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ARTICLE X : PHARMACEUTICAL BUILDING BLOCKS*

by Graham S. Pearson

Introduction

1. The rolling text¹ of the Protocol to strengthen the Biological and Toxin Weapons Convention (BTWC) being developed by the Ad Hoc Group includes provision for declarations of relevance to the Convention. These provisions include language, some parts of which are in square brackets, which addresses the declaration of production facilities. The current version of the rolling text states in Article III Compliance Measures D. Declarations that:

"5. *[The declarations shall include the following][The following shall be declared]:*

[(b) Facilities

(ii) Which produce vaccines [and/or toxoid/anatoxins][licensed by the State Party] for the protection of humans [against listed agents or toxins][with a production capacity as specified in Annex...][with primary production containment];

(iii) Which produce vaccines [and/or toxoid/anatoxins][licensed by the State Party] for the protection of animals [against listed agents or toxins][with a production capacity as specified in Annex...][with primary production containment];...

[(viii) Other microbiological production facilities [including development facilities] not working with listed agents which have an aggregate fermentation production capacity of [100][1000] litres or more

[with primary production containment]

[- which produce by fermentation (i) medicines and/or (ii) antibiotics or (iii) other microorganisms in closed systems]]"

It is thus evident that the Protocol to strengthen the BTWC is likely, and quite rightly, to require the declaration of production facilities producing vaccines for humans and animals and producing medicines or antibiotics.

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¹The current version of the rolling text is that produced following the January 1998 meeting together with the further changes issued following the March 1998 meeting. United Nations, *Procedural Report of the Ad Hoc Group of the States Parties to the Convention on the prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction*, BWC/AD HOC GROUP/39, 2 February 1998 and United Nations, *Procedural Report of the Ad Hoc Group of the States Parties to the Convention on the prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction*, BWC/AD HOC GROUP/40, 17 March 1998.

2. Many such production facilities, whether in the pharmaceutical or biotechnological industry, are increasingly producing products for human or animal use which are licensed by national regulatory bodies and are thus subject to regular inspections by national or foreign regulatory inspectorates -- the latter in the case of exports to foreign countries.

3. There are some fundamental requirements that apply to the production of any medicinal or veterinary products whether for human or animal use; first, that they should be safe to use and secondly that the product should be consistent -- in other words, that there should be no variation between batches of the product. In short, there is a need to assure the quality of the product for the safety, well-being and protection of the patient, whether human or animal. National regulatory systems are developed to achieve this.

4. Initially, national regulatory systems have been developed for human medicinal and veterinary products. These frequently have two key elements -- a **marketing authorisation**, which defines the product, assesses the clinical and other data and gives authority to market the product (an alternative name for a marketing authorisation is a "*product licence*"); and a **manufacturer's authorization**, which is essentially a manufacturer's licence to produce the product. These elements can be illustrated schematically:

	Requirements for Industry	Regulatory Authority Action
Marketing Authorization <i>Product Licence</i>	Safety, efficacy & quality data	Evaluation, Licensing
Manufacturing Authorization <i>Manufacturer's Licence</i>	Good Manufacturing Practice	Inspection, Licensing

Such a regulatory system requires the setting up of inspectorates to assess and monitor the suitability of manufacturers to be licensed to produce the product. More recently, there have been moves to achieve regional and international harmonization of the regulations controlling human medicinal and veterinary products in respect of both the data required to obtain product licences as well as a regional and international harmonization, particularly within Europe, of the carrying out of regular inspections of manufacturers by the regulatory inspectorates.

5. These moves to harmonize both requirements and inspections regionally and internationally have resulted from the market for human medicinal and veterinary products becoming more international. Thus companies which manufacture a product in one country may wish to market this in several countries or a company may produce the same product in more than one country and wish to market this product to other countries. The pharmaceutical industry has thus been keen to see a harmonization by the regulatory authorities of the requirements for the licensing of products and of manufacturers and for the mutual recognition of regulatory inspections.²

²Michael Murray, *Good Pharmaceutical Manufacturing Practice*, in F.O. Wells (ed), *Medicines: Good Practice Guidelines*, 17-27, The Queens University Belfast, 1990.

6. This Briefing Paper outlines national regulatory systems, using that of the UK as an example, and how this has developed into a regional European Union (EU) regulatory system. Various international harmonization initiatives are addressed, ranging from the International Conference on Harmonization (ICH) which seeks to harmonise the data requirements for product licences between the EU, Japan and the US, Mutual Recognition Agreements (MRAs) being developed between the EU and several other countries, the Pharmaceutical Inspection Convention (PIC) and the PIC/Scheme, to the WHO Certification Scheme. There are common elements between these schemes, notably in respect of the Good Manufacturing Practice guidelines being adopted in many countries. The contribution that can be made to the strengthening of the BTWC through the promotion of such standards internationally is considered.

National Regulatory Schemes

7. In the UK, control of the manufacture and supply of medicinal products is under the Medicines Act 1968³ and the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994⁴. These regulations⁵ define "medicinal product" in accordance with Article I of Directive 65/65/EEC as:

" Any substance or combination of substances presented for treating or preventing disease in human beings or animals.

Any substance or combination of substances which may be administered to human beings or animals with a view to making a diagnosis or to restoring, correcting or modifying physiological functions in human beings or animals is likewise considered a medicinal product."

Consequently, it is clear that the term "medicinal product" applies to products for both humans and animals.

8. The term "**marketing authorization**" is set out in Section 3 of Statutory Instrument No 3144 of 1994 which states that: "*Except, in accordance with any exception or exemption...*

*(a) no relevant medical product shall be placed on the market; and
(b) no such product shall be distributed by way of wholesale dealing,*

unless a marketing authorization in respect of that product has been granted in accordance with the relevant Community provisions by the licensing authority or the European Commission, and is for the time being in force in accordance with those provisions."

9. The term "**manufacturer's licence**" is defined in Section 8 of the Medicines Act which states that "*No person shall...manufacture or assemble any medicinal product except in accordance with a licence ... (in this Act referred to as a "manufacturer's licence")."*

³Her Majesty's Stationery Office, *Medicines Act 1968*, 1968 Chapter 67.

⁴Statutory Instruments, *The Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994*, 1994 No. 3144, Her Majesty's Stationery Office.

⁵Medicines Control Agency, *A Guide to What is a Medicinal Product*, Medicines Act Leaflet, MAL 8, December 1995.

