Comparative analysis between the possible regulatory approaches to GMP compliance

gnosis
advanced biotech

Dr. Fulvio CARLOTTI, GNOSIS SpA, Corporate QA Director

September 26, 2014

Scope of GMP

GMP compliance is widely-accepted as the best way to conduct business, putting product quality first.

GMP rules are a system for ensuring that products are consistently produced and controlled according to quality standards. It is designed to minimize the risks involved in any pharmaceutical production that cannot be eliminated through testing the final product.

Scope of GMP

We have to trust in the manufacturer and in the supply chain:

GMP history
USA

History begins in the USA when:

1938 – Federal Food, Drug & Cosmetic (FD&C) Act: new drug pre-marketing safety studies, prohibition of false therapeutic claims, introduction of factory inspections

1963 – First Drugs GMPs (28 FR 6385) after thalidomide tragedy: proof of efficacy, adverse events reporting to FDA, informed content for clinical studies

1978 – Human & Veterinary Drugs GMP revision (21 CFR Parts 210 and 211) resulted from FDA Task Force studying GMPs

GMP history
USA

1980s-1990s – Publishing of a series of FDA guidance documents

Some examples:

1983: *Guide to the Inspection of Computerized Systems in Drug Processing*
1987: *Guideline on General Principles of Process Validation*
1998: *Draft Guidance for Industry: Investigating OOS Test Results for Pharmaceutical Production*
1998: *Draft Guidance for Industry Manufacture, Processing or Holding Active Pharmaceutical Ingredients*

GMP history
Rest of world

Outside USA:

1963 – Resolution World Health Assembly16.36 (on drug safety and monitoring) reaffirmed the need for early action in regard to adverse drug reactions

1965 – European Union issued Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products
(where it is stated that marketing authorization is granted upon availability of physico-chemical, biological or microbiological tests, pharmacological and toxicological tests, clinical trials)

1968 – Medicines Act 1968, an Act of Parliament of the United Kingdom, which governs the control of medicines for human use and for veterinary use, which includes the manufacture and supply of medicines.

GMP history
Harmonization

As there was adequate international agreement on the technical aspects of Good Manufacturing Practices (GMP) for Pharmaceutical Products and further harmonisation action through ICH was not needed, attention has focused on the need to formalise GMP requirements for the components of pharmaceutical products - both active and inactive.

In February 1998, the ICH Steering Committee agreed that GMP for Active Pharmaceutical Ingredients (APIs) should be adopted as an ICH Topic.

ICH Tripartite Guideline Q7
Good manufacturing practice guide for Active Pharmaceutical Ingredients
(Finalised Guideline: November 2000)

GMP history
Harmonization

Implementation (step 5 of the harmonization process) occurred as follows:

MHLW Japan:
Adopted November 2001, PMSB/ELD Notification No. 1200

FDA:
Published in the Federal Register, 25 September 2001, Vol. 66, No. 186, p. 49028-9 (replaced FDA's 1998 draft guidance)

GMP history
Harmonization

EU:

Adopted by CPMP, November 2000, issued as CPMP/ICH/4106/00 and published in July 2001 as Annex 18 to the GMP Guide reflecting the EU's agreement to ICH Q7 and has been used by manufacturers and GMP inspectorates on a voluntary basis.

In October 2005 Annex 18 has been replaced by the new guidance **"GMP Part II: Basic Requirements for Active Substances used as Starting Materials"** (Eudralex, volume 4).
Last updating of GMP Part II has been published on August 2014 and is effective from September 1st , 2014.

EU approach to GMP compliance
- AIFA -

- Legal basis: Decree No. 219/2006, art. 53.
- Inspectors are spending more time looking at the equipment and the facility (e.g. cleaning procedures).
- Use of the concept of "Qualified Person", who in many cases can be held personally liable for any deviations.
- Plant tour and congruence with Site Master File.
- Verification of DMF compliance with Master/Executed Batch Record.
- Verification of Manufacturing Licence and Products produced.
- Consequences of non-compliance, which may result in penal or civil charges.

EU approach to GMP compliance
- EDQM -

- EDQM inspection programme is an integral part of Certification procedure and is elaborated in the context of the mandate given to EDQM by the European Commission in application of the Directives 2001/83/EC and 2001/82/EC as amended.
- It is aimed to check compliance with both GMP (Eudralex, Vol. 4, Part II) and the Certificate of Suitability (CEP) application (and any updates) at the manufacturing/distribution sites covered by CEPs.
- Every year, a programme of inspections is elaborated based on prioritisation, in accordance with the EU recommendations *(trigger doc. EMA/INS/GMP/459921/2010 - Compilation of Community Procedures on Inspections and Exchange of Information).*
- Inspections are carried out by official inspectors from the competent authorities in the EU/EEA, or in countries which have a Mutual Recognition Agreement with EU in GMP sector, as well as EDQM inspectors having the same qualification.

