

# EU GMP Evolution or Revolution

## Scope and drivers for EU GMP changes

August 2015

Gordon Farquharson



# EU & PIC/S Harmonisation at IWG level now



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

The European Medicines Agency

London, 8 May 2012  
EMA/352642/2012



Pharmaceutical Inspection Convention  
Pharmaceutical Inspection Co-operation Scheme

Geneva, 8 May 2012  
PS/W 2/2012

## **Addendum No. 1 to the Cooperation between the Pharmaceutical Inspection Co-operation Scheme PIC/S and the European Medicines Agency of 28 December 2010**

### **Harmonisation of PIC/S and GMP IWG Consultation Procedure**

Whereas the Co-operation between the PIC/S and the EMA of 28 December 2010 foresees an exchange of information, a harmonisation of the drafts developed should be achieved prior to and after public consultation in a procedure based manner described in this document.

# EU & PIC/S Harmonisation (1)

## 1. Scope of co-operation

The GMP Guide and related documents should be harmonised between PIC/S and the GMDP IWG (although they need not be identical) to keep the regulatory environment equivalent between the different regions and thus enable a better exchange and use of information concerning the manufacture of medicinal products.

To reach this goal, there should be an effective and co-operative exchange of information, including drafts and proposals, between both parties on all on-going revisions of existing documents or on the adoption of new documents, and this without delay.

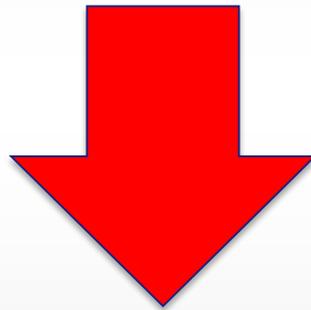
A list of documents subject to harmonisation will be established and contain regularly up-dated information on their status.

## What does this mean in practice?

- PIC/S follows EU (6 months delay)
- PIC/S nations adopt PIC/S changes (up to 6-12 months delay)
- Continuous revision to our GMP guidance
- And, in the case of Annex1, a joint revision has been announced.

# My objective in this presentation

To explain why we are moving from traditional fairly rigid GMP expectations



A much more flexible approach  
(Risk and Science based)

# Some key factors driving the Pharma & Life Sciences industry today

- Many APIs – Increasing potency & toxicity
- Reducing scale of manufacturing – personalised medicine
- Increased complexity
  - Products & Processes
- Increasing novelty
  - Products & processes
- Pressure to start facility projects as late as possible
  - Product development projects fail in late phase clinical trials.
  - Need to get into market quickly.
  - Need to be able to implement process improvement & efficiency.
- Squeezed profit margins
- Sustainability aspirations & targets
  - Energy saving
  - “Green chemistry”



# Evolution of our industry

Discussing the stock market, & the development of the companies  
blue chip R&D companies:

- “What we are seeing now is a similarly decisive distinction favoring companies that made an early commitment to focus on specialty biologics for hard-to-treat conditions affecting small target populations.”
- “.....the strategy dialogue within biopharmaceuticals today has shifted from celebrating bigness and scale—organizational attributes deemed critical to finding that “blue ocean space” beyond the reach of competitors—to embracing the concept of “fleetness,” where the ability to make rapid, turn-on-a-dime decisions is essential to keeping pace with a business environment in perpetual motion.”

*Both quotations from PharmExec June 2014*

# Evolution of our industry

Discussing the Generics & Biosimilars companies:

- “A combination of factors has been responsible for the trend of increased generic usage in the United States and globally. The expiration of patents, emerging markets, an aging population, the increase of chronic diseases, and the efforts of governments and health care service providers have all contributed to the increased use and acceptance of generic drugs.”
- “An important factor for increased generic drug usage is that the decreased cost of the generic is attractive to the consumer. Although much of prescription cost is covered by third parties, patient costs are often significantly less for generic products. The third parties or pharmacy benefit managers encourage or require the consumer to use a generic drug when possible.”

# Industry concerns

## EU GMP vs PIC/S GMP

- EU GMP generally applied in well developed markets with an open regulatory system.  
PIC/S GMP applied in a very broad spectrum of markets, some still looking for a more traditional constrained approach.
- Desire to avoid being forced into investing unnecessary segregated and dedicated facilities.



### Rigid GMP guidance:

- Some firms want clear/absolute guidance.
- Others want flexibility.
- Some want to be able to make post-approval changes more readily.

# Regulator concerns

## Regulator concerns:

- See firms often resistant to making process improvements; due to regulatory overhead.
- Feel there is a lack process improvement.
- Worry that 3-magic batches is perceived as the ultimate process quality & validation goal.



