



The Introduction of GMP for APIs in the European Union

European Directive 2004/27/EC, which was passed in the closing breath of the 2003/2004 European Parliament, will have massive repercussions on the manufacture and marketing of active pharmaceutical ingredient (API) products — and some excipients — across Europe. Norman Franklin gives a detailed guide to the Directive to help you through the maze of legislation, which takes force from October 2005.

Norman Franklin
is the founder of Interactive
Consulting Associates Ltd,
Switzerland.

At the end of the 2003/2004 parliamentary session, the European Parliament approved the modified proposals of the European Commission to amend the EU Directive 2001/83 on medicinal products for human use.

The amendments have been incorporated into the new Directive 2004/27 and will affect all companies holding a manufacturing authorization, for they will be obliged to use active substances (APIs) manufactured following GMP guidelines, which the Commission will publish.

This Directive will affect medicinal products manufactured for both marketing within the EU as well as exporting from the EU, and medicinal products manufactured outside the EU if these are to be marketed within the EU. This is very comprehensive legislation.

This Directive will also require certain excipients to be manufactured under GMP, but these have not been identified yet.

The commission has redefined manufacture to also include the principle of “partial manufacture” so

manufacturers of API intermediates, agents, importers, repackers and re-bellers of APIs who must follow GMP. Companies that import medicinal products will also need to ensure that the medicinal products they import contain APIs manufactured according to API GMPs.

The Commission and the European Medicines Agency (EMA) will establish a list of API manufacturers that comply with EU GMPs for APIs, presumably Annex 18 of the EU Guide to GMP.

The proposal also provides a legal basis for the inspection of all starting material manufacturers, who may request an inspection, but it is the competent authorities who will decide if an inspection is necessary.

The result of this legislation for API manufacturers is that if they wish to sell APIs to pharmaceutical manufacturers located in the EU, they will need to provide evidence that their APIs were manufactured according to EU GMPs for APIs.

Now that this Directive has been approved, the competent authorities in certain EU member states where there was no previous legal requirement to insist on GMPs for APIs, for example, Germany, the UK, Italy, etc, and the new member states are examining how they can conduct GMP inspections of API manufacturers to ensure that these are complying with GMPs for APIs before the Directive 2004/27 comes into force on 31 October 2005.

Clarification

It should be noted that none of the comments or remarks constitute legal advice, but are a common sense interpretation of the specific texts found in the "Proposals" and the "Directives" from the European Commission (the Commission) and the European Parliament, (the Parliament). The terms "active substance" and "API" are used interchangeably depending on the literature source used.

Historical Background

I previously reviewed the activities leading up to the proposals of the Commission for the regulation of APIs. Such regulation requires a legal instrument upon which a

guidance is based and in the EU this is a "Directive" and the "guidance" is GMP Guidelines.

An early move to provide the legal instrument occurred in October 1994 when the German Ministry of Health published a proposal for the "regulation of the manufacturers of active substances." Because this proposed regulation was also to be applied to manufacturers of APIs located outside Germany the Commission was forced to take action and make their own proposal. This occurred in February 1995.

The industry commented on these proposals, and at the same time took the initiative in drawing up guidance on GMPs for APIs. This guidance was published in August 1996 as a Conseil European des Federations de l'Industrie Chimique/European Federation of Pharmaceutical Industries (CEFIC/EFPIA) handbook called *Good Manufacturing Practices for Active Ingredient Manufacturers*.²

At the same time negotiations were being held with the US on a Mutual Recognition Agreement (MRA) on GMPs and, to decrease, if not eliminate, FDA inspections of API manufacturers in Europe it was requested that such inspections be included in the negotiations. Following these negotiations in May 1997, and the inclusion of GMP inspections of APIs in the agreement, the Commission needed to make firm proposals on how to introduce GMPs into the API industry.

This was included in the *First Draft of a Legislative Proposal* from 30 September 1997 and again the industry was asked to submit its comments.

We do not need to go into the details of how these proposals were reviewed, revised, reviewed again, republished and superseded.

Suffice to say that the Commission, who had had placed this topic on their list of "Items to be completed in 1998" was forced to wait until February 1999 before publishing what it hoped would be its "final" proposals for a Directive.³

Even these were not the "final" proposals and they were modified and republished again in November 2001.⁴

Introducing GMP for APIs

Alongside these legal proposals the Commission also need a regulation or a guide on GMP for "starting materials" (i.e. any component of a medicinal product, be it an active substance or an excipient).

A subcommittee of the PIC/S (Pharmaceutical Inspection Convention Scheme) had in fact been working on such a document since early 1997, but because it appeared that this would not be the only GMP Guide for APIs — with the resulting chaos if an API manufacturer had to try to follow both a PIC/S and an FDA GMP guide for APIs — the Commission proposed that this question of GMPs for "starting materials" be put to the ICH Steering Committee as a proposed topic and this was accepted in February 1998, a full year before the Commission published its first final "Draft Proposal" in February 1999.³

An API manufacturing facility in India that has been inspected by a "Competent Authority" and where there were "No major reservations." This facility should receive its "Certificate of GMP."



