SECTORAL ANNEX
FOR
PHARMACEUTICAL GOOD MANUFACTURING PRACTICES
(GMPs)

PREAMBLE

This Annex constitutes a Sectoral Annex to the Agreement on Mutual Recognition between the United States and the European Community.

CHAPTER 1

DEFINITIONS, PURPOSE, SCOPE AND COVERAGE

Article 1

Definitions

1. "Equivalence" of the regulatory systems means that the systems are sufficiently comparable to assure that the process of inspection and the ensuing inspection reports will provide adequate information to determine whether respective statutory and regulatory requirements of the authorities have been fulfilled. "Equivalence" does not require that the respective regulatory systems have identical procedures.

2. "Enforcement" means action taken by an authority to protect the public from products of suspect quality, safety and efficacy or to assure that products are manufactured in compliance with appropriate laws, regulations, standards and commitments made as part of the approval to market a product.

3. "Good Manufacturing Practices" (GMPs): (The U.S. and EC have agreed to revisit these concepts)

   GMPs mean the requirements found in the respective legislations, regulations, and administrative provisions for methods to be used in, and the facilities or controls to be used for the manufacturing, processing, packing, and/or holding of a drug to assure that such drug meets the requirements as to safety, and has the identity and strength, and meets the quality and purity characteristics that it purports or is represented to possess.

   GMPs are that part of quality assurance which ensures that products are consistently produced and controlled to quality standards. For the purpose of this Annex, GMPs include therefore the system whereby the manufacturer receives the specifications of the product and/or process from the Marketing Authorization/Product Authorization or License holder or applicant and ensures the product is made in compliance with its specifications (Qualified Person certification in the EC).

4. "Inspection" means an on-site evaluation of a manufacturing facility to determine whether such manufacturing facility is operating in compliance with Good Manufacturing Practices and/or commitments made as part of the approval to market a product.

5. "Inspection Report" means the written observations and Good Manufacturing Practices compliance assessment completed by an authority listed in Appendix 2.

6. "Regulatory System" means the body of legal requirements for Good Manufacturing Practices, inspections, and enforcements that ensure public health protection and legal authority to assure adherence to these requirements.

Article 2

Purpose

The provisions of this Annex govern the exchange between the Parties and normal endorsement by the receiving authority of official Good Manufacturing Practices (GMPs) inspection reports after a transitional period aimed at determination of the equivalence of the regulatory systems of the Parties, which is the cornerstone of this Annex.

Article 3

Scope

The provisions of this Annex shall apply to pharmaceutical inspections carried out in the United States and Member States of the European Community before products are marketed (hereafter referred to as "pre-approval inspections") as well as during their marketing (hereafter referred to as "post-approval inspections").

Appendix 1 names the laws, regulations and administrative provisions governing these inspections and the GMPs requirements.

Appendix 2 lists the authorities participating in activities under this Annex.

Articles 6, 7, 8, 9, 10 and 11 of the Agreement do not apply to this Annex.

Article 4

Product coverage

These provisions will apply to medicinal products for human or animal use, intermediates and starting materials (as referred to in the EC) and to drugs for human or animal use, biological products for human use, and active pharmaceutical ingredients (as referred to in the United States), only to the extent they are regulated by the authorities of both Parties as listed in Appendix 2.

Human blood, human plasma, human tissues and organs, and veterinary immunologicals are excluded from the scope of this Annex. Human plasma derivatives (such as immunoglobulins and albumin), investigational medicinal products/new drugs, human radiopharmaceuticals and medicinal gases are also excluded during the transition phase, their situation will be reconsidered at the end of the transition period. Products regulated by the Center for Biologics Evaluation and Research as devices are not covered under this Annex.

Appendix 3 contains an indicative list of products covered by this Annex.

CHAPTER 2

TRANSITION PERIOD

Article 5

Length of transition period

A three-year transition period will start immediately after the effective date of the Agreement.

Article 6

Equivalence assessment

1. The criteria to be used by the Parties to assess equivalence are listed in Appendix 4. Information pertaining to the criteria under Community competence will be provided by the Community.