10. Another Section (112) of the Act addresses the rights of the inspectors and states that they *"shall have the right to inspect--*

- (a) any substance or article appearing to him to be a medicinal product;*
- (b) any article appearing to him to be a container or package used or intended to be used to contain any medicinal product...;*
- (c) any plant or equipment appearing to him to be used or intended to be used in connection with the manufacture or assembly of medicinal products, and any process of manufacture or assembly of any medicinal products and the means employed, at any stage in the process of manufacture or assembly, for testing the materials after they have been subjected to those processes."*

In addition, he shall have the right to take a sample of the substance or article. Furthermore, he shall have the right

- "(a) to require any person carrying on a business which consists of or includes the manufacture, assembly, sale or supply of medicinal products...*
- (b) to produce any books or documents relating to the business which are in his possession or under his control;*
- (c) to take copies of, or of any entry in, any book or document ..."*

A later Section (118) sets out restrictions on disclosure of information making it clear that *"If any person discloses to any other person --*

- (a) any information with respect to any manufacturing process or trade secret obtained by him in premises that he has entered..., or*
- (b) any information obtained by or furnished to him in pursuance of this Act,*

he shall, unless the disclosure was made in the performance of his duty, be guilty of an offence."

11. Standard provisions are specified for manufacturing authorizations in Statutory Regulations issued in 1971⁶ and for marketing authorizations in Statutory Regulation 3144 issued in 1994. For marketing authorizations these require that *"Every holder of a United Kingdom marketing authorization for a relevant medicinal product shall comply with all obligations which relate to him by virtue of the relevant Community provisions...including, in particular, obligations relating to providing or updating information, to making changes, to applying to vary the authorization, to pharmacovigilance, and to labels and package leaflets."*

12. The standard provisions for a manufacturer's licence require that *"The licence holder shall provide and maintain such staff, premises and plant as are necessary for the carrying out in accordance with his licence and the relevant product licences of such stages of the manufacture and assembly of medicinal products as are undertaken by him, and he shall not carry out any such manufacture or assembly except at the premises specified in his manufacturer's licence."* It also requires that *"The licence holder shall conduct all manufacture and assembly operations in such a way as to ensure that the medicinal products conform with the standards of strength, quality and purity applicable to them under the*

⁶Statutory Instruments, *Medicines (Standard Provisions for Licences and Certificates) Regulations 1971*, 1971 No. 972, Her Majesty's Stationery Office.

relevant product licences." Other requirements are that *"The licence holder shall provide such information as may be requested by the licensing authority for the purposes of the Act, about the products currently being manufactured or assembled under his licence and of the operations being carried out in relation to such manufacture or assembly."*

13. The UK Medicines Act did not provide any more detailed requirements in respect of the standards that should be adopted in the manufacture of medicinal products. The need for a base line for both the inspectorate and the inspected facilities to work from resulted in the production in 1971 of a guide to Good Manufacturing Practice (GMP). The principal reasons for such a GMP guide and its particular importance in respect of medicinal products stem firstly from the chain of implicit trust from the patient back through those administering, dispensing, prescribing and distributing a medicinal product to those manufacturing the medicine, and secondly from the limitations of end-product sampling and the very great potential hazards of even a small proportion of defective items within a batch.⁷ Later versions were produced in 1977 and 1983. These have subsequently been superseded by European Community Guide on GMP first issued in 1989 and with its latest revision in 1997.

14. Other countries have closely similar arrangements for the evaluation of products and the inspection of the premises in which the product is to be manufactured.

Regional Regulatory Schemes

15. The original European Community Directive which regulates the marketing of pharmaceuticals in the European Community is 65/65/EEC.⁸ This Directive introduced a system of marketing authorizations issued by Member States to ensure that all medicinal products are assessed by a competent authority to ensure compliance with the contemporary standard of safety, quality and efficacy. *"Medicinal products"* was defined as *"Any substance or combination of substances presented for treating or preventing disease in human beings or animals."* and as *"Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a medicinal product."* 10 years later, two further Directives (75/318/EEC and 75/319/EEC) further advanced the harmonization of the regulatory system in the European Community. Directive 75/318/EEC⁹ addresses the analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of medicinal products with particular reference to the information required to accompany applications for authorizations to place a medicinal product on the market (marketing authorization or product licence). Directive 75/319/EEC¹⁰ introduced a system of manufacturing authorizations (ie manufacturing licences) to ensure that all producers of medicinal products for human use within the member States are authorized and regularly inspected by the competent authorities:

⁷J. R. Sharp, *Background to the new "Orange guide"*, *Pharmaceutical Journal*, 25 June 1983, 718-721.

⁸Council Directive, *On the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products*, 65/65/EEC, 26 January 1965, *Official Journal of the European Communities*, 369/65, 9 February 1965, 20-24.

⁹Council Directive, *On the approximation of the laws of Member States relating to analytical, pharmacotoxicological and clinical standards and protocols in respect of the testing of proprietary medicinal products*, 75/318/EEC, 20 May 1975, *Official Journal of the European Communities*, No L 147/1, 9 June 1975, 1-12.

¹⁰Council Directive, *On the approximation of provisions laid down by law, regulation or administrative action relating to proprietary medicinal products*, 75/319/EEC, 20 May 1975, *Official Journal of the European Communities*, No L 147/13, 9 June 1975, 13-22.

Article 16 of the Directive states that *"All Member States shall take all appropriate measures to ensure that the manufacture of ... medicinal products is subject to the holding of an authorization."* It is made clear that such an authorization shall be required for both total and partial manufacture, and for the various processes of dividing up, packaging and presentation. It is also evident that *"The authorization shall apply only to the premises specified in the application and to the ... medicinal products specified in that same application."* This same Directive contains the requirements that require compliance with Good Manufacturing Practice (GMP) and repeated inspections by the regulatory authorities.

16. Parallel requirements were specified for veterinary medicinal products by Directive 81/851/EEC¹¹; the language in many of its Articles is identical or closely similar to that in Directive 75/31/EEC. The next step came in January 1988 when the European Commission proposed that compliance with the principles of GMP should be compulsory for all manufacturers within the European Community. This was agreed by the Council of Ministers who further agreed that the principal and guidelines of GMP for medicinal products should be adopted as a Directive. The need for a European Guide to GMP led to the start in 1986 of the drafting of such a guide by a group of inspectors drawn from six of the Member States. It is interesting to note that consideration was given to basing the Guide on the International Standard for Quality Management Systems, ISO 9000, but this was rejected. It needs to be recognised that ISO 9000 is a general quality control system that can be widely applied; it would, however, be insufficiently detailed for setting out the requirements for the pharmaceutical industry. It was also evident when the drafting began that there were already national guides, such as the UK GMP guide, which the pharmaceutical industry were familiar with and it would be more productive to develop an EC GMP guide based on a harmonization of the existing national guides. The EC GMP was issued in its first edition in 1989 and a second edition was issued in 1992.¹²

17. Two almost identical Directives, 91/356/EEC¹³ for medicinal products for human use and 91/412/EEC¹⁴ for veterinary medical products, set out the principles and guidelines of good manufacturing practice (GMP). These Directives include the requirement in Article 4 that *"the manufacturer shall ensure that the manufacturing operations are carried out in accordance with good manufacturing practice and with the manufacturing authorization."* It goes on to state that *"For [veterinary] medicinal products imported from third countries, the importer shall ensure that the [veterinary] medicinal products have been manufactured by manufacturers duly authorized and conforming to good manufacturing practice standards, at least equivalent to those laid down by the Community."* [Emphasis added]. It is thus clear that compliance with the principles and guidelines of GMP is a statutory requirement within the European Community.

