of the batch should be in place and communicated to the Q.P. of the “Official Importer”.

If there are different national marketing authorisations there must be at least one importer which has a Q.P. as required in Article 41 of Directive 2001/83/EC (Article 45 of Directive 2001/82/EC) to obtain a manufacturing authorisation. If there is a single importer the Q.P. of this importer takes responsibility of the batch and the concept of the “Official importer” is not applicable.

Question 7:

If a Q.P. is delegating duties to another Q.P. – how can this be done if the Q.P. is not on the licence?

The authorised manufacturer for batch release must be named in Part 1A of the Marketing authorisation. The competent authorities of the Member States are responsible for the granting of manufacturing authorisations. They check in advance that the manufacturer has at his disposal the services of at least one Q.P. The name of the Q.P. would be in the files of the competent authorities and changes are required to be notified.

This Q.P. may delegate duties to other Q.P.s within a Quality System and on the basis of written contracts. They certify the manufacturing steps that were conducted at the site of their responsibility

Question 8:

Can the Responsible Pharmacist in Switzerland be the contact point for defects and recalls in the EU as defined in Art. 5b Directive 92/25/EEC?

No.

SECTION 5

Variations of Marketing Authorisations

Question 1:

Does the EMEA or the national authority need to be informed of a change of the manufacturer(s) responsible for Batch Release into the EU/EEA?

Yes.

According to Regulations 541/95 and 542/95 such change would be a Type I variation (Annex I, No.1, 3rd indent “Change of the manufacturing site(s) for part or all of the manufacturing process of the medicinal product”).

For the data requirements refer to the Guideline on Dossier Requirements for Type I variations. In addition, it would be prudent to take the opportunity to ask the MAH to provide the following:

- Amended flow chart (with amended pages of Part IA)
- Clarification/confirmation of contact details for person responsible for product recalls and batch defects. If this has changed too, amended Part IA pages. Note – this person must be based in the EU.

The variation can be implemented only when it has been accepted by the EMEA or competent authority as appropriate.

If the product is not covered by the above regulations each national authority, which has granted a marketing authorisation, shall be informed about the variation according to national law.

Question 2:

Does the EMEA or the national authority need to be informed of a change of the Batch Control site(s)? (For example, a change from a site in France to a Swiss one.)

Yes.

According to Regulations 541/95 and 542/95 such a change would be a Type I variation (Annex I No.1, 3rd indent “Change of the manufacturing site(s) for part or all of the manufacturing process of the medicinal product”)For the data requirements refer to the Guideline on Dossier Requirements for Type I variations. In addition, it would be prudent to take the opportunity to ask the MAH to provide the following:

- Amended page(s) of Part IA. (The batch control site must be identified in section 2.5.1.2.)
- Amended flow chart
- Clarification/confirmation of site of Batch Release.
- Clarification/confirmation of contact details for person responsible for product recalls and batch defects. If this has changed too, amended Part IA pages. Note – this person must be based in the EU.

The variation can be implemented only when it has been accepted by the EMEA or competent authority as appropriate.

If the product is not covered by the above regulations each national authority, which has granted a marketing authorisation, shall be informed about the variation according to national law.

Question 3:

Does the EMEA or the national authority need to be informed if the MAH wants to remove the re-controlling activity from the current manufacturer responsible for Batch Release? (For example, a product, which meets the conditions of the CH MRA is currently subjected to Batch Control in CH, and then re-controlled in France and Batch Released from the same FR site. The MAH now wants to remove the re-controlling from the FR site, so that only Batch Release will be performed there.)

Yes.

According to Regulations 541/95 and 542/95 such a change would be a Type I variation (Annex I No.1, 3rd indent “Change of the manufacturing site(s) for part or all of the manufacturing process of the medicinal product”)

As the variation concerns only a deletion of the re-controlling activity at the site of batch release, it is considered an administrative variation that the Rapporteur need not assess and it can therefore be processed directly by the EMEA.

For the data requirements refer to the Guideline on Dossier Requirements for Type I variations. In addition, it would be prudent to take the opportunity to ask the MAH to provide the following:

- Amended page(s) of Part IA. (The batch control site must be identified in section 2.5.1.2.)
- Amended flow chart.
- Clarification/confirmation of contact details for person responsible for product recalls and batch defects. If this has changed too, amended Part IA pages. Note – this person must be based in the EU.

The variation can be implemented only when it has been accepted by the EMEA or competent authority as appropriate.

If the product is not covered by the above regulations each national authority, which has granted a marketing authorisation, shall be informed about the variation according to national law.