2. The authorities of the parties will establish and communicate to each other their draft programmes for assessing the equivalence of the respective regulatory systems in terms of quality assurance of the products and consumer protection. These programmes will be carried out, as deemed necessary by the authorities, for post- and pre-approval inspections and for various product classes or processes.

3. The equivalence assessment shall include information exchanges (including inspection reports), joint training, and joint inspections for the purpose of assessing regulatory systems and the authorities' capabilities. In conducting the equivalence assessment, the Parties will ensure that efforts are made to save resources.

4. Equivalence assessment for authorities added to Appendix 2 after the effective date of this agreement will be conducted as described in this Annex, as soon as practicable.

Article 7

Participation in the equivalence assessment and determination

The authorities listed in Appendix 2 will actively participate in these programs to build a sufficient body of evidence for their equivalence determination. Both parties will exercise good faith efforts to complete equivalence assessment as expeditiously as possible to the extent the resources of the authorities allow.

Article 8

Other transition activities

As soon as possible, the authorities will jointly determine the essential information which must be present in inspection reports and will cooperate to develop mutually agreed inspection report format(s).

CHAPTER 3

END OF TRANSITION PERIOD

Article 9

Equivalence determination

Equivalence is established by having in place regulatory systems covering the criteria referred to in Appendix 4, and a demonstrated pattern of consistent performance in accordance with these criteria. A list of authorities determined as equivalent shall be agreed to by the Joint Sectoral Committee at the end of the transition period, with reference to any limitation in terms of inspection type (e.g. post-approval or pre-approval) or product classes or processes.

The Parties will document insufficient evidence of equivalence, lack of opportunity to assess equivalence or a determination of non-equivalence, in sufficient detail to allow the authority being assessed to know how to attain equivalence.

Article 10

Authorities not listed as currently equivalent

Authorities not currently listed as equivalent, or not equivalent for certain types of inspections, product classes or processes may apply for reconsideration of their status once the necessary corrective measures have been taken or additional experience is gained.

CHAPTER 4

OPERATIONAL PERIOD

Article 11

Start of the operational period

The operational period shall start at the end of the transition period and its provisions apply to inspection reports generated by authorities listed as equivalent for the inspections performed in their territory.

In addition, when an authority is not listed as equivalent based on adequate experience gained during the transition period, the Food and Drug Administration (FDA) will accept for normal endorsement (as provided in Article 12) inspection reports generated as a result of inspections conducted jointly by that authority on its territory and another authority listed as equivalent, provided that the authority of the Member State in which the inspection is performed can guarantee enforcement of the findings of the inspection report and require that corrective measures be taken when necessary. FDA has the option to participate in these inspections, and based on experience gained during the transition period, the Parties will agree on procedures for exercising this option.

In the EC, the qualified person will be relieved of responsibility for carrying the controls laid down in Article 22 paragraph 1(b) of Council Directive 75/319/EEC provided that these controls have been carried out in the United States and that each batch/lot is accompanied by a batch certificate (in accordance with the WHO certification scheme on the quality of medicinal products) issued by the manufacturer certifying that the product complies with requirements of the marketing authorization and signed by the person responsible for releasing the batch/lot.

Article 12

Nature of recognition of inspection reports

Inspection reports (containing information as established under Article 8), including a GMP compliance assessment, prepared by authorities listed as equivalent, will be provided to the authority of the importing Party. Based on the determination of equivalence in light of the experience gained, these inspection reports will normally be endorsed by the authority of the importing Party, except under specific and delineated circumstances. Examples of such circumstances include indications of material inconsistencies or inadequacies in an inspection report, quality defects identified in the post-market surveillance or other specific evidence of serious concern in relation to product quality or consumer safety. In such cases, the authority of the importing Party may request clarification from the authority of the exporting Party which may lead to a request for re-inspection. The authorities will endeavour to respond to requests for clarification in a timely manner.

Where divergence is not clarified in this process, an authority of the importing country may carry out an inspection of the production facility.