¹¹Council Directive, *On the approximation of the laws of the Member States relating to veterinary medicinal products*, 81/851/EEC, 28 September 1981, Official Journal of the European Communities, No L 317/1, 6 November 1981, 1-15.

¹²European Community, *Guide to Good Manufacturing Practice for medicinal products*, reproduced in Medicines Control Agency, *Rules and Guidance for Pharmaceutical Manufacturers and Distributors 1997*, The Stationery Office, London, 1997.

¹³Council Directive, *Laying down the principles and guidelines of good manufacturing practice for medicinal products for human use*, 91/356/EEC, 13 June 1991, Official Journal of the European Communities, No L 193/20, 17 July 1991, 30-33.

¹⁴Council Directive, *Laying down the principles and guidelines of good manufacturing practice for medicinal products for veterinary medical products*, 91/412/EEC, 23 July 1991, Official Journal of the European Communities, No L 228/70, 23 July 1991, 70-73.

18. The introduction to the European Community *"Guide to Good Manufacturing Practice for medicinal products"*¹⁵ states that

"the pharmaceutical industry of the European Community maintains high standards of quality assurance in the development, manufacture and control of medicinal products. A system of marketing authorizations ensures that all medicinal products are assessed by a competent authority to ensure compliance with contemporary requirements of safety, quality and efficacy. A system of manufacturing authorizations ensures that all products authorised on the European market are manufactured only by authorised manufacturers, whose activities are regularly inspected by the competent authorities. Manufacturing authorizations are required by all pharmaceutical manufacturers in the European Community whether the products are sold within or outside the Community."

It goes on to state that *"The principles of GMP and the detailed guidelines are applicable to all operations which require the authorisation referred to in Article 16 of Directive 75/319/EEC and in Article 24 of Directive 81/851/EEC as modified."* In other words, GMP applies to all manufacturing, whether total or partial, as well as to the various processes of dividing up, packaging or presentation.

19. The GMP Guide consists of nine Chapters, each headed by a principle and a text which provides sufficient detail for manufacturers to be made aware of the essential matters to be considered when implementing the principle. The Chapters are on Quality management, Personnel, Premises and equipment, Documentation, Production, Quality Control, Contract manufacture and analysis, Complaints and product recall, and Self-inspection. The requirements are detailed and comprehensive. For example, the chapter on Production has the following Principle: *"Production operations must follow clearly defined procedures; they must comply with Good Manufacturing Practice (GMP) in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorizations."* Subsequently, the same chapter addresses topics such as 'Prevention of cross-contamination in production' stating *"Contamination of a starting material or of a product by another material or product must be avoided...Among the most hazardous contaminants are...biological preparations containing living microorganisms,...and other highly active materials."* Another section states that *"Cross-contamination should be avoided by appropriate technical or organisational measures, for example:*

Production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations and some other bacterials) or by campaign (separation in time) followed by appropriate cleaning..."

20. An Annex to the GMP Guide provides additional requirements for the 'Manufacture of Biological Medicinal Products for Human Use'. This Annex (2) notes that *"The methods employed in the manufacture of biological medicinal products are a critical factor in shaping the appropriate regulatory control. Biological medicinal products can be defined therefore largely by reference to their method of manufacture. Biological medicinal products produced by the following methods of manufacture will fall under the scope of this Annex:*

¹⁵European Community, *Guide to Good Manufacturing Practice for medicinal products*, reproduced in Medicines Control Agency, *Rules and Guidance for Pharmaceutical Manufacturers and Distributors 1997*, The Stationery Office, London, 1997.

- (a) *Microbial cultures, excluding those resulting from r-DNA techniques*
- (b) *Microbial and cell cultures, including those resulting from recombinant DNA or hybridoma techniques;*
- (c) *Extraction from biological tissues;*
- (d) *Propagation of live agents in embryos or animals."*

Within this annex, more detailed requirements are provided. For example, *"The risk of cross-contamination between biological medicinal products, especially during those stages of the manufacturing process in which live organisms are used, may require additional precautions with respect to facilities and equipment, such as the use of dedicated facilities and equipment, production on a campaign basis, and the use of closed systems. The nature of the product as well as the equipment used will determine the level of segregation needed to avoid cross-contamination."* This goes on to say that *"In principle, dedicated facilities should be used for the production of BCG vaccine and for the handling of live organisms used in production of tuberculin products."* and that *"Dedicated facilities should be used for the handling of Bacillus anthracis, of Clostridium botulinum and of Clostridium tetani until the inactivation process is accomplished."* Other Annexes provide detailed requirements for other classes of medicinal products such as, for example, 'Manufacture of immunological veterinary medicinal products'.

21. Consequently, there are clearly specified standards that apply throughout the European Community for the manufacture of human and veterinary medicinal products. Any such products that are to be marketed require both a marketing authorization (or product licence) and a manufacturing authorization (or manufacturer's licence). Compliance with both of these is monitored by repeated inspections by the appropriate inspectorate.

International Regulatory Schemes

22. As might be expected, following the regional harmonization of regulatory controls such as that achieved within the European Community, attention has been directed to wider harmonization. There are basically two strands: one relating to the harmonization of data requirements for product licences or for manufacturing licences, and the other relating to the international acceptance of inspections and inspection reports. In essence, there are four principal initiatives which have progressed to some extent in parallel. These are:

- a. **The Pharmaceutical Inspection Convention (PIC)** which was signed in 1970 and sought to enable regulatory authorities in one country to accept the results of inspections carried out by another regulatory authority in the other country. Its provisions, however, were incompatible with the legal requirements of the European Community. Consequently, the Pharmaceutical Inspection Convention in 1995 developed into the Pharmaceutical Inspection Co-operation Scheme (PIC/S) which avoided the clash with the European Community requirements. A related scheme is that for the Mutual Recognition of Evaluation Reports on Pharmaceutical Products (PER Scheme).
- b. **The International Conference on Harmonisation (ICH)** of technical requirements for registration of pharmaceuticals for human use. This brings together the regulatory authorities of Europe, Japan and the US and representatives from the pharmaceutical industry association representatives in the three regions to address how harmonisation of technical guidelines and requirements for product registration

might be achieved. Many such technical guidelines and requirements have now been agreed.

c. **Mutual Recognition Agreements (MRAs)** which are being developed between countries and between the European Community and other countries. These are aimed at recognizing that conformity with the regulatory standards in one country is acceptable in the other country. They are thus equivalence agreements.

d. **The World Health Organization (WHO) Certification Scheme** on the quality of pharmaceutical products moving in international commerce. In this, at the request of a commercially interested party, a Member State will attest to the competent authority of another Member State that a specific product is authorized to be placed on the market within its jurisdiction, that the plant in which it is produced is subject to regular inspections to establish that the manufacturer conforms to GMP as recommended to the WHO and that all submitted product information is currently authorized in the certifying country.

