EU Regulatory Update

Presented by Bryan Wright

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National GMP & Validation Forum

Hosted by PharmOut

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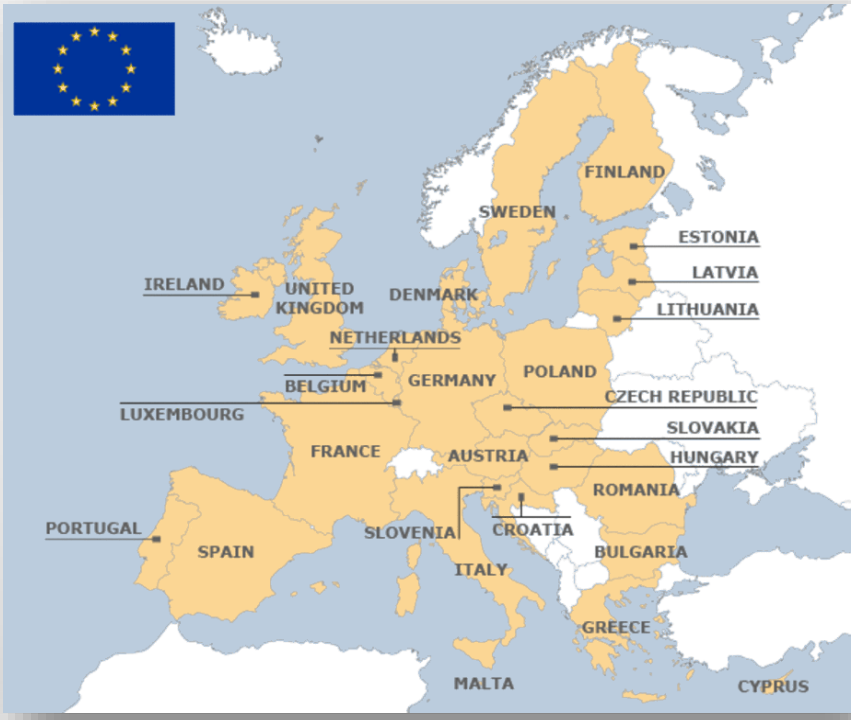
Why an EU Regulatory Update ?

- Parts of EU GMP and PIC/S GMP are similar
- What happens today in EU GMP is usually in other GMPs tomorrow
- EU GMP may offer a different way of looking at GMP issues
- Those who are producing for the EU market will need to ensure they are aware of and manufacture to current EU GMP guidelines



Due to size and complexity of the EU the legislation can be difficult to understand so we will look at GMP changes to clarify any confusion

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Overview

- Look at the EU GMP Guide and the drivers for change
- Brief review of what EU Regulatory Agencies do (e.g. EMA & MHRA)
- A review of recent past, ongoing and future EU GMP changes
  - Chapters 3, 5 & 8 and Annex 1, 13, 15, 16 & 17
  - Others – Falsified Medicines Directive, Shortages…
- Impact (context and significance) of the changes - not a full description of the regulatory change itself

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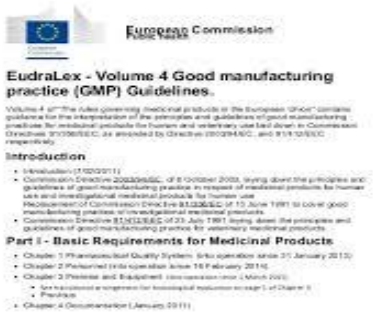
How many EU GMP Guides are there?

One Guide with three Parts

- Part 1 & Part 2 with Annexes enforceable
- Part 3 with advisory/reference documents


European Commission

EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines

Introduction

Part I - Basic Requirements for Medicinal Products

Or, is there more than one Guide ?

- In Sept '15 EC launched two consultation documents (effectively they changed legal framework to allow them to issue two additional GMP guidelines)
- The consultation was centered around withdraw Annex 13 from the current guide and re issue as a separate GMP guideline on IMPs
- Similarly a second consultation was launched for ATIMPs/ATMPs guidelines

How will this breakup of the existing Guide and the issue of updates to the new Guides be managed and what is the link to IWP and the Inspectors?