At the first meeting of the ICH Expert Working Group (EWG) — which was set up to draft this guideline on GMP for “starting materials” — it was agreed that this should be limited to giving advice on the application of GMP to active substances (subsequently called APIs in the EWG). The name then given to this EWG was ICH Q (for Quality) 7 (the seventh quality topic) and “a” (because it would only work on guidance for APIs). Hence the title ICH Q 7a.

Although some of the civil servants attached to the Commission expected that the EWG would rapidly complete their work by taking over this previously mentioned and, by that time, almost completed PIC/S GMP Guide for APIs, this was not to be. Both the European industrial representatives on the ICH Q 7a EWG and the people nominated by the Commission to represent the EU itself had grave reservations about this PIC/S draft and, as no unanimous agreement could be reached, this was not adopted, and the work started afresh.

An API manufacturing facility in China was inspected by FDA inspectors who concluded: “The premises were very dirty. Although this facility was only 4 years old when this picture was taken it is extremely unlikely that this facility will receive a “Certificate of GMP” unless major improvements are made.”



This reformulation of some of the basic concepts of GMP was not concluded overnight, but I, as a one-time member of this ICH Q 7a Expert Working Group, believe that the 2 years of intensive work that the governmental and industrial representatives spent in this rewriting, and reconsidering the wording, resulted in a document that is a classic example of how both industry and the authorities can effectively contribute to a very pragmatic document, which clearly takes into account the daily situations that arise in an API plant and how to deal with these.

By November 2000, however, the ICH Q 7a document had reached Step 4 of the harmonization process and was signed off by the representatives of the EU, FDA and the Japanese Ministry of Health and Welfare.

Thus, the Commission had their GMP Guide for APIs, but no legislative means for introducing this. This GMP Guide for APIs was published by the EMEA in November 2000,⁵ but with the comment that the “date for coming into operation for this guideline will be released by the European Commission, DG Enterprise, Unit for Pharmaceuticals.”

Unfortunately, although the Commission had completed the “Draft Legislative Proposal” in February 1999,³ and the required GMP Guide for APIs had been published by the EMEA in November 2000 as “Notes for Guidance”⁵ (and as Annex 18 to the EU GMP Guide in July 2001⁶), these were not incorporated into the new Pharmaceutical Directive 2001/83 passed on 6 November 2001.⁷

There were good reasons for decoupling these two pieces of legislation, and fast tracking those necessary changes to the EU pharmaceutical legislation into the Directive called 2001/83, but this “fast tracking” also meant that the legislation on GMPs for APIs was “slow-tracked.”

Thus the formal proposal to incorporate GMP for active substances (APIs) into European legislation was not repropoed until 26 November 2001,⁴ and was not finally approved until 31 March 2004 in Directive

2004/27/ EU.⁷ It had in fact taken nearly 10 years from the date of the first German proposal for GMP for APIs in October 1994 until this was passed into European legislation in March 2004.

Although it does not say in EU Directive 2004/27/EC that Annex 18 of the EU GMP Guide will be the Guidance that will be applied to determine whether an API manufacturer is manufacturing its products “according to GMP,” it is now accepted that this will be the case. This paper will assume that an API manufacturer will be judged against the guidance given in ICH Q 7a (now called Annex 18 in the EU).

Thus, we now have both a Directive (2004/27/EC) that requires that APIs used in medicinal products made or imported into the EU be made under GMP and the necessary GMP Guide, (Annex 18 to the EU GMP Guide).

Reasons for the Legislation.

In addition to the reasons already mentioned, that is, the need to extend the German proposed regulation on APIs to the whole of the EU, and the need to introduce GMPs into the API industry to meet the objectives of the MRA with the US (which has now quietly been “laid to rest”) the Commission has also included the need that “the quality of medicinal products manufactured or available in the Community should be guaranteed by requiring that the active substances ... comply with the principles of GMP” as a reasoning for the proposals.⁷

The Commission points out that when an application for a market authorization for a pharmaceutical is made to any member state, this is evaluated on its scientific merits. There is, however, no mechanism to control whether the statements made concerning starting materials are correct, or whether such starting materials are manufactured according to GMP.

The Commission also included the words “or available in the Community” to indicate that this Directive is applicable not only to medicinal products manufactured in the Community but also to medicinal products imported into the Community.

The Commission was also concerned about the risks associated with APIs that have passed through several hands and the Directive is applicable to “both total and partial manufacture or import of an active substance.”

The inclusion of the words “partial manufacture” means that the manufacture of API intermediates, will be subject to GMP, but the words “import of an active substance” may lead to different interpretations, which will be discussed later.