Each of these is considered in turn.

23. **The Pharmaceutical Inspection Convention (PIC).** It is useful to consider the historical development of PIC and its subsequent transformation into the PIC/S. The idea of a PIC arose in the 1960s when there was recognition by the member countries of the European Free Trade Association (EFTA) or those related to the Association that they had some 10 different inspection systems which carried out closely similar inspections of their pharmaceutical companies. Consequently, trade in pharmaceutical products was inhibited by the need to meet the differing requirements of the different inspectorates in the different countries of EFTA. It was also a time when there was a sense of change in the pharmaceutical inspection arena as the system of control through analysis of samples taken during the manufacturing process was being gradually abandoned in favour of Good Manufacturing Practice (GMP) inspections at all stages of manufacture. The idea was thus developed that building on the cooperation which already existed between national inspectors in the Nordic area, the regulatory system in one country should recognise inspections carried out by the inspectorate of another country of a plant in that country as meeting their own requirements for an inspection. For this to be implemented, it was necessary to ensure that the inspection systems of the individual EFTA countries were comparable or equivalent, although not necessarily identical.

24. This led to the signing in Geneva on 8 October 1970 of the Pharmaceutical Inspection Convention (PIC)¹⁶ by Austria, Denmark, Finland, Iceland, Liechtenstein, Norway, Portugal, Sweden, Switzerland and the United Kingdom. The PIC came into force in May 1971. The PIC defines "*pharmaceutical product*" as meaning:

"(a) any medicine or similar product intended for human use which is subject to control by health legislation in the manufacturing Contracting State or in the importing Contracting State; and
(b) any ingredient which the manufacture uses in the manufacture of a product referred to in subparagraph (a) above."

¹⁶European Free Trade Association, *Convention for the Mutual Recognition of Inspections in respect of the Manufacture of Pharmaceutical Products*, Geneva, October 1970.

The heart of the PIC lies in Article 7 which addresses the mutual recognition of inspections stating that:

"The Contracting States accept and recognize as equivalent to their own national inspections in respect of the manufacture of pharmaceutical products those carried out in conformity with the provisions of this Convention by the competent authority of the manufacturing Contracting State, provided that full information is supplied in respect of the requirements in force in the importing Contracting State."

The PIC also sets out what is entailed in Inspections by saying that *"Inspection within the meaning of this Convention shall cover personnel, premises and facilities, equipment, hygiene and manufacturing and control procedures. The essential factors to be covered are product quality specifications and production control..."*. It is interesting that PIC also provides guidance in respect of information to be exchanged under the Convention by saying that *"Information provided under this Convention shall not extend to data concerning financial and commercial matters or, in so far as they are not related to quality control of manufacture, to data containing technical "know-how", research information and personal data other than those relating to the duties of the persons involved."*

25. The PIC also requires that the competent authorities of the member States should meet at least once a year in order to:

"(a) make recommendations and proposals for standards of good manufacturing practice;..."

This has resulted in the publication of PIC Guidelines on various aspects of Good Manufacturing Practice for pharmaceuticals¹⁷ which has contributed to the harmonization of standards for GMP in the PIC member States. Finally, PIC also makes provision for the extension of the membership of PIC in Article 11 which states that: *"Any State being a member of the United Nations ... and having the national arrangements necessary to apply an inspection system comparable to that referred to in this Convention may ... accede to this Convention."* The procedures for accession¹⁸ make it clear that detailed information has to be supplied by the applicant State on:

*"(a) the national laws regulating the manufacture and control of medicinal products,
(b) the national GMP rules applied to the manufacture of medicinal products,
(c) the national inspection system with regard to the control of the manufacture of medicinal products,
(d) the structure and organisation of the inspectorate and their quality system,..."*

26. By 1996, the PIC was operating between 18 countries: Australia, Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Liechtenstein, Norway, Portugal, Romania, Sweden, Switzerland and the United Kingdom. However, in the early 1990s warnings were voiced by the European Commission that the Community States might not be able to remain in the Convention if its scope was not amended in respect of its

¹⁷European Free Trade Association, *Guide to Good Manufacturing Practice for Medicinal Products*, PH 1/97, February 1997, Geneva.

¹⁸European Free Trade Association, *On Technical Requirements to be fulfilled by a State joining the Pharmaceutical Inspection Convention or the Pharmaceutical Inspection Co-operation Scheme*, PH 6/87, June 1987 (rev. 95), Geneva.

provisions for the mutual recognition of inspections as the PIC provisions were in conflict with the legal undertakings of the European Community Directives. It was therefore decided to set up a new type of arrangement which, unlike the PIC which was an international treaty between governments, provided for cooperation between the national authorities responsible for the inspection of the manufacture of pharmaceuticals. This new arrangement, the **Pharmaceutical Inspection Co-operation Scheme** (known as **PIC/S**)¹⁹ was agreed in November 1995 and entered into force immediately.

27. The PIC/S was designed as an informal arrangement between the inspectorates of the PIC Contracting States which would be open for the participation of the inspectorates of other countries. The PIC/S, which may eventually replace the Convention, retains and builds upon the main features of the Convention -- ie networking and confidence building between the national inspection authorities, the exchange of information and experience, the development of quality standard systems, the training of inspectors and other related experts and its work towards global harmonisation of GMP. The procedures for accession to PIC/S require the submission of detailed information on national laws, national GMP rules, the national inspection system and on the structure and organisation of the inspectorate. In 1996, thirteen inspectorates participated in the PIC/S from Australia, Denmark, Finland, Iceland, Ireland, Hungary, Liechtenstein, the Netherlands, Norway, Romania, Sweden and Switzerland (two inspectorates). The other PIC competent authorities were expected to join the scheme as soon as possible.²⁰

28. Membership of the PIC/S was extended on 1 January 1997 to the inspectorates of the Czech and of the Slovak Republics. On 1 January 1998, further extension took place to the inspectorate of Spain. Currently, Singapore and Canada have formally applied to participate in PIC/S as have Estonia and Latvia. South Africa and Poland are also actively preparing their applications. The remaining PIC Contracting States that have yet to join the PIC/S (Austria, Belgium, France, Germany, Portugal, United Kingdom) are expected to do so shortly.²¹ PIC/S has clearly been very valuable in helping States to achieve equivalent regulatory schemes and inspectorates prior to the expansion of the European Community and to the entering into of Mutual Recognition Agreements in respect of pharmaceutical Good Manufacturing Practice.

29. The 1997 edition of the PIC - PIC/S Guide to Good Manufacturing Practice for Medicinal Products has been harmonised with that of the European Community. Its introduction makes it clear that they are identical apart from a few editorial changes. It states that *"The standards and principles contained in this Guide are intended to serve as a reference for the preparation of information on manufacturing practice as requested under the Pharmaceutical Inspection Convention or the Pharmaceutical Inspection Cooperation Scheme."* It goes on to state that *"The standards set out herein, apply to medicines and similar products intended for human use. It is recommended, however, that the same kind of attention be given to the manufacture of veterinary products."*

¹⁹European Free Trade Association, *Pharmaceutical Inspection Co-operation Scheme*, PIC/s 1/95, November 1995, Geneva.