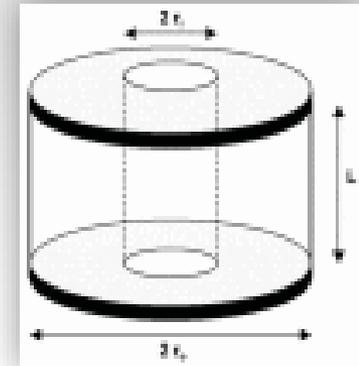
# Our GMPs were rigid.....they are now becoming more flexible

The core of the text was written in the 1970s; when life was different.

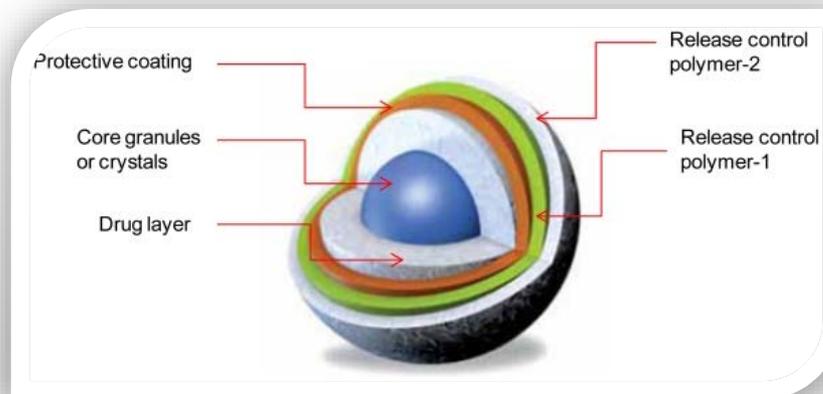
- Pharma industry likes to be safe and have a consistent approach.
- Historically there were NOT many different ways of formulating and presenting products:
  - OSD – tablet, & capsule.
  - Sterile liquids in vials or ampoules.
  - Sterile powders – dry fill or lyophilised.
  - Oral liquids.
  - Topicals.
  - Inhalations.

**Life was simple** for the Industry and its **GMP Inspectors**.

# But now our products are becoming more sophisticated

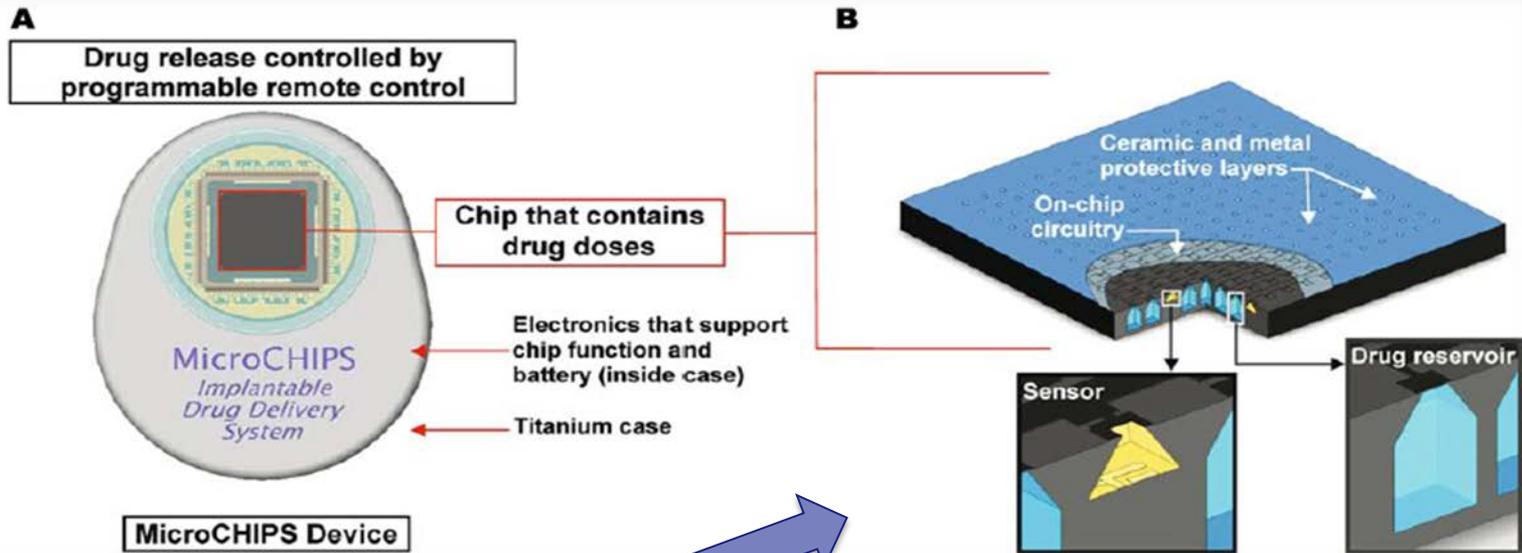


A novel compression-coated doughnut-shaped tablet design for zero-order sustained release.  
[Eur J Pharm Sci. 2004]



A schematic representation of Sodas® multilayer tablet technology  
(adapted from Elan drug technologies)

# But now our products are becoming more sophisticated

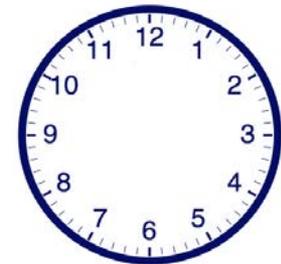


A novel micro-chip implantable drug delivery device.