After the incident in Haiti in 1996 “when a number of children died as a result of taking a medicinal product contaminated with diethylene glycol”⁴ (more than 88 children died and the solvent used to make the medicinal product was primarily diethylene glycol “contaminated” with sugar and water)⁸ the Commission also announced that the “manufacture of starting materials” would include “the various processes of dividing up, packaging or presentation including repackaging and relabelling as carried out by a starting material wholesaler, broker or trader.” Thus the Directive also applies to brokers and traders in pharmaceutical starting materials, who were specifically excluded from the original German draft of 1994.

There is little point in speculating whether the use of this “synthetic glycerine” in the manufacture of the syrup for children in Haiti would have been prevented if the proposed German regulation had included “agents, brokers, repackers and relabellers” — because the actual handling of the drums of “synthetic glycerine” occurred outside Germany, even if the Certificate of Analysis was ‘issued’ in Hamburg.⁸

Another concern that originally influenced the thinking of the Commission was the risk of transmission of BSE because of the use of starting materials derived from animal sources, and therefore originally the Commission was not willing to limit the requirement to observe GMP solely to active substances, but specifically included two nonactives (gelatine and tallow).³

Although the Scientific Committee on Medicinal Products and Medical Devices believed that



GMPs should be applied to as broad a range of starting materials as possible, in the end this Directive 2004/27/EC stated that “certain excipients should be subject to these requirements which shall be established by a Directive adopted by the Commission.”⁹

The Commission will not immediately introduce GMPs for a large number of excipients (which is what some members of the Scientific Committee would have preferred), but I have been informed that it is intended to gain experience with applying GMPs to APIs before taking action on excipients, (assuming no repeat of the Haiti incident).

A further cause for concern, included in the original proposal of September 1997, was that starting material manufacturers could make changes to their products, but the medicinal product manufacturer would never be aware of these. Thus it was originally proposed that the manufacturer of the starting material should obtain the prior agreement of the medicinal product manufacturer for such changes. However although this concern had already been dropped in the official “Proposal” of 26 November 2001,⁴ it was later incorporated elsewhere in the Directive 2003/63/EC.¹¹

Legislation — Title II

Exclusions from the applicability of this Directive 2004/27/EC are found in Title II, Scope of the Directive 2004/27/EC, where in the amendments to Articles 2,11 it is said that this Directive shall apply to medicinal products prepared either industrially or manufactured by a method involving an industrial process.

This exclusion means that APIs used by pharmacies in their own compounding to a physicians prescription need not necessarily have been manufactured in accordance with GMP for APIs.

Similarly the activities of companies that divide up, package or present such active substances directly for pharmacies are not to be viewed as “active substance manufacturers” within the meaning of this Directive.

Scientifically speaking it appears difficult to justify this exclusion of pharmacies that use APIs for their own compounding. However, perhaps this requirement will be incorporated into legislation specific for pharmacies so that they also should only use APIs made under GMP, and thus give their patients protection equal to that provided to patients taking industrially prepared medicinal products.

A second exclusion is also found in Title II where, in the amendments

to Article 3, it says that this Directive shall not apply to medicinal products intended for research and development, but without prejudice to Directive 2001/20 EC.¹²

This exclusion means that it is not necessary to use active substances (APIs) manufactured according to GMP in materials for clinical trials, although the ICH Q 7a EWG specifically wrote Chapter 19 of this guide to cover this particular use of APIs.

It is, at present, not known whether the Commission will consider amending Directive 2001/20/EC (The Clinical Trials Directive)¹³ to require that clinical trials materials must also contain APIs made under appropriate GMP, but at present this does not seem likely — although the situation is known to the responsible staff of the EMEA.¹⁵

Legislation — Title IV

The key to the whole part of the legislation is found in Title IV, Manufacture and Importation of the Directive 2004/27/EC, where in the amendment to Article 46 it is said in Subsection (f):

The holder of a manufacturing authorization shall at least be obliged to comply with the principles and guidelines of good manufacturing practices for medicinal product and

to use only active substances which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials.⁹

This wording transfers the responsibility of complying with GMP for APIs from the API manufacturer to the API user.

This is primarily because there is insufficient legal authority to insist that an API manufacturer should follow GMP if the manufacturer was located outside the EU, that is, the EU cannot insist that an API manufacturer located in China follow EU GMPs for APIs.

Thus if the user (*not* the API manufacturer) is located within the EU, they must hold a manufacturing authorization and, therefore, must use APIs made under GMP.

If the medicinal products themselves are manufactured outside the EU then the holder of the marketing authorization is the importer of such medicinal products. It is, therefore, the responsibility of such an importer of medicinal products to ensure that such products, even if manufactured outside the EU, nevertheless contain APIs manufactured according to GMP for APIs.

This assignment of responsibility for ensuring that only “APIs made under GMP” may be used to make

medicinal products to the holder of a manufacturing authorization means those subsidiaries of, for example, Swiss or US parent companies will also be affected by the proposed Directive if they import from their parent company, because they will have to ensure that the medicinal products they import only contain “APIs made under GMP.”