²⁰Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme, *Annual Report 1996*, PH 8/97, 27 June 1997, Geneva.

²¹Pharmaceutical Inspection Convention, Pharmaceutical Inspection Co-operation Scheme, *Joint Meeting of the PIC Committee of Officials and of the PIC/S Committee*, Press Release, 5 December 1997.

30. The PIC/S is also addressing, in conjunction with representatives from the European Community, the WHO and other authorities such as the FDA, the preparation of a single document on Good Manufacturing Practice on Active Pharmaceutical Ingredients which would be suitable for adoption by health authorities as a harmonised GMP. Observers from countries such as China and India have also been present at these discussions. A draft Guide was issued in the latter half of 1997 with comments due by 1 March 1998. Work on the preparation of the final draft is scheduled for April 1998.

31. The Scheme for the Mutual Recognition of Evaluation Reports on Pharmaceutical Products (PER Scheme). In 1975 following the adoption of the Pharmaceutical Inspection Convention (PIC), the EFTA Council established a working group to study the problem of the registration of pharmaceutical products. A comparative survey was made of the various legislative provisions on registration which were then in force in the EFTA countries. This survey identified the difference and also brought out the similarities of the national regulations and procedures. It was clear that the work carried out by a national authority for the registration of a particular pharmaceutical product involving the monitoring and evaluation of the data and documentation provided by the manufacturer had to be repeated again by the national authorities in the other countries in which the same product was to be registered. This duplication often involved considerable loss of time, delayed the accessibility of the product to the patient and occasioned increased costs. Consequently, a scheme to avoid such duplication was developed which was based on the same "mutual recognition" principle as in the PIC. As national authorities were not yet prepared for full mutual recognition of evaluation carried out in another country, the PER scheme was developed in which evaluation reports would be exchanged on request. This scheme²² for the exchange of evaluation reports for the registration of pharmaceutical products has been in force since 1979. It currently has as Contracting States the following European countries: Austria, Czech Republic, Finland, Germany, Hungary, Iceland, Ireland, Italy, the Netherlands, Norway, Sweden, Switzerland, United Kingdom and from outside of Europe: Australia, Canada, South Africa and New Zealand. The purpose of the Scheme is:

"to facilitate, having due regard to public health aspects, trade in pharmaceutical products between the countries of the participating authorities by eliminating, through the exchange of evaluation reports, unjustified duplication of evaluation of scientific data for registration. The Scheme shall also contribute to facilitating international co-operation in the registration of pharmaceutical products. The aim is the mutual recognition of evaluation of scientific data by the participating authorities."

Under the scheme, pharmaceutical product *"means any medicine or similar product, intended for human or veterinary use, which is subject to evaluation in accordance with national legislation on the registration of such products."* The Scheme sets out the requirement that the evaluation report shall be elaborated either in accordance with the guideline incorporated in the scheme or in accordance with the EU Guideline on the Assessment Report adopted on 18 November 1994. This reflects the general policy that the rules and guidelines of the PER Scheme are harmonized as much as possible with those of the European Community, thereby facilitating the implementation of the PER Scheme in all EU countries. It is also made clear in the PER Scheme that the evaluation report shall not be handed over to the requesting

²²European Free Trade Association, *Scheme for the Mutual Recognition of Evaluation Reports on Pharmaceutical Products (PER Scheme)*, available on the EFTA web site at <http://www.efta.int/docs/Efta.../ConventionsSchemes/2552.html>

authority without first obtaining the consent of the registration holder and that the evaluation report shall have the same confidential status as all other registration documents.

32. **The International Conference on Harmonisation (ICH)** of technical requirements for registration of pharmaceuticals for human use brings together the regulatory authorities of Europe (European Agency for the Evaluation of Medicinal Products), Japan (Ministry of Health and Welfare) and the USA (Food and Drug Administration) with representatives from the industrial associations in the three regions (European federation of Pharmaceutical Industries Associations (EFPIA), Japan Pharmaceutical Manufacturers Association (JPMA) and Pharmaceutical Research and Manufacturers of America (PhRMA). Observers attend from the WHO, EFTA and Canada with the International Federation of Pharmaceutical Manufacturers Associations (IFPMA) participating as an 'umbrella' organisation for the pharmaceutical industry and providing the ICH Secretariat.²³

33. The ICH was established in 1990 as a joint regulatory/industry project to improve, through harmonisation, the efficiency of the process for developing and registering new medicinal products in the three regions in order to make these products available to patients with a minimum of delay. The focus for the discussions of tripartite harmonisation are international conferences which are held at approximately two yearly intervals (Brussels, 1991, Orlando, 1993, Yokohama, 1995 and Brussels 1997). A particular point is made by the ICH that the process of harmonisation should be carried out in a transparent manner and that ICH discussions and recommendations are presented in an open forum. It is noted that some 30 countries from outside the ICH regions were represented at the Brussels 1997 meeting.

34. The ICH process comprises some five stages:

a. Development of consensus. Preliminary discussions are held by an Expert Working Group with representatives from the six co-sponsors of ICH. A preliminary draft is prepared (guideline, policy statement, recommendation, points to consider) and when consensus is reached forwarded to the ICH Steering Committee.

b. Consensus text released for consultation. The draft after acceptance by the ICH Steering Committee is sent to the three regulatory agencies for formal consultation using their normal internal and external consultation processes.

c. Consideration of comments from consultation. Comments obtained are exchanged between the regulatory agencies and the draft is amended in the light of the comments. When significant changes result, the revised draft may be recirculated for further consultation. The eventual revised draft is then sent to the ICH Steering Committee for adoption.

d. ICH guideline finalised. The final draft is discussed by the Steering Committee and "signed off" by the three regulatory parties to the ICH. It is then recommended to the three regulatory bodies for adoption.

²³International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Background and Status of Harmonisation*, ICH Secretariat, c/o IFPMA, Geneva, March 1997.

e. Implementation. The process is complete when the full recommendations are incorporated into domestic regulations or other appropriate administrative measures.

This process has been applied to a range of topics grouped under the headings of safety, quality, efficacy and multidisciplinary. At the Fourth ICH Conference in Brussels in July 1997, it was agreed that ICH should move into a second phase of harmonisation in which work would commence on harmonising the format and content of the documentation to be used in seeking product licences.²⁴ This was seen as the next logical step following reaching agreement on technical guidelines for generating the data required for submissions for product licences. The ICH estimate that the work of achieving consensus on a common technical document for product licence applications will take about 2 years from the first meeting of the expert groups in February 1998. In addition, the ICH is now also addressing the preparation of a document on Good Manufacturing Practice on Active Pharmaceutical Ingredients which will take forward the PIC/S document through consultations with industry representatives and result in an ICH document.