SECTION 6

Pre-Authorisation Inspections (Centralised Procedure)

Question 1:

Will there still be pre-authorisation GMP-inspections from the EMEA in Switzerland?

In principle no. GMP-certificates of the Swiss authority will in principle be accepted.

If there are product-related questions, the EU authority may ask Swissmedic to conduct an inspection. The rapporteur or a EU-expert may accompany the inspection conducted by Swissmedic.

SECTION 7

Official Batch Release

Question 1:

Will official batch release be recognised?

Yes.

Official batch release (= Official Control Authority Batch Release, OCABR) carried out by one authority of the exporting Party will be recognised by the other Party. The manufacturer shall provide the certificate of the official batch release.

Question 2:

Does every EU Member State accept the Swiss batch release?

Yes.

There have been problems in the past because there was no reference to EU-law on the Swiss certificates. In the future there will be a reference.

SECTION 8

Miscellaneous

Question 1:

Does industry have to pay extra for the MRA?

No.

The regime of inspection/establishment fees is determined by the manufacturer's location. Inspection/establishment fees will not be charged to manufacturers located on the territory of the other Party.

However fees for applications or holding a manufacturing authorisation for import apply as regulated in the MS of the importing site.

Question 2:

To apply the MRA, is the date of manufacture, the date of batch release or the date of import of the medicinal product of importance? Are the following possibilities correct?

- a) *A batch is manufactured in Switzerland before the date of entry into force, released in Switzerland before the date of entry into force and imported into the EU/EEA before the date of entry into force, the MRA is not applicable and re-control at import is required.*
- b) *A batch is manufactured in Switzerland before the date of entry into force, released in Switzerland before the date of entry into force and imported into the EU/EEA **after** the date of entry into force, the MRA is applicable and re-control at import is not required.*
- c) *A batch is manufactured in Switzerland before the date of entry into force, released in Switzerland **after** the date of entry into force and imported into the EU/EEA **after** the date of entry into force, the MRA is applicable and re-control at import is not required*
- d) *A batch is manufactured in Switzerland before the date of entry into force, released in Switzerland **after** the date of entry into force and imported into the EU/EEA **before** the date of entry into force (physically present in the EU, but still in quarantine), the MRA is applicable and re-control at import is not required.*
- e) *A batch manufactured in Switzerland **after** the date of entry into force, released in Switzerland **after** the date of entry into force and imported into the EU/EEA **after** the date of entry into force, the MRA is applicable and re-control at import is not required.*
- f) *Are there any other possibilities?*

For the MRA to be applicable, the date on which the batch of medicinal product was imported into the EU must be after the date of entry into force of the agreement. This can be taken as a general rule with respect to the five possibilities raised.

“For medicinal products covered by Chapter 15, each party shall recognise the conclusions of inspections of manufacturers carried out by the relevant inspection services of the other party and the relevant manufacturing authorisations granted by the competent authorities of the other party.

The manufacturer's certification of the conformity of each batch to its specifications shall be recognised by the other party without re-control on import.”

Question 3:

What is the difference between Import licence and manufacturing licence?

Directives 2001/83/EC and 2001/82/EC only mention manufacturing authorisations. An importer of products from a third country needs a manufacturing authorisation according to Article 40 of Directive 2001/83/EC or Article 44 of Directive 2001/82/EC.

However, in some EU Member States (D, UK) this is referred to as an import licence.

GMP-certificates can be requested by importers, exporters, and competent authorities from either importing country or exporting country, see list of contact points.

Clarification:

Importers need a manufacturing authorisation to import from a third country.

If they source from another EU Member State this is not importation, but trading within the single market.

Abbreviations

API	Active pharmaceutical ingredient
CH	Switzerland
EC	European Community used synonymously with EU in the text
EEA	European Economic Area = EU + Norway, Iceland, Liechtenstein
EFTA	European Free Trade Association = CH + Norway, Iceland, Liechtenstein
EMA	The European Agency for the Evaluation of Medicinal Products
EU	European Union (– 15 Member States)
MAH	Marketing Authorisation Holder
MRA	Mutual Recognition Agreement
Q.P.	Qualified Person (EU)
RP	Responsible Person (CH)

