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

Preamble

On June 21 1999, the EC and Switzerland signed an Agreement on Mutual Recognition in relation to Conformity Assessment (MRA). The MRA includes a Chapter (Chapter 15 of Annex 1) on Medicinal Products GMP Inspection and Batch Certification. In order to ensure a proper and uniform implementation and application of this Chapter, and to allow industry to make the necessary arrangements, the European Commission and the Swiss Authorities have established these Explanatory Notes, which shall be read in conjunction with the MRA. These Notes represent the Commission's and the Swiss Authorities' common interpretation of Chapter 15, taking into account the legislative, regulatory and administrative provisions existing at the end of 1999 and are without prejudice to further changes. They will be applicable from the date of entry into force of the MRA.[1]

Part I: Finished Products

The batch certificate shall be signed by the person responsible for releasing the batch for sale or supply. In the EU, this person is called the "Qualified Person" and in Switzerland the "Responsible Person".

As the MRA assumes equivalence of the two GMP systems, a manufacturer in Switzerland can release a batch of medicinal product for sale or supply onto the EU market and vice versa, subject to the following paragraphs:

When importing into the EU from Switzerland, an additional responsibility is laid down by Council Directives 75/319/EEC and 81/851/EEC. The importer[2] of the batch has to receive and keep the batch certificate issued by the manufacturer. There should only be one "Official Importer" into the EU per entire batch of medicinal product, and it is the Qualified Person of this importer who bears overall responsibility for the import and subsequent traceability of the batch within the EU and for the retention of the manufacturer's batch certificate. The Qualified Person of the "Official Importer" takes account of the manufacturer's batch certificate, normally without further recontrol, and certifies in a register that the requirements of Article 22 of Council Directive 75/319/EEC or Article 30 of Council Directive 81/851/EEC have been satisfied. However since the importer's role is then confined to the fulfilment of administrative procedures, it is possible that physical import of parts of a single batch may take place at different times and at different importing sites within the EU, 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 Qualified Person of the "Official Importer".
The Qualified Person of the "Official Importer" must certify that each part of the batch meets the requirements of Article 22 of Council Directive 75/319/EEC or Article 30 of

[1] Expected to be in early 2001

[2] According to Article 16 of Council Directive 75/319/EEC (medicinal products for human use) and Article 24 of Council Directive 81/851/EEC (medicinal products for veterinary use) a manufacturing authorisation is needed to import a medicinal product into the Community. This means that each importer is required to have a Qualified Person at his disposal.

Council Directive 81/851/EEC before it can be released for sale by the Qualified Person(s) at the other importing sites in the EU.

For imports into Switzerland from the EU the importer of the batch has to receive and keep the batch certificate issued by the manufacturer. The Responsible Person of the importer bears the responsibility for the import and subsequent traceability of the batch within Switzerland and for the retention of the manufacturer's batch certificate and samples. The Responsible Person of the importer takes account of the manufacturer's batch certificate, normally without further recontrol, and keeps records of all batches released by him onto the market. By doing this the Responsible Person of the importer assures that each batch or part of a batch meets the requirements of Article 24ter of the Swiss Regulations of 25 May 1972, and particularly of Article 11 and 14 of the Swiss Wholesale Directives of 20 May 1976, Article 14 of the Swiss Manufacturing Directives of 18 May 1995, or Article 4 and 5 of the Ordinance of 23 August 1989 on immunobiological products before it can be released for sale. It is possible that physical import of parts of a single batch of a product may take place at different times and sites. In the latter case the Responsible Person at either site may release the batch or parts of the batch of a product onto the market.

The above provisions do not relieve the manufacturer and importer from the obligation to have an effective batch recall system in place to ensure prompt recall of a medicinal product at any time (Article 13 of Commission Directive 91/356/EEC, Article 13 of Commission Directive 91/412/EEC, Article 16 of the Swiss Manufacturing Directives or Article 8a, para 3d of the Ordinance of 23 August 1989 on immunobiological products).

Investigational medicinal products in their final packaging are treated similarly.

Part II: Bulk and Intermediate Products

Bulk and intermediate products[3] should be treated in a similar way to finished products. These include: not finished medicinal products such as bulk of medicinal products (e.g. tablets, coated tablets, vials), partially packed products (e.g. blisters, unlabelled ampoules), pharmaceutical intermediates (e.g. granules, solutions), active substances, also known as active pharmaceutical ingredients (API), chemical intermediates for API.

An imported batch should be accompanied by a manufacturer’s batch certificate, stating - in addition to the relevant items contained in a batch certificate for finished products - the production stage that has been reached. All subsequent manufacturing steps in the respective territories have to be carried out under the responsibility of the Qualified Person(s) (EU) or the Responsible Person(s) (Switzerland) at the manufacturing site(s).

When releasing the product to the market the Qualified Person or the Responsible Person takes account of the previous manufacturing steps covered by the batch certificate. They are however not relieved of the responsibility for carrying out any further checks and controls required for the subsequent manufacturing steps.

[3] The definitions in Volume 4 of *The Rules Governing Medicinal Products in the European Union* are applicable.

Part III: Specific Issues

1. Responsibilities

The responsibilities of the manufacturer and of the importer, the responsibilities of the Qualified Person(s) in the EU and the Swiss Responsible Person(s) should be defined in a formal document (contractual or technical agreement).

As knowledge of and trust in the Quality Assurance system at the manufacturing site is of great importance, the Qualified Persons in the EU and the Swiss Responsible Persons are expected to have free access to the respective manufacturing plant(s) and to the relevant batch documentation. If deemed necessary these rights may be laid down in a written contract.

2. Contents of batch certificates

Guidance consistent with the principles of the MRA will be developed jointly.

3. Alert procedure

The two-way-alert system referred to in the agreement will be based on the current rapid alert system operational in the EU and Switzerland (PIC/S).

Part IV: Official Batch Release for Vaccines and Blood products

Official Batch Release in the EU is based on the EU document ”Control Authority Batch Release of vaccines and blood products, 1999” or subsequent versions. Switzerland will follow these procedures.

The present MRA applies only to products which are subject to official batch release in Switzerland and in at least one Member State and to the extent that specifications and testing procedures are similar.

The Swiss and EU Official Medicines Control Laboratories (OMCL) are entitled to exchange the individual analytical results of a batch.

Should a batch be found not to comply with the specifications, this information should be provided rapidly using the rapid information OMCL Network System.

Switzerland will be included and will participate in the OMCL Network at the latest when the MRA enters into force.

Brussels 20/2/2000