The same is also true for importers of generic medicinal products if these were made outside the EU.

Starting materials — Article 111

It is neither the role of the competent authorities nor the EMEA to check that each starting material manufacturer is following GMP, (that is the job of the medicinal products manufacturer), but “to ensure that, by means of repeated inspections, and if necessary unannounced inspections ... that the legal requirements governing **medicinal products** are complied with.”¹⁷

Under certain circumstances the Directive also provide for “unannounced inspections at the premises of API manufacturers ... when there are grounds for suspecting noncompliance with ... GMP.”¹⁷

The Directive also permits the EDQM to request an inspection “to verify whether the data submitted to obtain a conformity certificate comply with the monographs of the European Pharmacopoeia.”¹⁶

There is thus now legislative support for the EDQM practice of requesting inspectors from certain “competent authorities” to confirm the statements made by applicants for a European “Certificate of Suitability” that the product “is manufactured following GMP.” Such a request by the EDQM must however, not necessarily be made to a “competent authority” but may be made to the Commission or the EMEA, thus the initiative lies with the EDQM. This will be discussed later in the section covering the GMP status of API manufacturers.

Finally the “competent authorities” *may* carry out inspections of starting materials manufacturers at the specific request of the manufacturer himself.¹⁶

This wording of Article 111 makes the difference between inspection of medicinal products manufacturers



and starting material manufacturers quite clear. In the first case the competent authorities must conduct “repeated inspections” of medicinal products manufacturers whilst the inspection of starting materials manufacturers by the competent authorities will only be done under one of three circumstances:

- when the authorities suspect noncompliance with GMP
- when EDQM wishes to check the veracity of statements made in an Application for a Certificate of Suitability
- when a starting material manufacturer specifically requests an inspection, and a competent authority has agreed to conduct such an inspection.

In the latter case the disturbing word in the Directive — from the point of view of a starting material manufacturer — is the word “may.”

The “competent authorities” have been given an “approval” to inspect when requested, but are not required to do so. Some authorities that are under severe financial restraints specifically requested this limitation.

There is no provision in the Directive for GMP “self-certification” as practised under the Ph. Eur. “Certificate of Suitability” scheme, so one must presume that in the future a “Certificate of Suitability” will only be issued if there is firm evidence, for example, through entry in the “Community Register,” that the API manufacturer is truly in compliance with the ICH Q 7a GMP guide.

The control mechanism by which the “competent authorities” will check whether the APIs used in medicinal products were made under GMP is the repeated inspections of the medicinal products manufacturer because, under the legislation, it is the responsibility of the medicinal products manufacturer to know if the APIs used were manufactured under GMP.

One must therefore presume that medicinal products that are not using APIs manufactured in accordance with GMP will not be in compliance with GMP for medicinal products. This fact will presumably then be a cause for an entry in the Community GMP Register with the EMEA as a

critical GMP deviation because it is contrary to the Directive.

Consequences for starting material manufacturers

Starting material manufacturers who are not manufacturing in accordance with ICH Q7a GMP will probably not be able to sell their products to the European pharmaceutical industry after 2005, even if their products are of Ph. Eur. standard or have a Ph. Eur. Certificate of Suitability, (unless they have been inspected by EDQM within the last 2 years).

Similarly foreign manufacturers of medicinal products who are not using APIs manufactured in accordance with EU GMP (i.e. ICH Q 7a) will not be able to market their products in Europe after late 2005.

Further parts of the legislation regulating this use of APIs made under GMP are also found in Title IV, “Manufacture and Importation,” where a new article 46a is added.¹⁷ This covers the concepts of total and partial manufacture and states: *For the purpose of this Directive, manufacture of APIs shall include both total and partial manufacture or import of an API and the various processes of dividing up, packaging or presentation prior to its incorporation into a medicinal product, including repackaging or relabelling as are carried out by a distributor of starting materials.*

As stated earlier the use of the wording “partial manufacture” allows the authorities to inspect — either “for cause” or “on request” — a manufacturer of an intermediate for an API, (but NOT an API starting material manufacturer, as these manufacturers were specifically excluded from the need to follow GMP in the ICH Q 7a (Annex 18) documents).⁴ It also permits a contract micronizer to request an inspection as an API manufacturer under the situation described in 4.4 (c) above, as this activity is also “partial manufacturer of an active substance.”

The inclusion of the word “import” has been raised earlier. The intention of both the Commission and the ICH Q 7a Expert Working Group in their wording of Chapter 17 of Annex 18⁵ was to close the link

in the distribution chain from the manufacturer of the API to the patient. This was not only to ensure that the source of the API is known to the medicinal product manufacturer, (so it can be checked that this source is complying with GMP for APIs), but also to prevent a repeat of the Haiti incident.

If the “starting material wholesaler, broker or trader” does not actually “import” the API into the EU, that is, it remains in bond in a community port, it is still intended that this activity will fall under the Directive. For example, if any additional label is applied to the containers of the API before forwarding to a third country this activity would be covered by this Directive 2004/27/EC.

