CHAPTER 15

MEDICINAL PRODUCTS GMP INSPECTION AND BATCH CERTIFICATION

SCOPE AND COVERAGE

The provisions of this Chapter cover all medicinal products which are industrially manufactured in Switzerland or the European Community, and to which Good Manufacturing Practice (GMP) requirements apply.

For medicinal products covered by this Chapter, each Party shall recognise the conclusions of inspections of manufacterers 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 recontrol at import.

In addition, official batch releases carried out by an authority of the exporting Party will be recognised by the other Party.

"Medicinal products" means all products regulated by the pharmaceutical legislation in the European Community and Switzerland as listed in Section I of this Chapter. 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 of veterinary medicated feedingstuffs, and, where appropriate, vitamins, minerals, herbal remedies and homeopathic medicinal products.

"GMP" is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation and products specifications. For the purpose of this Chapter it includes the system whereby the manufacturer receives the specification of the product and the process from the marketing authorisation holder or applicant and ensures that the medicinal product is made in compliance with this specification (equivalent to « Qualified Person » for certification in the EC).

With respect to medicinal products covered by the legislation of one Party but not the other, the manufacturing company can request, for the purpose of this agreement, an inspection be made by the locally competent inspection service. This provisions shall apply i.a. to the manufacture of active pharmaceutical ingredients, intermediate products and investigational medicinal products, as well as to pre-marketing inspections. Operational arrangements are detailed under section III, paragraph 3.

<u>Certification of manufacturers</u>

At the request of an exporter, importer or the competent authority of the other Party, the authorities responsible for granting manufacturing authorisations and for supervision of the manufacture of medicinal products shall certify that the manufacturer:

- is appropriately authorised to manufacture the relevant medicinal product, or to carry out the relevant specified manufacturing operation
- is regularly inspected by the authorities

- complies with the national GMP requirements recognised as equivalent by the two Parties, and which are listed in Section I of this Chapter. In case different GMP requirements would be used as reference, this is to be mentioned in the certificate.

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

Certificates shall be issued expeditiously, and the time taken should not exceed thirty calendar days. In exceptional cases, i.a. when a new inspection has to be carried out, this period may be extended to sixty days.

Batch certification

Each batch exported shall be accompanied by a batch certificate established by the manufacturer (self certification) after a 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. This certificate shall attest that the batch meets its specifications and shall be kept by the importer of the batch. It will be made available upon request of the competent authority.

When issuing a certificate, the manufacturer shall take account of the provisions of the current WHO certification scheme on the quality of pharmaceutical products moving in international commerce. The certificate shall detail the agreed specifications of the product, the reference of the analytical methods and the analytical results. It shall contain a statement that the batch processing and packaging records were reviewed and found in conformity with GMP. The batch certificate shall be signed by the person responsible for releasing the batch for sale or supply, i.e. in the European Community the "qualified person" referred to in article 21 of Directive 75/319/EEC, and in Switzerland the responsible person referred to in Articles 4 and 5 of the Ordinance on immunobiological products, Articles 4 and 5 of the Ordinance on immunobiological products for veterinary use and Article 10 of the Directives of the IOCM on the manufacture of medicinal products.

Official Batch Release

When an official batch release procedure applies, official batch releases carried out by an authority of the exporting Party (listed in Section II) will be recognised by the other Party. The manufacturer shall provide the certificate of the official batch release.

For the European Community, the official batch release procedure is specified in document "Administrative EC Batch Release Procedure III/3859/92" and different specific batch release procedures. For Switzerland, the official batch release procedure is specified in Articles 22-27 of the Ordinance on immunobiological products, Articles 20-25 of the Ordinance on immunobiological products for veterinary use and Articles 4-6 of the Directives of the IOCM on the Authority Batch Release.

SECTION I

With regard to GMP, the relevant parts of the legislative, regulatory and administrative provisions listed below apply. However, the reference quality requirements of products to be exported, including their manufacturing method and product specifications, shall be those of the relevant marketing authorisation granted by the competent authority of the importing Party.