# And our processes are becoming more sophisticated

- Increased automation (not a bad thing because of personnel variability).
- Closed v.s. Open.
- Continuous & Semi-continuous vs Batch
- PAT:
  - Real-time measurement of product attributes.
  - Real-time release testing.



# So we can look at these trends as a risk matrix



Risk	1 Low	2 Medium	3 High
<b>Dosage form</b>	Non-sterile	Low bio-burden	Sterile
<b>Product design</b>	Simple		Complex
<b>Manufacturing technology</b>	Well proven Established		Novel
<b>Process equipment</b>	Simple		Complex
<b>Supply chain Complexity</b>	Single party		Multiple parties

# Some underpinning requirements of the EU & PIC/S GMPs

From the introduction:

- The Guide is not intended to place any restraint upon the development of any new concepts or new technologies which have been validated and which provide a level of Quality Management at least equivalent to those set out in this Guide.
- The GMP guide will be regularly revised in order to reflect continual improvement of best practices in the field of Quality.



# So this all drives a more open style of risk/criticality based approach

- GMPs continually evolve.
- GMPs must become less prescriptive because our industry is more complex.
- Risk and science based approach enable educated practice, and continuous improvement:
  - ICH Q8, 9 &10 implementation.
  - PAT & RTRT
- We should take advantage of available technology.
- Technology itself initiates change.



# Keeping up to date – essence of cGMP



U.S. Food and Drug Administration  
Protecting and Promoting Public Health

[www.fda.gov](http://www.fda.gov)

## Would you consider the following CGMP Compliant?

4. Firm is using significantly outdated production technology that allows for excessive variation, leading to major manufacturing and quality problems. The firm has never implemented any of multiple, highly capable contemporary *innovations* in processing equipment that would resolve the problem. In contrast, these technological improvements to process design are routinely used by many others (feasible and valuable) to assure a robust and reproducible process.

*Richard L. Friedman, Associate Director, Office of Manufacturing and Product Quality Office of Compliance Center for Drug Evaluation and Research FDA, September 2012*

# How do GMPs deal with all this ?

**Answer:** Risk and Science based thinking!

They push the problem back to us!

- We must know the critical quality attributes of the product (CQAs).
- We know what affects the quality, & how to make it consistently (CPPs).
- We know how to confirm the quality (QC test, parametric release, or real-time release testing *RTRT*).
- We must use best practice and available technology.

We explore and document our conclusions through formalised processes of Quality Risk Management ICH Q9 (Part III – GMP related documents).

# The Risk based approach everywhere

It places responsibility with us...

## It is...

- having a clear understanding about the impact of the Process & Process Parameters (CPPs) (ICH Q9).
- undertaking appropriate Qualification and Process Validation with on-going verification (continued/continuous) Annex 15.
- using a scientific basis (instead of woolly words) for evaluating the risk of cross-contamination.
  - New Chapter 3 – using toxicological evaluation.
  - New Chapter 5.17 to 5.22 – measures based on the assessment of risk, and toxicological evaluation.

# The Risk based approach everywhere

It places responsibility with us...

**It is not** taking a calculated risk about the safety and efficacy of the product.

**Will be all about a** new version of Annex 1 for sterile products (now in revision).

# And finally!

- We have seen a huge amount of change in 2014.
- Risk based thinking allows the GMPs to have broader coverage by being more general and inclusive.
- 2015 looks just as interesting (from EMA Inspectors working group)!

**GMP guide : annex 1** – To provide a draft text for public consultation.

**GMP guide : annex 13** – To update the annex in the light of the new clinical trials regulation.

**GMP guide: annex 15 (validation)** – To finalise the revision to update guidance including any necessary changes to maintain consistency with the new CHMP guideline on process validation in the light of ICH Q8, Q9, Q10.

**GMP guide: annex 17 (parametric release)** – To finalise the revision aimed at updating this annex.

**GMP guide: annex 21 (New: Importation of medicinal products)**

– To prepare a Concept Paper and to provide a draft text for public consultation;

Thank you for your time.  
Questions?



**Gordon Farquharson**

Executive Consultant

[gordon.farquharson@pharmout.net](mailto:gordon.farquharson@pharmout.net)

[www.pharmout.net](http://www.pharmout.net)