EU approach to GMP compliance
- EMA -

- The European Medicines Agency's Manufacturing and Quality Compliance Section coordinates GMP inspections of manufacturing sites connected to centrally authorised human and veterinary medicines, according to the Standard Operating Procedure "Co-ordination of GMP/GDP inspections" (document No. SOP/INSP/2048 effective from September 27, 2012).
- As manufacturers located within the EEA are under the direct supervision of **regulatory authorities in Member States**, the Agency does not specifically request inspections of manufacturers located in the EEA except when the need arises for a specific medicine, usually during the pre-authorisation phase of a centralised marketing-authorisation application.
- The majority of inspections requested by the Agency are in **countries outside the EU** ('third countries').

EU approach to GMP compliance
- EMA -

The Agency has conducted two pilot programs of inspections with international partners. One of this concerns APIs.

- Representatives from authorities in Europe, including EMA, five EU Member States (France, Germany, Ireland, Italy and UK) and EDQM conducted a joint initiative with the United States FDA and the Australian TGA on international GMP inspections of **APIs manufacturers** located outside the participating countries.
- Objectives of the initiative included **sharing of information** on inspection planning, policy and inspection reports and **joint inspections**.
- The programme began with a **pilot**, which ran from December 2008 until December 2010. During the pilot, the participants shared their surveillance lists and found 97 sites common to all three regions, resulting in the exchange of nearly 100 inspection reports and in nine joint inspections.

EU approach to GMP compliance
- EMA -

- This led to increased levels of understanding between the agencies, and a greater number of inspections of value to more than one authority.
- An interim report on the pilot was published in October 2010 and the final report was published in August 2011.
- Based on the positive experience, the agencies have agreed to **continue with their collaboration**, taking into account the experiences and lessons learned during the pilot. This has paved the way for all EU Member States to participate actively in this collaboration.
- The project has contributed substantially to a better understanding of regional approaches to inspection and the building of mutual confidence.

EU approach to GMP compliance
- EMA -

From the experience gained so far, the following measures have been recommended in order to improve international collaboration for the benefit of public health:

- to include in a shared database an all extensive list of API manufacturers registered in the different participants countries in order to identify, all shared sites which should be subjected to regular work sharing but also identify other "critical" sites for example in terms of monopoly position, etc. → EUDRA-GMDP database
- to consider the development and implementation amongst the participants of a common policy related to the re-inspection of shared sites located in third countries (frequency based on risk).

FDA approach to GMP compliance

- Investigators are focused on GMPs (deviation handling and failure investigation) and registration issues.
- Audit technique: document trail.
- Specific GMP topics:
  - Label reconciliation
  - Pre-numbered worksheets
  - Annual Product Review
  - Out of specification handling
- Consequences of non-compliance, which may result in criminal or civil charges.

Mutual Recognition Agreements (MRAs)

Mutual Recognition Agreements are essential to avoid multiple inspections, which are becoming a major problem for manufacturers.

MRAs can avoid:

- Costly re-analysis of imported products
- Have the potential to promote GMP harmonization

Stumble points to such agreements include standards equivalence and national inspection system

Mutual Recognition Agreements (MRAs)

Status of MRAs in place:

- *Australia*: Fully operational
- *Canada*: In operation, except for preapproval inspections and medicinal products derived from blood or blood plasma
- *Israel*: Operational with some exclusions
- *Japan*: Operational on 29 May 2004 - with limited scope
- *New Zealand*: Fully operational
- *Switzerland*: Fully operational
- *USA*: Not in operation

Written Confirmation

Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products introduces EU-wide rules for the importation of active substances:

- according to Article 46b(2) of Directive 2001/83/EC, active substances shall only be imported if, inter alia, accompanied by a **written confirmation** from the competent authority of the exporting third country which, as regards the plant manufacturing the exported active substance, confirms that the standards of good manufacturing practice and control of the plant are equivalent to those in the Union.

Written Confirmation

The template for the written confirmation has been published in **Part III of EudraLex, Volume 4**. The core of the declaration is the following:

THE ISSUING REGULATORY AUTHORITY HEREBY CONFIRMS THAT:
The standards of good manufacturing practice (GMP) applicable to this manufacturing plant are at least equivalent to those laid down in the EU (= GMP of WHO/ICH Q7);
The manufacturing plant is subject to regular, strict and transparent controls and to the effective enforcement of good manufacturing practice, including repeated and unannounced inspections, so as to ensure a protection of public health at least equivalent to that in the EU;
and
In the event of findings relating to non-compliance, information on such findings is supplied by the exporting third country without delay to the EU.6.

Written Confirmation

Whenever an active substance manufacturing site is found not to comply with EU GMP for active substances following an inspection by a EU member state, a statement of non-compliance (NCS) is issued and entered in EudraGMDP .
NCS are now publicly available and can be accessed through the "GMP" tab of the EudraGMDP database.

A NCS issued by a EU Member State for a specific active substance manufacturing site normally results in measures taken by the relevant EU authorities to prevent the use across the EU of the active substance(s) produced in the site in question. A NCS therefore **supersedes the corresponding written confirmation** (if it exists) issued by the third country.