Provisions according to Article 1, paragraphe 2

European Community	Council Directive of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products (65/65/EEC), as last amended by Council Directive 93/39/EEC of June 14, 1993 (OJ n° L 214 of 24.8.1993, p.22) Council Directive of 20 May 1975 on the approximation of the laws of the Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products (75/319/EEC), as last amended by Council Directive 89/341/EEC of May 3, 1989 (OJ n° L 142 of 25.5.1989, p.11) Council Directive of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products (81/851/EEC), as last amended by Council Directive 90/676/EEC of December 13, 1990 (OJ n° L 373 of 31.12.1990, p.15) Commission Directive of 13 June 1991 laying down the principles and guidelines of good manufacturing practice for medicinal products for human use (91/356/EEC) (OJ n° L 193 of 17.7.1991, p.30) Commission Directive of July 23, 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products (91/412/EEC) (OJ n° L 228 of 17.8.1991, p.70) Council Regulation of July 22, 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products (2309/93/EEC) as last amended by Commission Regulation of March 23, 1998 (OJ n° L 88 of 24.3.1998, p. 7) Council Directive of March 31, 1992 on the whole-sale distribution of medicinal products for human use (92/25/EEC) (OJ n° L 113 of 30.4.1992. p.1) & Guide to Good Distribution Practice Guide to Good Manufacturing Practice Volume IV of Rules Governing Medicinal Products in the European Community.
Switzerland	Federal law of October 6, 1989 on the pharmacopoeia (RO 1990 570) Ordinance of August 23, 1989 on immunobiological products (RO 1989 1797), as last amended on February 24, 1993 (RO 1993 963) Ordinance of June 22, 1994 on radioprotection (RO 1994 1947) Federal law of March, 22, 1996 on the control of blood,

blood products and transplants (RO 1996 2296)

Ordinance of June 26, 1996 on the control of blood, blood products and transplants (RO 1996 2309)

Federal law of July 1, 1966 on epizootics (RO 1966 1621)

Ordinance of June 27, 1995 on immunobiological products for veterinary use (RO 1995 3716)

Intercantonal Convention of June 3, 1971 on the control of medicines (RO 1972 1026), as last amended on January 1, 1979 (RO 1979 252)

Regulations of May 25, 1972 for the implementation of the intercantonal convention on the control of medicines, as last amended on May 14, 1998

Directives of May 18, 1995 of the Intercantonal Office for the Control of Medicines (IOCM) on the manufacture of medicinal products

IOCM Directives of May 23, 1985 of the IOCM on the manufacture of active pharmaceutical ingredients

IOCM Directives of May 20, 1976 of the IOCM for the wholesale of medicines

IOCM Directives of November 24, 1994 of the IOCM on the Authority Batch Release

IOCM Directives of May 19, 1988 of the IOCM on the manufacture and distribution of medicated feeding stuff.

IOCM Directives of November 19, 1998 for the Inspection of Manufacturers of Medicinal Products (Inspection Directives)

SECTION II

CONFORMITY ASSESSMENT BODIES

For the purpose of this Chapter «Conformity Assesment Bodies» means the official GMP inspection services of each Party.

European Community

- Austria
  Bundesministerium für Arbeit, Gesundheit und Soziales, Vienna

- Belgium
  Ministerie van Sociale Zaken, Volksgezondheid en Leefmilieu/Ministère des Affaires Sociales, Santé Publique et Environnement; Algemene Farmaceutische Inspectie/ Inspection Générale de la Pharmacie , Brussel, Bruxelles.

- Denmark
  Lægemiddelstyrelsen, Danish Medicines Agency, Brønshøj

- Finland
  Lääkelaitos/Läkemedelsverket (National Agency for Medicines), Helsinki

- France
  Agence du Médicament, Direction de l'inspection et des établissements, Saint-Denis (human)
  Agence Nationale du Médicament Véterinaire, Fougères

- Germany
  Bundesministerium für Gesundheit, Bonn
  Paul-Ehrlich-Institut, Langen (biologicals only)

- Greece
  Ministry of Health and Welfare, National Drug Organization (E.O.F.), Athens

- Ireland
  Irish Medicines Board, Dublin

- Italy
  Ministero della Sanità, Dipartimento Farmaci e Farmacovigilanza, Rome (human)
  Ministero della Sanità, Dipartimento alimenti e nutrizione e sanità pubblica veterinaria - Div. IX, Rome

- Luxembourg
  Direction de la Santé, Division de la Pharmacie et des Médicaments, Luxembourg

- Netherlands
  Staatstoezicht op de Volksgezondheid, Inspectie voor de Gezondheidszorg, Rijswijk

- Portugal
  Instituto da Farmácia e do Medicamento (INFARMED), Lisboa

- Spain
  Ministerio de Sanidad y Consumo, Subdirección General de Control Farmaceutico, Madrid

- Sweden
  Läkemedelsverket (Medical Products Agency), Uppsala

- United Kingdom
  Medicines Control Agency, London
  Veterinary Medicines Directorate, Addlestone

European Union: European Commission, Brussels
European Agency for the Evaluation of Medicinal Products (EMEA)

Switzerland

Swiss Federal Office for Public Health, Division of Biologicals Bern (for immunolobiogical products for human use)

Institute for Virology and Immunoprophylaxis, Bern (for immunolobiogical products for veterinary use)

Intercantonal Office for the Control of Medicines, Bern (for all other medicinal products for human and veternary use).