Article 13

Transmission of post-approval inspection reports

Post-approval GMP inspection reports concerning products covered by this Annex will be transmitted to the authority of the importing country within 60 calendar days of the request. Should a new inspection be needed, the inspection report will be transmitted within 90 calendar days of the request.

Article 14

Transmission of pre-approval inspection reports

A preliminary notification that an inspection may have to take place will be made as soon as possible.

Within 15 calendar days, the relevant authority will acknowledge receipt of the request and confirm its ability to carry out the inspection. In the EC, requests will be sent directly to the relevant authority, with a copy to the European Agency for the Evaluation of Medicinal Products (EMEA). If the authority receiving the request cannot carry out the inspection as requested, the requesting authority shall have the right to conduct the inspection.

Reports of pre-approval inspections will be sent within 45 calendar days of the request that transmitted the appropriate information and detailed the precise issues to be addressed during the inspection. A shorter time may be necessary in exceptional cases and these will be described in the request.

Article 15

Monitoring continued equivalence

Monitoring activities for the purpose of maintaining equivalence shall include review of the exchange of inspection reports and their quality and timeliness; performance of a limited number of joint inspections and the conduct of common training sessions.

Article 16

Suspension

Each Party has the right to contest the equivalence of an authority. This right will be exercised in an objective and reasoned manner in writing to the other Party.
The issue shall be discussed in the Joint Sectoral Committee promptly upon such notification. Where the JSC determines that verification of equivalence is required, it may be carried out jointly by the Parties in a timely manner, pursuant to Article 6.

Efforts will be made by the Joint Sectoral Committee to reach unanimous consent on the appropriate action. If agreement to suspend is reached in the Joint Sectoral Committee, an authority may be suspended immediately thereafter. If no agreement is reached in the Joint Sectoral Committee, the matter is referred to the Joint Committee. If no unanimous consent is reached within 30 days after such notification, the contested authority will be suspended.

Upon the suspension of an authority previously listed as equivalent, a Party is no longer obligated to normally endorse the inspection reports of the suspended authority. A Party shall continue to normally endorse the inspection reports of that authority prior to suspension, unless the authority of the receiving party decides otherwise based on health or safety considerations. The suspension will remain in effect until unanimous consent has been reached by the Parties on the future status of that authority.

CHAPTER 5

JOINT SECTORAL COMMITTEE

Article 17

Role and composition of the Joint Sectoral Committee

A Joint Sectoral Committee is set up to monitor the activities under both the transitional and operational phases of this Annex.

The Committee will be co-chaired by a representative of FDA for the U.S. and a representative of the EC who each will have one vote. Decisions will be taken by unanimous consent.

The Joint Sectoral Committee's functions will include:

1. making a joint assessment, which must be agreed by both Parties, of the equivalence of the respective authorities,

2. developing and maintaining the list of equivalent authorities, including any limitation in terms of inspecting type or products, and communicating the list to all authorities and the Joint Committee,

3. providing a forum to discuss issues relating to this Annex, including concerns that an authority may be no longer equivalent and opportunity to review product coverage,

4. consideration of the issue of suspension.

The Joint Sectoral Committee shall meet at the request of either Party and, unless the co-chairs otherwise agree, at least once each year. The Joint Committee will be kept informed of the agenda and conclusions of meetings of the Joint Sectoral Committee.

CHAPTER 6

INFORMATION EXCHANGE

Article 18

Regulatory collaboration

The Parties and authorities shall inform and consult one another, as permitted by law, on proposals to introduce new controls or to change existing technical regulations or inspection procedures and to provide the opportunity to comment on such proposals.

The Parties shall notify each other in writing of any changes to Appendix 2.

Article 19

Information relating to quality aspects

The authorities will establish an appropriate means of exchanging information on any confirmed problem reports, corrective actions, recalls, rejected import consignments and other regulatory and enforcement problems for products subject to this Annex.

Article 20

Alert System

The details of an alert system will be developed during the transitional period. The system will be maintained in place at all times. Elements to be considered in developing such a system are described in Appendix 5.