So although the intention of the Directive is clear, the final word on this type of activity may be subject to national interpretation when the

Another API manufacturing facility in China that has been inspected by FDA with the comment: “The lack of maintenance was apparent in spite of the recent painting of the equipment.” This facility had been “modernized” before this picture was taken, but the recent painting was done before the rust was removed. The facility has introduced major quality system improvements and is preparing for a reinspection.



Directive is transformed into legislation in the member states, too lax an interpretation may however result in the medicinal product manufacturers avoiding those sites of importation if the Directive does not fully apply there, with the consequent loss of Community business at the importer.

The inclusion of the wording "various processes of dividing up, packaging ... prior to its incorporation into a medicinal product" is another, and sensible, addition to ensure that APIs are not contaminated if they are repacked into smaller units for further distribution or that they are not mislabelled.

There may be some who contend that this Article 46a (1) will not apply to those distributors of starting materials who do not perform any of the activities specifically listed in Article 46a (1). However by including earlier in the paragraph the words "partial manufacture" (which per GMP includes even just attaching an additional "Distributors Name Label") the intention of the Commission is clear, namely that any distributor of an API (and later the specified excipients) will need to follow the "detailed guidelines on GMP for starting materials" irrespective of where the facility is located or whether the company

involved just takes a sample for analysis, (another GMP activity).

In this context an interesting scenario is the broker located in a "third country" who handles an API that will be used to manufacture a medicinal product in this "third country," which then is exported to the EU. This author sees this broker also falling under Article 46 a, (1) as a "manufacturer of an active substance" and, therefore, subject, (at least) to Chapter 17 of Annex 18 of the EU GMP Guidelines, i.e. subject to ICH Q 7a).⁵

In contrast to the GMPs for medicinal products, the Commission does *not* intend to adopt GMP for APIs in the form of a Directive, but in the form of detailed guidelines.

Thus also in Title IV, Manufacture and Importation of the Directive 2004/27/EC, a new paragraph is added to Article 47¹⁸ that covers the principles of GMP for APIs as follows: *The principle of good manufacturing practice for active substances (APIs) used as starting materials referred to in Article 46, Point (f) shall be adopted in the form of detailed guidelines.*⁹ This wording was initially introduced before the proposal was accepted that such GMPs should be internationally harmonized via the ICH process resulting in the document ICH Q 7a, which was published by the Commission in July 2001 as Annex 18 to the EU GMP Guide. Although it does not say in this EU Directive 2004/27/EC that Annex 18 of the EU GMP Guide will be the Guidance that will be applied, it is now accepted that this will be the case. The wording does, however, permit the Commission to introduce any additional "detailed guidelines" without the need to go through the legal hurdles of getting another Directive approved.

The conduct of the inspections referred to in §1 of Article 111, includes

- inspecting manufacturing or commercial establishments and any laboratory entrusted by the holder of the manufacturing authorization with the task of performing checks according to §20
- taking samples
- examining any documents relating to the object of the inspection.

This wording makes it clearer that not only "manufacturers" (i.e. both total and partial manufacturers) are subject to inspection, but also that other commercial establishments, such as distributors, repackers and/or relabellers as well as contract laboratories entrusted with the examination of imported products are subject to "repeated inspections."

During such inspections the authorities were given wide powers in Directive 2001/83/EC⁷ to examine documents albeit with certain limitations placed on the description of the method of preparation of medicinal products. These limitations however *do not apply* to the description of the method of preparation of an API, and thus the "documents relating to the object of the inspection" also cover the master production instructions mentioned in Annex 18, § 6.4.⁵

Essentially, as far as inspections of manufacturers are concerned, the wording of Article 111 § 3 of Directive 2001/83/EC is not changed, although this now applies not only medicinal product, but to API manufacturers as well.

Thus it is the duty of the officials representing the competent authorities (i.e. the "GMP inspectors") to "report" whether the both the medicinal products and the API manufacturer comply with the principles of GMP, albeit different GMPs.

However, in a new paragraph inserted into of Article 111 of Directive 2004/27/EC,¹⁹ after such an inspection a "Certificate of Good Manufacturing Practices" shall be issued to a manufacturer within 90 days of the inspection. We must therefore assume that the "report" referred to in § 3 of Article 111 must also be issued within 90 days (otherwise how can a Certificate be issued?).

This part of Directive 2004/27/EC corrects the no longer acceptable situation in which once a manufacturing authorization had been granted there was no legal compulsion to ensure that the original situation which lead to the granting of this authorization was still valid. Such a "GMP Certificate" is also one way of providing evidence to a medicinal product manufacturer that the starting material manufacturer complies with the appropriate GMPs.