Glossary

Batch	<p>A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous (Vol.4 Glossary).</p> <p>For the control of the finished product, a batch of a medicinal product comprises all the units of a pharmaceutical form which are made from the same initial quantity of material and have undergone the same series of manufacturing and/or sterilization operations or, in the case of a continuous production process, all units manufactured in a given period of time (Directive 2001/83/EC, Annex I, Part 2, F 1 and Directive 2001/82/EC, Annex I, Title I, Part 2 F 1).</p>
Batch control	<p>Full qualitative analysis, a quantitative analysis of all the active ingredients and all the other tests or checks necessary to ensure the quality of the product in accordance with the requirements of the marketing authorisation (Chapter 15, MRA).</p>
Batch release	<p>A declaration after certification by the Q. P. , that a batch can be distributed or sold.</p>
Bulk product	<p>Any product, which has completed all processing stages up to, but not including, final packaging (The Rules Governing Medicinal Products in the European Union Volume 4 - Glossary).</p>
Bulk production batch (Annex 16)	<p>A batch of product, of a size described in the application for a marketing authorisation, either ready for assembly into final containers or in individual containers ready for assembly to final packs. (A bulk production batch may, for example, consist of a bulk quantity of liquid product, of solid dosage forms such as tablets or capsules, or of filled ampoules).</p>
Batch Confirmation	<p>A signed statement that the process or test has been conducted in accordance with GMP and the relevant marketing authorisation, as agreed in writing with the Q.P. responsible for certifying the finish product batch before release (Annex 16 to the EU Guide to GMP).</p>
Certification of the finished product	<p>The certification in a register or equivalent document by the Q. P., as defined in Article 51 of Directive 2001/83/EC and Article 55 of Directive 2001/82/EC, before a batch is released for sale or distribution (Annex 16 to the EU Guide to GMP).</p>

Finished Product	A medicinal product, which has undergone all stages of production, including packaging in its final container (The Rules Governing Medicinal Products in the European Union Volume 4 - Glossary).
Finished product batch (Annex 16)	With reference to the control of the finished product, a finished product batch is defined in Part 2 section F 1 of the Annexes to Directives 2001/83/EC and 2001/82/EC (see “Batch”). In the context of the Annex 16 the term in particular denotes the batch of product in its final pack for release to the market.
Importer	Site with an authorisation according to Article 40 (3) of Directive 2001/83/EC and Article 44 (3) of Directive 2001/82/EC for the importation of specified products into a Member State
Intermediate product	Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.
Official importer	The “official” importer in the context of the MRA EC-CH fulfils the duties of the “importer of the first part of the batch” as described in Paragraph 6.3.3 of Annex 16 to the EU Guide to Good Manufacturing Practice (Explanatory notes to Chapter 15 of Annex 1 of the EC-Swiss MRA, 22/10/2002).
Reference samples	Samples of all package presentations of the batch (= witness samples) in sufficient quantity for analytical testing of the batch in case of necessary analysis due to problems.
Re-control	Batch control procedures according to Article 51 of Directive 2001/83/EC (Article 55 of Directive 2001/82/EC) after the receipt by an importer in the EU, of a batch imported from a third country- see also MRA EC-CH Chapter 15, Scope and Coverage, 3 rd paragraph.

References

[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

[Directive 2001/82/EC](#) of the European Parliament and of the Council of 6 November 2001 on the Community Code relating to veterinary medicinal products

[Commission Directive 91/356/EEC](#), of 13 June 1991, laying down the principles and guidelines of good manufacturing practice for medicinal products for human use

[Commission Directive 91/412/EEC](#), of 23 June 1991, laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products

[The Rules Governing Medicinal Products in the European Union, Volume 4, GMP](#)

[Annex 16 to the EU Guide to Good Manufacturing Practice](#) (in operation since January 2002) Certification by a Qualified Person and Batch Release

[Notice To Applicants Vol. 2A \(Jan 2001\)](#) Procedures for marketing authorisation Chapter 4 Centralised Procedure

[Notice To Applicants Vol. 6A \(April 2001\)](#) Procedures for marketing authorisation Chapter 4 Centralised Procedure

[Commission Regulation \(EC\) No 541/95](#), as amended, concerning the examination of variations to the terms of a marketing authorization granted by a competent authority of a Member State.

[Commission Regulation \(EC\) No 542/95](#), as amended, concerning the examination of variations to the terms of a marketing authorization falling within the scope of Council Regulation (EEC) No 2309/93.

Agreement between the European Community and the Swiss Confederation on mutual recognition in relation to conformity assessment (OJ L 114 of 30 Apr 02), [Chapter 15](#)

[Explanatory Notes to Chapter 15](#) (Medicinal Products GMP inspection and batch certification) of Annex 1 of the EU-Swiss MRA