35. Thus ICH has now moved into a second phase with a continuing commitment to increased international harmonisation aimed at ensuring that good quality, safe and effective medicines are developed in the most expeditious and cost effective manner.

36. **Mutual Recognition Agreements (MRAs).** These are being developed between countries and between the European Community and other countries with the aim of reaching a formal undertaking that the two parties will accept the results of conformity assessment procedures produced by the designated Conformity Assessment Bodies or Authorities in the other country. Six such MRAs have been initialled by the EU in 1997; with Australia, Canada, Israel, New Zealand, Switzerland and the United States. In most of these, there is a framework agreement together with Sectoral Annexes addressing matters such as Telecommunications Equipment, Electromagnetic Compatibility, Electrical Safety, Recreational Craft, Good Manufacturing Practice for Pharmaceuticals, and Medical Devices. The MRA with Israel is different in that it has no Annex on Pharmaceutical GMP. In the case of the MRA initialled by the European Community and the United States, additional Sectoral Annexes are being negotiated for Veterinary Biologics and for Industrial Fasteners. Negotiations have begun on MRAs between the EU and Japan and with the Czech Republic, Hungary and Poland. The latter three will be different in character as they are in preparation for the expansion of the EU and therefore seek to achieve harmonization of the regulatory schemes in those countries planning to join the EU with that in the EU. All the other MRAs are aimed at recognising the certification of the other party in respect of pharmaceuticals produced in accordance with GMP although the MRA with Switzerland is somewhat intermediary in nature as it contains an element of alignment with the EU regulations.

37. Taking the EU-Canada MRA²⁵ as an example, the Sectoral Annex on GMP states that this Annex on *"Good manufacturing Practices (GMP) Compliance Certification pertaining to medicinal products/drugs has been developed by the European Community (EC) and Canada to:*

²⁴International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, *Fourth International Conference on Harmonisation, 16-18 July 1997, Brussels*, ICH Secretariat, c/o IFPMA, Geneva, July 1997.

²⁵European Union, *Agreement on Mutual Recognition between Canada and the European Community*, available on the EU web site at <http://www.europa.eu.int/en.comm/dg01/mra05.htm>

- a) enhance bilateral regulatory cooperation;*
- b) establish mutual recognition for GMP compliance certification and acceptance of Manufacturing Authorizations/Licences directly issued by the authorities designated equivalent after the successful completion of a confidence building exercise;*
- c) develop an infrastructure for on-going communications/consultations between Canada, the European Commission, and the regulatory Authorities of the EC Member States to enable regulators to determine and maintain the equivalency of their GMP compliance programmes."*

In its General Considerations, it is stated that *"The underlying premise behind an MRA for GMP compliance certification is that it can be demonstrated that Canada and the EC Member States have equivalent GMP compliance programmes, and therefore the issuance of a Certificate of Manufacturing Authorization/Licence by an authority of one Party certifying that a facility is in compliance with GMPs, would be all the evidence required by the other Party to accept that facility as being in compliance for the manufacturing/control of medicinal/drug products or to issue a similar Certificate of Manufacturing Authorization/Licence. It should be understood that equivalent does not mean identical but it does mean leading to the same result."*

38. The Sectoral Annex includes an Indicative list of Products covered by the Agreement as being:

- human pharmaceuticals...
- human biologicals including vaccines,... and immunologicals;
- veterinary pharmaceuticals,...

The Sectoral Annex sets out a Transition Period lasting 18 months after the signing of the MRA during which a Joint Confidence Building Programme will be carried out enabling each Party to determine the capability of the other Party's authority to perform GMP compliance certification. The Confidence Building Programme will have three phases:

1. Review and evaluation of documentation (exchange of documentation) including legal instruments (Regulations/Legislations/Directives)/Guidelines on GMPs,...
2. Evaluation of processes and procedures including Audit of systems and procedures, Exchange/evaluation of reports, Joint inspections of manufacturers to determine equivalency of inspection methods,...
3. Decision making on the success of the exercise and conclusions including evaluation of the results of the confidence building exercise, Determination of competent agencies that meet evaluation criteria,...

Confidentiality is also addressed in the Sectoral Annex which states that:

- "1. Each Party will protect from public disclosure any non-public confidential technical, commercial and scientific information, including trade secrets and proprietary information that is provided by the other Party.*
- 2. Each Party reserves the right to make public the results of any conformity assessment, including the conclusions of inspection reports, provided by the other Party, in situations in which public health safety may be affected."*

39. The MRA between the EU and the US is broadly similar²⁶ although it is laid out differently. The purpose of the Sectoral Annex on Pharmaceutical Good manufacturing practices (GMPs) is stated to be "*The provisions of this Annex govern the exchange between the Parties and normal endorsement by the receiving authority of official Good Manufacturing Practices (GMP) 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.*" Product coverage is detailed as applying to "*medicinal products for human or animal use, intermediates and starting materials (as referred to in the EU) and to drugs for human or animal use, biological products for human use, and active pharmaceutical products (as referred to in the United States)...*". The transition period between the EU and the US is 3 years (twice as long as with Canada). The other MRAs do not have transition periods because the States involved have had a long history of PIC collaboration which has built up confidence in the equivalence of their regulatory systems.

40. Equivalence assessment will include "*information exchanges (including inspection reports), joint training, and joint inspections for the purpose of assessing regulatory systems and the authorities' capabilities.*" Detailed criteria to assess equivalence are set out. It is also specified that following the transition period there shall be continued monitoring of equivalence which will 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.*" The aim of the joint inspections and joint training under the MRAs is to ensure that the regulatory systems in the two parties remain equivalent.

41. The texts of MRA with Canada was initialled on 10 June 1997²⁷ and that with the USA on 20 June 1997²⁸; these and the other MRAs which have been initialled are due to be signed in summer 1998 which, in the case of the US and Canada, will see the start of the transitional periods. Negotiations of MRAs with countries such as Indonesia, Singapore, Philippines, South Africa and China will be started at some later date provided that the country concerned has joined the GATT on Technical Barriers to Trade. In respect of the Pharmaceutical GMP Annexes a preliminary evaluation as to whether the certification system in the particular country is equivalent in its standards with that of the EU is made in Brussels. A series of visits in both directions is then carried out, coordinated by the European Medicines Evaluation Agency using inspectors from the Member States of the EU, aimed at building understanding and confidence.