SECTION III

ADDITIONAL PROVISIONS

1. Transmission of inspection reports

Upon reasoned request, the relevant inspection services shall forward a copy of the last inspection report of the manufacturing site or, in case analytical operations are contracted out, of the control site. The request may concern a "full inspection report" or a "detailed report" (see item 2 below). Each Party shall deal with these inspection reports with the degree of confidentiality requested by the providing Party.

Parties will ensure that inspection reports are forwarded in no more than thirty calendar days, this period being extended to sixty days should a new inspection be carried out.

2. Inspection reports

A "full inspection report" comprises a Site Master File (compiled by the manufacturer or by the inspectorate) and a narrative report by the inspectorate. A "detailed report" responds to specific queries about a firm by the other Party.

3. Reference GMP

a) Manufacturers shall be inspected against the applicable GMP of the exporting Party (see section I).

b) With respect to medicinal products covered by the pharmaceutical legislation of the importing Party but not the exporting one, the locally competent inspection service willing to carry out an inspection of the relevant manufacturing operations shall inspect against its own GMP or, in the absence of specific GMP requirements, against the applicable GMP of the importing Party.

   For specific products or classes of products (e.g. investigational medicinal products, starting materials not limited to active pharmaceutical ingredients), equivalence of GMP requirements shall be determined according to a procedure established by the Committee.

4. Nature of inspections

a) Inspections will routinely assess the compliance of the manufacturer with GMP. These are called general GMP inspections (also regular, periodic, or routine inspections).

b) "Product- or process-oriented" inspections (which may be "pre-marketing" inspections as relevant) focus on the manufacture of one or a series of product(s) or process(es) and include an assessment of the validation of and compliance with specific process or control aspects as described in the marketing authorisation. Where necessary, relevant product information (the quality dossier of an application/authorisation dossier) shall be provided in confidence to the inspectorate.

5. Fees

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.

6. Safeguard clause for inspections

Each Party reserves the right to have its own inspection conducted for reasons identified to the other Party. Such inspections are to be notified in advance to the other Party and will, in accordance with Article 8 of the Agreement, be carried out jointly by the competent authorities of the two Parties. Recourse to this safeguard clause should be an exception.

7. Exchange of information between authorities and approximation of quality requirements

In accordance with the general provisions of the Agreement, the Parties shall exchange any information necessary for the mutual recognition of inspections.

The relevant authorities in Switzerland and in the EU shall also keep each other informed of any new technical guidance or inspection procedure. Each Party shall consult the other before their adoption and will endeavour to proceed towards their approximation.

8. Inspectors training

In accordance with Article 9 of the Agreement, training sessions for inspectors, organised by the authorities, shall be accessible to inspectors of the other Party. The Parties to the Agreement will keep each other informed on these sessions.

9. Joint Inspections

In accordance with Article 12 of the Agreement, and by mutual agreement between the Parties, joint inspections may be organised. These inspections are intended to develop common understanding and interpretation of practice and requirements. The setting up of these inspections and their form shall be agreed through procedures approved by the Committee established under Article 10 of the Agreement.

10. Alert system

Contact points shall be agreed between both Parties to permit authorities and manufacturers to inform the authorities of the other Party with the appropriate speed in case of quality defect, batch recalls, counterfeiting and other problems concerning quality, which could necessitate additional controls or suspension of the distribution of the batch. A detailed alert procedure shall be agreed.

The Parties shall ensure that any suspension or withdrawal (total or partial) of a manufacturing authorisation, based on non compliance with GMP and which could have public health implications, are communicated to each other with the appropriate degree of urgency.

11. Contact points

For the purpose of this Agreement, the contact points for any technical question, such as exchange of inspection reports, inspectors training sessions, technical requirements, are:

for the E.C.

the Director of the European Agency for the Evaluation of Medicinal Products and

for Switzerland

the official GMP inspection services listed in Section II above.

12. Divergence of views

Both Parties shall use their best endeavours to resolve any divergence of views concerning i.a. compliance of manufacturers and conclusions of inspection reports. Unresolved divergences of view will be referred to the Committee established under Article 10 of the Agreement.