Contact points will be agreed between both Parties to permit authorities to be made aware with the appropriate speed in case of quality defect, recalls, counterfeiting and other problems concerning quality, which could necessitate additional controls or suspension of the distribution of the product.

CHAPTER 7

SAFEGUARD CLAUSE

Article 21

Each Party recognizes that the importing country has a right to fulfil its legal responsibilities by taking actions necessary to ensure the protection of human and animal health at the level of protection it deems appropriate. This includes the suspension of the distribution, product detention at the border of the importing country, withdrawal of the batches and any request for additional information or inspection as provided in Article 12.

APPENDIX 1

List of applicable laws, regulations and administrative provisions

For the European Community:

Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products, as extended, widened and amended.

Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products, as extended, widened and amended.

Council Directive 81/851/EEC of 28 September 1981 on the approximation of the laws of the Member States relating to veterinary medicinal products, as widened and amended.

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 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products.

Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products.

Council Directive 92/25/EEC of 31 March 1992 on the wholesale distribution of medicinal products for human use.

Guide to Good Distribution Practice (94/C 63/03).

Current version of the Guide to Good Manufacturing Practice, Rules Governing Medicinal Products in the European Community, Volume IV.

For the United States:

Relevant sections of the United States Federal Food, Drug, and Cosmetic Act and the United States Public Health Service Act.

Relevant sections of Title 21, United States Code of Federal Regulations (CFR) Parts 1-99, Parts 200-299, Parts 500-599, and Parts 600-799.

Relevant sections of the FDA Investigations Operations Manual, the FDA Regulatory Procedures Manual, the FDA Compliance Policy Guidance Manual, the FDA Compliance Program Guidance Manual, and other FDA guidances.

APPENDIX 2

List of Authorities

United States:

In the United States, the regulatory authority is the Food and Drug Administration.

European Community:

In the European Community, the regulatory authorities are the following:

BELGIUM	Inspection générale de la Pharmacie Algemene Farmaceutische Inspectie
DENMARK	Laegemiddelstyrelsen
GERMANY	Bundesministerium für Gesundheit for immunologicals: Paul-Ehrlich-Institut, Federal Agency for Sera & Vaccines
GREECE	.ΠΥΘΡδΖ 8ΨΚΙΥΘ[ΤδΖ >ΙΨΤΔΡΩ] Ministry of Health and Welfare National Drug Organization (E.O.F.)

SPAIN	for medicinal products for human use: Ministerio de Sanidad y Consumo Subdirección General de Control Farmacéutico for medicinal products for veterinary use: Ministerio de Agricultura, Pesca y Alimentación (MAPA) Dirección General de la Producción Agraria
FRANCE	for medicinal products for human use: Agence du Médicament for veterinary medicinal products: Agence Nationale du Médicament Vétérinaire
IRELAND	Irish Medicines Board
ITALY	for medicinal products for human use: Ministero della Sanità Dipartimento Farmaci e Farmacovigilanza for medicinal products for veterinary use: Ministero della Sanità Dipartimento alimenti e nutrizione e sanità pubblica veterinaria ⇨ Div. IX

LUXEMBOURG	Division de la Pharmacie et des Médicaments
NETHERLANDS	Staat der Nederlanden
AUSTRIA	Bundesministerium für Arbeit, Gesundheit und Soziales
PORTUGAL	Instituto da Farmácia e do Medicamento ⇨ INFARMED
FINLAND	Lääkelaitos/Läkemedelsverket (National Agency for Medicines)
SWEDEN	Läkemedelsverket ⇨ Medical Products Agency
UNITED KINGDOM	for human and veterinary (non-immunologicals): Medicines Control Agency for veterinary immunologicals: Veterinary Medicines Directorate
EUROPEAN COMMUNITY	Commission of the European Communities European Agency for the Evaluation of Medicinal Products (EMEA)

APPENDIX 3

Indicative list of Products covered by the Sectoral Annex

Recognizing that precise definition of medicinal products and drugs are to be found in the legislation referred to above, an indicative list of products covered by the agreement is given below:

- human medicinal products including prescription and non-prescription drugs;
- human biologicals including vaccines, and immunologicals;
- veterinary pharmaceuticals, including prescription and non-prescription drugs, with the exclusion of veterinary immunologicals;
- pre-mixes for the preparation of veterinary medicated feeds (EC), Type A medicated articles for the preparation of veterinary medicated feeds (US);
- intermediate products and active pharmaceutical ingredients or bulk pharmaceuticals (US)/starting materials (EC).