42. **World Health Organization (WHO) Certification Scheme.** This is based on the recognition that a comprehensive system of quality assurance must be based on a reliable system of product licences and independent analysis of the finished product as well as on an assurance obtained through independent inspection that all manufacturing operations are carried out in conformity with accepted norms, referred to as Good Manufacturing Practice (GMP). In 1969, the World Health Assembly endorsed²⁹ requirements for "Good Practices in the Manufacture and Quality Control of Drugs" which are subsequently known as "GMP as

²⁶European Union, *Agreement on Mutual Recognition between the United States of America and the European Community*, available on the EU web site at <http://www.europa.eu.int/en.comm/dg01/mra03.htm>

²⁷European Union, *Agreement on Mutual Recognition between Canada and the European Community*, available on the EU web site at <http://www.europa.eu.int/en.comm/dg01/mra04.htm>

²⁸European Union, *Agreed Minutes on the Agreement on Mutual Recognition between the United States of America and the European Community*, 20th June 1997, available on the EU web site at <http://www.europa.eu.int/en.comm/dg01/mra07.htm>

²⁹World Health Assembly, *Quality Control of Drugs*, WHA Resolution 22.50, 25 July 1969.

recommended by WHO". These have subsequently been revised in 1975 and in 1990 and are fully consonant with those operative within the countries participating in the PIC Convention and other major industrialized countries.³⁰ They provide the basis for the WHO Certification Scheme which requires *"each participating Member State, upon application by a commercially interested party, to attest to the competent authority of another participating Member State that:*

- a specific product is authorized to be placed on the market within its jurisdiction or, if it is not this authorized, the reason why that authorization has not been accorded;*
- the plant in which it is produced is subject to inspections at suitable intervals to establish that the manufacturer conforms to GMP as recommended by WHO; and*
- all submitted product information, including labelling, is currently authorized in the certifying country."* ^{31, 32}

43. A Member State may opt to participate solely to control the **import** of pharmaceutical products and substances or a Member State may also use the Scheme to support the **export** of pharmaceutical products. In the latter case, the WHO Scheme states that the Member State *"should first satisfy itself that it possesses:*

- an effective national licensing system, not only for pharmaceutical products, but also for the responsible manufacturers and distributors;*
- GMP requirements, consonant with those recommended by WHO, to which all manufacturers of finished pharmaceutical products are required to conform;*
- effective controls to monitor the quality of pharmaceutical products registered or manufactured within the country, including access to an independent quality control authority;*
- a national pharmaceuticals inspectorate, operating as an arm of the national drug regulatory authority, and having the technical competence, experience and resources to assess whether GMP or other controls are being effectively implemented, and the legal power to conduct appropriate investigations to ensure that manufacturers conform to these requirements by, for example, examining premises and records and taking samples;*

³⁰World Health Organization, *Good manufacturing practices for pharmaceutical products*, Annex 1 in WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second report, WHO Technical Report Series 823, 1992, Geneva.

³¹World Health Organization, *Proposed guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce*, Annex 3 in WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second report, WHO Technical Report Series 823, 1992, Geneva. Endorsed by World Health Assembly, *Proposed guidelines for the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce*, WHA Resolution 45.29, 14 May 1992.

³²World Health Organization, *Proposed guidelines for implementation of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce*, Annex 10 in WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-fourth report, WHO Technical Report Series 863, 1996, Geneva. Endorsed by World Health Assembly, *Guidelines on the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce*, WHA Resolution 50.3, 12 May 1997.

-- the administrative capacity to issue the required certificates, to institute inquiries in the case of complaint, and to notify expeditiously both WHO and the competent authority in any Member State known to have imported a specific product that is subsequently associated with a potentially serious quality defect or other hazard."

44. The WHO Scheme goes on to state that *"Each Member State assumes the responsibility to determine, by self-evaluation, whether it satisfies these prerequisites. The Scheme contains no provision, under any circumstance, for external inspection or assessment, either of a competent national authority or of a manufacturing facility."* This is the central element of the WHO Certification Scheme which differs significantly from the approach adopted by PIC and PIC/S or by the MRAs which require joint inspections to build confidence that the other State has a equivalent standard of inspection scheme.

45. Three documents can be requested under the WHO Certification Scheme:

-- **Certificate of a Pharmaceutical Product.** This is intended for use by the competent authority within an importing country in two situations:

- when the product in question is under consideration for a product licence that will authorize its importation and sale;
- when administrative action is required to renew, extend, vary or review such a licence.

The product licence holder or other commercially interested party in the exporting country (the applicant) should submit the following information for each product:

- the name and dosage form;
- the name and the amount of active ingredient(s) per unit dose;
- the name and address of the product-licence holder and/or manufacturing facility;
- the formula (the complete qualitative composition including all excipients); this is particularly important when no product licence exists or when the formulation differs from that of the licensed product;
- product information for medical professionals and for the public (patient information leaflets) as approved in the exporting country.

The certificate is a confidential document and as such, it can be issued by the competent authority in the exporting authority **only** with the permission of the applicant and, if different, the product licence holder.

-- **Statement of Licensing Status.** This attests only that a licence has been issued for a specified product, or products, for use in the exporting country. It is intended for use by importing agents when considering bids made in response to an international tender. It is only intended to facilitate the screening and preparation of information.

-- **Batch Certificate of a Pharmaceutical Product.** This is normally issued by the manufacturer for an individual batch of a pharmaceutical product and only *exceptionally* as in the case of vaccines, sera and certain other biological products, by the competent authority of the exporting country. The batch certificate is intended to accompany and provide an

attestation concerning the quality and expiry date of a specific batch or consignment of a product that has already been licensed in the importing country.

46. The WHO Scheme makes it clear that *"when the applicant is the manufacturer of the finished dosage form, the certifying authority should satisfy itself, before attesting compliance with GMP, that the applicant:*

(a) applies identical standards to the production of all batches of pharmaceutical products manufactured within the facility, including those destined exclusively for export;

(b) consents, in the event of identification of a quality defect...to relevant inspection reports being released, in confidence, to the competent authority in the country of import, should the latter so require."

47. A particular value of the WHO Scheme is to exporting countries. For example, in the UK the number of export certificates issued under the WHO Scheme has risen from under 8,000 in 1994/95, to 12,500 in 1996/97 and is expected to rise to 15,000 a year.³³ Currently 141 Member States of the WHO have advised that they wish to participate in the Scheme through their designated national authorities. The texts³⁴ of the replies of the participating countries demonstrate the variability in the way in which the Scheme is operated. It is clear that the value of the WHO Certification Scheme is in that it provides a guideline as to what States should endeavour to do. The aim, however, should be for States to achieve regulatory schemes that are equivalent and are recognised as such through Mutual Recognition Agreements involving joint inspections, joint training and the updating of documents in both States ensuring that equivalence is maintained.

48. Guidelines for the inspection of pharmaceutical manufacturers³⁵ are also provided by the WHO in order to promote harmonization of inspection practices among WHO Member States. These guidelines are consistent with the approaches taken by national regulatory inspectorates such as the MCA in the UK and the FDA in the US. The WHO guidelines state that these *"are directed to government inspectors - particularly those operating within small national regulatory authorities - to assist them in assessing manufacturers' compliance with good manufacturing practices (GMP)."* It is emphasized that inspection and licensing of pharmaceutical manufacturing facilities on the basis of compliance with GMP are pivotal to the operation of the WHO Certification Scheme.