Comparatively modern API manufacturing facilities in China showing mother liquors being collected to recover a second crop of crystals. Although this facility was only 4 years old when this picture was taken, it illustrates the lack of precautions to prevent oxidation of the product resulting in "unknown" by-products in the API. Again it is unlikely that this facility will receive a "Certificate of GMP" unless major improvements are made.



Up to the passing of this Directive 2004/27/EC only certain member states had legislation that required GMP inspections of (certain) API manufacturers, but the competent authorities of *all member states* can expect to receive requests for GMP inspections of API facilities falling under their jurisdiction well before 30 October 2005. Otherwise one cannot insist that only APIs made following these GMP principles are used in the manufacture of medicinal products after that date.

As it is left to the competent authorities of the member states to decide whether they should inspect or not, the requirements contained in these paragraphs may, in a couple of years time, not be so valuable to a starting material manufacturer.

This is because there is no obligation for the competent authorities to perform "repeated inspection" as is the case for medicinal product manufacturers. Thus starting material manufacturers who already have a GMP Certificate of Compliance (for example, due to a European Pharmacopoeia inspection as part of the granting of a "Certificate of Suitability") may be forced to use other means to demonstrate that they are continuing to be in compliance with GMPs for APIs, particularly as the EU Certificates of GMP are only valid for 3 years.²⁰

All that remains of the original proposal of the Commission requiring API manufacturers to comply with GMP is the requirement that "manufacturers established ("located"?) in a third country (i.e. outside the EU) may be required to undergo an inspection."²¹

This wording suggests that the Commission was thinking of "for cause" inspections, that is to say, possibly, as condition for granting a marketing authorization, the manufacturer situated in a "third" country must agree to be inspected, — a scenario not adequately covered by legislation in Directive 2001/83/EC.

This paragraph of Article 111 would also permit manufacturers of starting materials located in a "third country" to be inspected by "officials representing competent authorities" for other causes. For example, to inspect the manufacturer of the "synthetic glycerine," which caused

the deaths in Haiti, (if it was known who this was!).

Who is responsible for inspections?

In the past the question as to who would actually be responsible for performing GMP inspections was not entirely clear. However, the wording paragraph of Article 111 of Directive 2004/27/EC makes this clearer.¹⁶

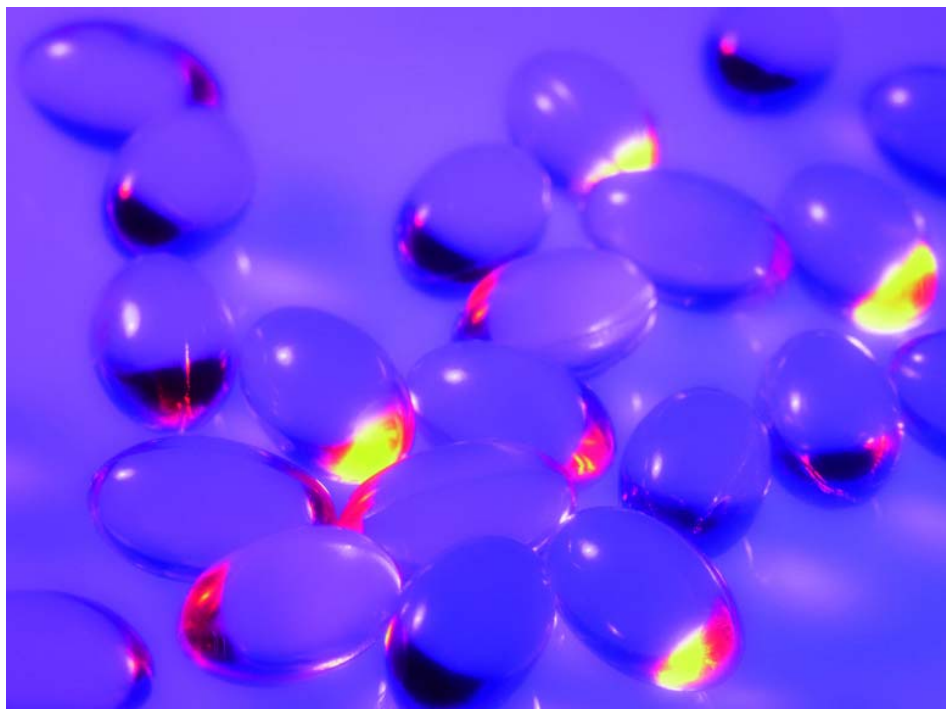
The responsibility is assigned to those authorities in the member state where the legal requirements must be checked. For example, if a medicinal product manufacturer located in Denmark is using an API and this API is being imported via Hamburg, Germany, then the Hamburg authorities are responsible for inspecting the importer for compliance with Chapter 17 of Annex 18⁵ (as a minimum).

Even assuming the Danish medicinal product manufacturer is the only user up to the present of the API this still does not compel the Danish Authorities to inspect the foreign API manufacturer, but they *may* perform such an inspection. The Danish Authorities are however compelled to inspect the Danish medicinal product manufacturer to determine whether they are using an API manufactured in compliance with API GMPs.