APPENDIX 4

Criteria for Assessing Equivalence for Post- and Pre-Approval

I. Legal/Regulatory authority and structures and procedures providing for post- and pre-approval:

A. Appropriate statutory mandate and jurisdiction.

B. Ability to issue and update binding requirements on GMPs and guidance documents.

C. Authority to make inspections, review and copy documents, and to take samples and collect other evidence.

D. Ability to enforce requirements and to remove products found in violation of such requirements from the market.

E. Substantive current good manufacturing requirements.

F. Accountability of the regulatory authority.

G. Inventory of current products and manufacturers.

H. System for maintaining or accessing inspection reports, samples and other analytical data, and other firm/product information relating to matters covered by this Sectoral Annex.

II. Mechanisms in place to assure appropriate professional standards and avoidance of conflicts of interest.

III. Administration of the regulatory authority:

A. Standards of education/qualification and training.

B. Effective quality assurance systems measures to ensure adequate job performance.

C. Appropriate staffing and resources to enforce laws and regulations.

IV. Conduct of Inspections:

A. Adequate pre-inspection preparation, including appropriate expertise of investigator/team, review of firm/product and databases, and availability of appropriate inspection equipment.

B. Adequate conduct of inspection, including statutory access to facilities, effective response to refusals, depth and competence of evaluation of operations, systems and documentation; collection of evidence; appropriate duration of inspection and completeness of written report of observations to firm management.

C. Adequate post-inspection activities, including completeness of inspectors' report, inspection report review where appropriate, and conduct of follow-up inspections and other activities where appropriate, assurance of preservation and retrieval of records.

V. Execution of regulatory enforcement actions to achieve corrections, designed to prevent future violations, and to remove products found in violation of requirements from the market.

VI. Effective Use of Surveillance Systems:

A. Sampling and analysis.

B. Recall monitoring.

C. Product defect reporting system.

D. Routine surveillance inspections.

E. Verification of approved manufacturing process changes to marketing authorizations/approved applications.

VII. Additional specific criteria for pre-approval inspections

A. Satisfactory demonstration through a jointly developed and administered training program and joint inspections to assess the authorities' capabilities.

B. Pre-inspection preparation includes the review of appropriate records, including site plans and drug master file or similar documentation to enable adequate inspections.

C. Ability to verify chemistry, manufacturing and control data supporting an application is authentic and complete.

D. Ability to assess and evaluate research and development data as scientifically sound, especially transfer technology of pilot, scale up and full scale production batches.

E. Ability to verify conformity of the on site processes and procedures with those described in the application.

F. Review and evaluate equipment installation, operational and performance qualification data, and evaluate test method validation.

APPENDIX 5

Elements to be Considered in Developing a Two-way Alert System

1. Documentation

   - Definition of a crisis/emergency and under what circumstances an alert is required
   - Standard Operating Procedures (SOPs)
   - Mechanism of health hazards evaluation and classification
   - Language of communication and transmission of information

2. Crisis Management System

   - Crisis analysis and communication mechanisms
   - Establishment of contact points
   - Reporting mechanisms

3. Enforcement Procedures

   - Follow-up mechanisms
   - Corrective action procedures

4. Quality Assurance System

- Pharmacovigilance programme
- Surveillance/monitoring of implementation of corrective action

5. Contact points

For the purpose of this agreement, the contact points for the alert system will be:

for the European Community:
the Executive Director of the European Agency for the Evaluation of Medicinal Products, 7, Westferry Circus, Canary Wharf, UK London E14 4HB, England. Telephone +44-171-418 8400, Fax 418 8416.

for the United States:
(to be provided by the U.S.)