49. The guidelines set out the various types of inspections:

"Routine inspection

This is a full inspection of all applicable components of GMP and licensing provisions. It may be indicated when the manufacturer:

³³Medicines Control Agency, *Annual Report and Accounts 1996/97*, London, The Stationery Office, 17 July 1997.

³⁴World Health Organization, *WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce with updated list of Participating Countries*, WHO/PHARM/82.4 Rev. 5, June 1997.

³⁵World Health Organization, *Provisional guidelines on the inspection of pharmaceutical manufacturers*, Annex 2 in WHO Expert Committee on Specifications for Pharmaceutical Preparations, Thirty-second report, WHO Technical Report Series 823, 1992, Geneva.

- is newly established;
- requests renewal of a licence to operate;
- has introduced new product lines or new products, or has made significant modifications to manufacturing methods or processes, or has made changes in key personnel, premises, equipment, etc;
- has a history of non-compliance with GMP
- has not been inspected during the last 3 - 5 years.

Concise inspection

Manufacturers with a consistent record of compliance with GMP through previous routine inspections are eligible for concise inspections. The focus of a concise inspection is on a limited number of GMP requirements selected as indicators of overall GMP performance, plus the identification of any significant changes that could have been introduced since the last inspection. Collectively, the information obtained will indicate the overall attitude of the firm towards GMP. Evidence of unsatisfactory GMP performance observed during a concise inspection should trigger a more comprehensive inspection.

Follow-up inspection (reassessment or re-inspection)

Follow-up visits are made to monitor the result of corrective actions. They are normally carried out from 6 weeks to 6 months after the initial inspection...

Special inspection

Special visits may be necessary to undertake spot checks following complaints or recalls related to suspected quality defects in products....

Special visits may also be made to establish how a specific product is manufactured as a prerequisite for marketing approval or issuance of an export certificate..."

It is also interesting to note what the guidelines have to say about the conduct of inspections:

"Announced inspections cover regular visits to evaluate new plants and new production lines and to decide on the renewal of a licence.

Unannounced inspections are necessary for concise, follow-up and special visits."

The guidelines add that

"In certain countries regular inspections are unannounced as a matter of policy."

50. The guidelines also set out how the inspection shall be prepared for and how it is carried out:

"The visit usually begins with a meeting between the inspector(s), representatives of the company or plant management, and those responsible for the products or areas to be inspected. Credentials should be presented, letters of authority inspected, and an explanation given of why the inspection is being carried out....

The meeting may be followed by a perusal of the company's documents by the inspector or by a walk-through visit, or both. This will permit the inspector to finalize the plan for the inspection. It is recommended that the inspector both develops and follows this plan independently, rather than accepting guidance from company management....

Without prejudice to the need to verify documentation, it is essential that the inspection be based largely on observation and cover the total working hours of the manufacturer. It is recommended that the inspector start the plant tour as soon as possible after arrival....

Collecting samples. It is normal practice during the visit for the inspector to take samples for testing by the official quality control laboratory. Samples are usually taken from released products... but may also be taken from stocks of raw materials or in-process material. In order to protect sample integrity, any protocol meant for enforcement or legal purposes should set out the procedures for sample collection, analysis and documentation...."

Information is also provided on the form of the report of the inspection. It is stated that:

"Inspection reports may be treated as confidential documents depending on national legislation. Under certain international agreements, reports may be exchanged between drug regulatory authorities."

Analysis and Conclusions

51. It is evident that there is considerable harmonization world-wide in respect of the GMP standards to be achieved in facilities producing medicinal products for humans and for animals. There is already mutual recognition within the European Community. MRAs have been initialled between the European Community and countries such as the US, Canada, Australia, New Zealand and Switzerland and a start made in the negotiation of MRAs with other countries such as Japan and the candidate states for the expansion of the EU. There are several international harmonization schemes which can usefully be put into context using the schematic relating product and manufacturing licences:

	Requirements for Industry	Regulatory Authority Action
Marketing Authorization <i>Product Licence</i>	Safety, efficacy & quality data EEC, ICH	Evaluation, Licensing EEC, PER
Manufacturing Authorization <i>Manufacturer's Licence</i>	Good Manufacturing Practice EEC, PIC, WHO	Inspection, Licensing EEC, PIC, MRAs

The WHO Certification Scheme has been omitted from this schematic as although it is linked to the product licence element, it does not fit easily or simply into this figure.

52. Manufacturer's authorizations (product licences) usually have a five year life and the aim generally is to reinspect manufacturers every two years. It needs to be recognized that the purpose of those inspections are to ensure that the facilities being used to manufacture a licensed medicinal product are compliant with GMP and that the processes used are such that cross-contamination of the product will not occur. Consequently, the inspection is limited to those parts of a manufacturing facility used in the production of the licensed product -- this will include everything from receipt and storage of raw materials, through production to packaging together with all aspects of the quality control of the product. Other parts of the facility which are not involved in the product manufacture will not be inspected.

53. Although there is much commercial sensitivity, the existence of both manufacturing and product licences are in the public domain -- although the linkage between a product licence and where that product is manufactured is commercially secret. It is noted that in the US steps have recently been taken to release to the public on request copies of the Establishment Inspection Report together with inspectional observations made by Food and Drug Administration (FDA) inspectors.³⁶

54. Consequently, it is clear that in pharmaceutical and biotechnological production facilities engaged in manufacturing licensed products, these facilities will increasingly be inspected at regular intervals by national regulatory authorities to monitor their compliance with internationally harmonised standards for GMP in order for these facilities to be licensed. Insofar as the Protocol being negotiated by the Ad Hoc Group is concerned, the information as to whether a production facility is licensed to GMP standards should be part of the information to be provided in declarations of such facilities. This information, together with the GMP standard to which it has been inspected, and the date of the last such inspection by the national regulatory authority will help to build confidence that the facility is compliant and is engaged in permitted purposes.

55. It follows that measures to assist developing countries establish a national regulatory system of product and manufacturers' licences to internationally agreed standards would both directly implement Article X of the BTWC and also contribute to building confidence in compliance with the Convention. Such measures would also be in accord with the actions being taken by developed countries following the Rio Summit of 1992 and the emphasis on aiding capacity building in developing countries.

56. These building blocks together with those addressed in Briefing Papers No 6 and No 7³⁷ are all measures that improve national, regional and international standards of health and safety so bringing clear public health and environmental safety benefits to all States. They also help to ensure that microorganisms and toxins are not misused for prohibited purposes and hence directly contribute to building increased transparency and enhanced confidence that the States concerned are in compliance with the Convention thus providing both national and international security benefits.

³⁶United States, *Release of Establishment Inspection Report to the Inspected Establishment*, Federal Register, 18138, Vol. 62, No 71, 14 April 1997.

³⁷University of Bradford, *Article X: Some Building Blocks*, Briefing Paper No 6, March 1998 and University of Bradford, *Article X: Further Building Blocks*, Briefing Paper No 7, March 1998. These are available on the web at <http://www.brad.ac.uk/acad/sbtwc>