This division of responsibilities between Hamburg and Denmark may be satisfactory to the authorities, but may leave open who should inspect the actual API manufacturer in China.

Should "the point of entry" be the criteria for assigning the responsibility, then the German inspectorate in Hamburg will have their hands more than full in having to cover all the manufacturers in Asia (maybe as many as 700!), which use Hamburg as their port of importation and it is hoped that these authorities responsible for inspections in Hamburg accept that the retention of this import trade in Hamburg will depend upon the service that the inspectorate can give to the rest of the EU and that they will, therefore, make provisions for this additional work load on their inspectors.

The German/Danish inspection scenario described above may however be ameliorated by the "Community Register" described in Paragraph 6 and 7 of Article 111 of Directive 2004/27/EC²² in which the "member states shall enter the Certificates of GMP which they issue in a Community Register" (evidently to be managed by the EMEA in London). This register is however also to be used to record the fact that the manufacturer *does not comply* with GMP.



Although the Scientific Committee on medicinal products would have liked all excipients to be subject to GMP, insurmountable difficulties at present prevented the Commission for complying with this wish immediately and Annex II has been eliminated altogether.

Although it is stated that the member states shall make entries in the register, it is left open as to whether *only* member states may make entries. Thus a scenario could be envisaged in which an API manufacturer requests an inspection, but no member state can perform such an inspection in the immediate future.

The API manufacturer may then turn to an independent organization that is knowledgeable enough about API GMPs and has at its disposal well-qualified auditors to perform a "contract audit." Although such contract auditors may not issue a "Certificate of GMP" — this is reserved for the competent authorities of the member states — nevertheless one could imagine the EMEA acting as a repository of such an "evaluation of Compliance with GMP" as has already been indicated by responsible people in the EMEA.¹⁴

The advantage of the Community Register of GMP Compliance for the authorities is clear: it will prevent two or more different member states performing inspections at the same API manufacturer.

However, this Community Register should also be opened up to medicinal product manufacturers. This will then provide a holder of a manufacturing authorization with one way of checking if their API manufacturer has been inspected, (and the "results" of such an inspection). Other advantages are that

- When the European Pharmacopoeia issues its Certificates of Suitability they can be sure that such Certificates of Suitability are only issued to starting material manufacturers who have a GMP Certificate.
- As part of the Mutual Recognition Agreements (for example, with Canada, Australia and New Zealand), when there is a request

from a foreign power for an inspection of a manufacturer of either a starting materials or medicinal product (Pharmaceutical Manufacturer) the EMEA can check whether a new inspection is necessary, or whether there was a recent inspection.

In the latter case, whether the report of this last inspection or the Certificate of GMP is forwarded to the requesting authority will depend on the circumstances.

Originally in the Proposals to modify Directive 2001/83/EC^{3,4} it was envisaged that inspections in other member states may be done on behalf of the EU. This has however, been modified and incorporated into the Article on exchange of information between the Member States — Article 122 of Directive 2004/27/EC.²⁴

Some member states did not want to accept this original proposal at all, as it opens the door to Community Inspections and by having such an instrument on the statute books it would also imply that inspections by some member states are more "thorough" than those by other member states, a presumption that the responsible officials in the Commission have always denied.

The Commission had, therefore, to propose another way of dealing with matters if one member state could not accept the conclusions reached by another member state, (don't forget there is no "Office of Compliance" in the EU that has "the final say" in the event of such a dispute!).

Such disputes "for reasons of public health" shall be so resolved that the original inspector shall be asked to repeat the inspection; the inspector *may* be accompanied by two other inspectors from member states who are not parties to the dispute.²⁴ This elegant solution should take the heat out of any disagree-

ment between two member states who are contesting the inspection evaluation.

It is also presumable that Paragraph 3 of Article 122, which states: "The conclusions following an inspection shall be valid throughout the Community" will also apply to the conclusions reached after such repeat inspection, that is, be binding on the original parties in dispute.²⁴

It was also initially proposed that APIs should be subject to manufacture in compliance with GMP (Annex 1 Products), together with certain excipients (Annex II Products), but no specific excipients are now listed (i.e. both Annex 1 and Annex II have been dropped) and secondly the introduction of GMP for excipients has been made the subject of a "Directive adopted by the Commission."¹⁰

The initial Annex II only contained two products, gelatine and tallo as these were thought to provide the greatest risk for BSE transmittance, but then there was a proposal to add glycerine, possibly because of the serious incident in Haiti mentioned earlier.

Although the Scientific Committee on medicinal products would have liked all excipients to be subject to GMP, insurmountable difficulties at present prevented the Commission for complying with this wish immediately and Annex II has been eliminated altogether.

The timetable

The provisions of this Directive shall be applied from 30 October 2005. Although in some member states the necessary legislation will be in place before that date, there have been protests that the traditional period of 18 months between the enactment of the Directive (31st March 2004) and the date of coming in to effect, (30 October 2005) is far too short for API manufacturers to introduce the necessary GMP guidance at their establishments.