Written Confirmation

Listing of third countries assessed or currently under assessment for equivalence of GMP system:

Country	Date of request	Status, Date of publication in the Official Journal of the European Union
Switzerland	4 April 2012	Adopted, Commission implementing Decision (OJ L 325, 23.11.2012)
Israel	9 May 2012	Contacts ongoing.
Australia	18 September 2012	Adopted, Commission implementing Decision (OJ L 113, 25.4.2013)
Singapore	17 September 2012	No listing for the moment (the relevant Singapore legislation provides for a non-mandatory GMP certification scheme). Contacts ongoing. In the meantime, Singapore issues written confirmation.
Brazil	4 October 2012	Equivalence assessment ongoing
Japan	6 December 2012	Adopted, Commission implementing Decision (OJ L 152/52, 5.6.2013)
United States	17 January 2013	Adopted, Commission Implementing Decision (OJ L 169/71, 21.06.2013)
New Zealand	26 June 2013	Assessment ongoing

USP Verification Services

U.S. Pharmacopoeia offers verification services for dietary supplement finished products, dietary ingredients, pharmaceutical ingredients, and excipients. Products and ingredients that meet all USP verification requirements—including a GMP audit, product and ingredient testing, and manufacturing documentation review—are awarded use of the distinctive USP Verified Marks.

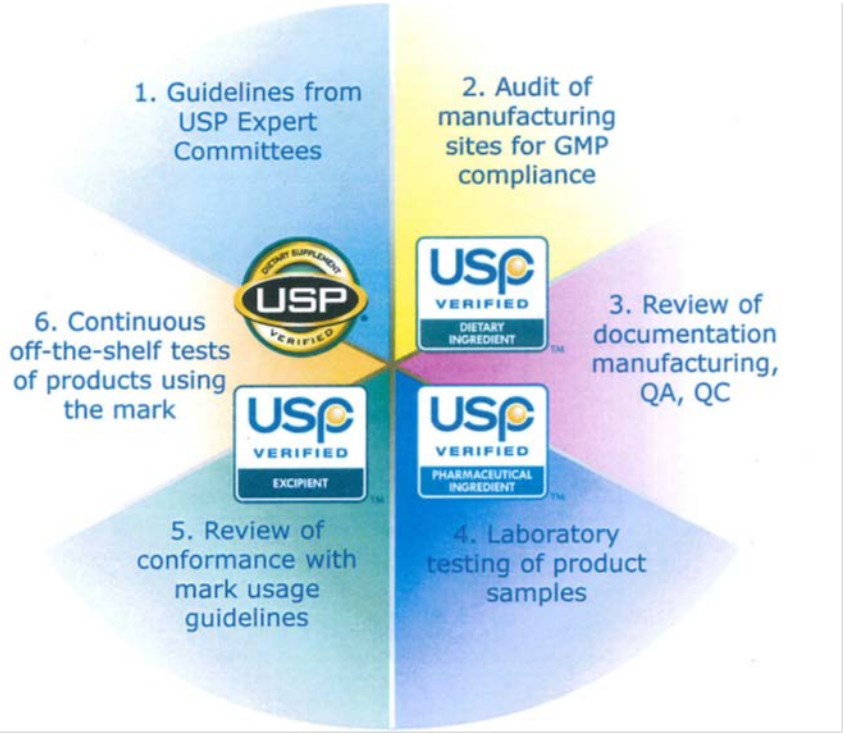
Participation is voluntary and available to manufacturers worldwide.

USP's verification services draw upon experience setting federally recognized public standards of quality for medicines, dietary supplements, and foods. USP has been establishing standards since 1820, and, today USP standards are used in more than 140 countries.

USP Verification Services

Key Elements of the Verification Programs

Participating companies go through several months of rigorous tests and reviews to meet USP's high standards and earn the USP verified mark.



USP Verified Pharmaceutical Ingredients

U.S. Pharmacopoeia offers a rigorous third-party verification program to help companies reach best practice quality management for drug substances used in the manufacture of drug products and demonstrate that their ingredients are of consistent high quality. USP experts provide participants with a good manufacturing practice (GMP) audit of manufacturing facilities and operations based on ICH Q7; a review of drug substance chemistry, manufacturing and controls (CMC) documentation; laboratory testing of drug substances for conformance to specifications; and ongoing change monitoring and surveillance.

USP Verified Pharmaceutical Ingredients

Ingredients that meet USP's stringent requirements are awarded a Certificate of Standards Compliance and use of the USP Verified Pharmaceutical Ingredient Mark.

The Mark can be used on the bulk label of each container of verified ingredients and on the accompanying certificate of analysis. The Mark provides assurance that the ingredient is manufactured in accordance with internationally accepted GMPs for pharmaceutical ingredients; meets label and certificate of analysis claims for identification, strength, purity, and quality; meets acceptable limits for impurities and contaminants; and is consistent in quality from batch to batch.

Conclusion

Based on this brief excursus, we can say that regulatory approaches on GMP compliance have reached a good degree of harmonization, allowed by the great efforts carried out by all the regulatory bodies involved.

Thank you for the attention.