Foreign manufacturers of medicinal products will have an even shorter transition period because they have to ensure that if their products are in the hands of their importers after 30 October 2005 these products will need to have been manufactured from APIs that are themselves made

under GMP. There is pressure to delay the date of introduction of this part of the Directive.

The officials of the Commission however take the view that these proposals to introduce GMP for APIs have been known since September 1997 and the GMP guidelines themselves were published by the Commission in July 2001 as Annex 18 to the EU GMP Guide so that in actual fact the "transition period" is at least 4 years and not just 18 months.

Although it is anticipated that certain member states that traditionally take far too long to convert EU Directives into national legislation will not meet this deadline of 30 October 2005, this will be of little help for an API manufacturer who is relying on such a delay.

If their API is used in a medicinal product sold in a member state that has met the deadline then this API will have to have been made under GMP — and at least three member states already have this legislation in place.

One can, therefore, conclude that unless the pharmaceutical manufacturer is certain that their API manufacturer will meet the requirements of Annex 18 of the EU GMP within the next 12 months, then they better start looking VERY QUICKLY for an alternative API supplier.

Any API Manufacturer whose products are used in Europe to manufacture a medicinal product should assume that the deadline of 30 October 2005 will be enforced in at least some member states of the EU, so time is running out to comply fully with GMPs for APIs.

References

- European Pharmaceutical Review*, Vol. 2, No. 3, March (1999).
- Good Manufacturing Practices for Active Ingredient Manufacturers, Joint publication by CEFIC and EFPIA, (CEFIC APIC – GMP Committee, Avenue E. van Nieuwenhuyse 4, PO Box 2, B 1160 Brussels, Belgium August 1996).
- Draft Proposal for a European Parliament and Council Directive on GMP for Starting Materials and Inspection of Manufacturers, European Commission, DG III February 1999.
- 2001/0253 (COD) Proposal for a Directive of the European Parliament and of the Council for amending Directive 2001/83/EC from 26 November 2001.
- EMA "ICH Q 7a GMP Guide for APIs" ICH Step 5, EMA, London, 16 November 2000.
- The Rules Governing Medicinal Products in Europe, Volume 1V, GMP for Medicinal Product, Annex 18 GMP for Active Pharmaceutical Ingredients.
- Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community code relating to medicinal products for human use, *Official Journal of the European Union*, **L 311** pp 67–128 (28.11.2001).
- Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, *Official Journal of the European Union*, **L 136** pp 34–57 (30.4.2004).
- Results of FDA analysis of samples taken by FDA Investigator David Pulham from the two remaining drums of the solvent at the site of the pharmaceutical manufacturer in Haiti.
- Article 46 (f) of Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004, *Official Journal of the European Union*, **L 136** pp 34–57 (30.4.2004).
- Directive 2003/63/EC of the European Parliament and the Council of 25 June 2003 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, *Official Journal of the European Union*, **L 159** pp 46–78 (27.6.2003).
- Article 2, § 1 and Article 3, § 2 of Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004, *Official Journal of the European Union*, **L 136** pp 34–57 (30.4.2004).
- Article 3, § 1 of Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004, *Official Journal of the European Union*, **L 136** pp 34–57 (30.4.2004).
- Directive 2001/20/EC of the European Parliament and of the Council on the implementation of GCP in the conduct of clinical trials on medicinal products, *Official Journal of the European Communities*, **L 121** pp 34–44, (1.5.2001).
- Statement made by a senior EMA representative at the 5th CEFIC Annual Conference on GMPs for APIs, Barcelona, November 2002.
- Article 40 §3 of Directive 2001/83/EC, *Official Journal of the European Union*, **L 311** pp 67–128 (28.11.2001).
- Article 111, § 1 of Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004, *Official Journal of the European Union*, **L 136** pp 34–57 (30.4.2004).
- Article 46 (a) of Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004, *Official Journal of the European Union*, **L 136** pp 34–57 (30.4.2004).
- Article 47 of Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004, *Official Journal of the European Union*, **L 136** pp 34–57 (30.4.2004).
- Article 111, § 5 of Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004, *Official Journal of the European Union*, **L 136** pp 34–57 (30.4.2004).
- EU Certificate of GMP Compliance of a Manufacturer, Doc. Ref.: EMEA/MRA/48/02 Final, EMA London, 26 April 2002.
- Article 111, § 4 of Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004, *Official Journal of the European Union*, **L 136** pp 34–57 (30.4.2004).
- Article 111, §6 of Directive 2004/27/EC of the European Parliament and the Council of 31 March 2004, *Official Journal of the European Union*, **L 136** pp 34–57 (30.4.2004).
- Article 122 of Directive 2004/27/EC of the European Parliament and the Council of 31st March 2004, *Official Journal of the European Union*, **L 136** pp 34–57 (30.4.2004). ■