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Some aspects of what EMA does

- Protects public health by scientific evaluation and supervision of medicines
- Propose amendments and new legislation and implements same
- Act as the Supervisory Authority for centralized products*
- Ensures collaboration globally e.g. MRAs & interaction with HMA
- Relatively small but active Compliance Unit (5 to 8 staff – no inspectors!)
- Coordinates and is subject to equivalence programs e.g. BEMA and JAP
- Hold ***IWP meetings*** **- EU GMP revisions** & Compilation of community procedures (Quality System)
- Publishes EudraGMDP – database of MA, MAI, GMP certificates and non compliance statements – publically accessible

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Drug Shortages –as an example of work undertaken by EMA

Increasing awareness of the issue and coordinating actions:

- Published a reflection paper
- Delivered workshops and many presentations on shortages – for all stakeholders
- Established and runs a virtual regulatory group with reps from NCAs
- Established an Inter Association Task Force (ISPE, PDA & EFPIA)
- Publications & Gap Assessment Tools were produced and are available free e.g. ISPE
- Looked at potential changes to EU Guide re shortages
- Continues to lead by establishment of project work streams and plans for additional conferences/work shops in the future

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National Competent Authorities (NCA)

- Agencies with Reporting lines to their (local) government
- Goal to protect patient health by monitoring safety quality and efficacy
- Exact number of Inspectors and Assessors vary depending on Agency
- All operate to a Quality System subject to routine audit (BEMA & JAP)
- Issue manufacturing and (**national**) marketing Authorizations (MA)
- Responsible for *sites on own territory and overseas* (third countries)
- Contract receiver (e.g. for EMA inspection work) and **attends IWP** meeting
- Different Agencies exhibit different degrees of leadership with different regulatory issues

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MHRA as an example of a NCA

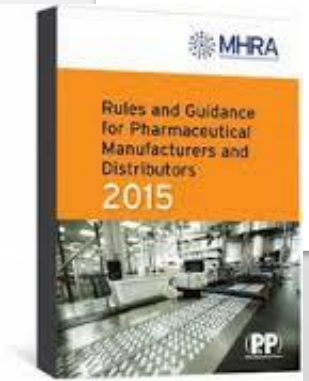
Some examples of what MHRA & their Inspectorate does (in addition to inspections!):

Communicate to all stakeholders

- Publish Inspection findings
- Hold regular consultation meetings with industry representatives
- Hold their own conferences (on a regular basis) and present at others
- Publish Blogs for guidance

Ensure regulation is not a detriment to pharmaceutical development

- Innovation office



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Blogs

MHRA recognizes the importance of giving appropriate interaction and guidance to Industry as an aid to compliance:

A range of blogs from all parts of GxP are published; perhaps the most notable is a series of short articles on data integrity:

GMP Date Integrity: a new look at an old topic – *Part 1 (June 2015)*

Part 2 (July 2015) and Part 3 (August 2015)

These established MHRA as one of the main players in the harmonization of data integrity requirements – there have been numerous presentations on this subject since publication.

Recent blogs: **QP Discretion & Review of blogs so far and future issues**

Industry Seminars and Inspection findings

Seminars (Consultative Committees meetings): various types e.g. Blood, GCP & GMP/GDP

- Membership – representative heads of different sectors of industry
- Meeting Frequency – roughly twice a year
- Role - Forum for discussion of issues (processes on web page)

Inspection findings (metrics):

- For all areas of GxP (GMP/GDP, GCP, GPVP etc.)
- Actively look at different ways of presenting these so actually helpful to industry e.g. with case studies etc.
- These are also picked up in the various symposiums and as appropriate the consultative committees

Minutes of meetings and details of findings (each year) on web

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MHRA Innovation Office

Intention is to recognize innovation and bring new products speedily and safely to patients. Actively promoted and backed by a ministerial strategy group

Functions as a cross regulatory agency advice source i.e. covers

MHRA, HTA, HFEA & HRA. Hence allows a single industry input to deliver recommendations to various areas of government.

From personal experience – efficient and easy to use and confidentiality is assured – web site has various case studies…

Similar in some ways to **FDA Emerging Technology Teams** – see FDA "Guidance for Industry on Advancement of Emerging Technology Applications To Modernize the Pharmaceutical Manufacturing Base"

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EU GMP change and time lines

YEAR	YEAR	YEAR	YEAR
2014	2015	2016	2017
Regulation	**Regulation**	**Regulation**	**Regulation**
Prior to this date - **FMD** - various legislation to be implemented over coming years	**Chapter 3 / 5**: dedicated facilities **Chapter 5:** starting material controls **Chapter 8:** clarifies reporting responsibilities **Annex15:** validation	**Annex 16** certification by QP **Annex 17** " parametric release **Annex 21** importation control	**Annex 1**

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Directive 2011/62/EU on Falsified Medicinal Products

An example of a Regulation from the past influencing the future:

Supply chain

- Delegated Act on appropriate GDP for APIs and GMP for Excipients (These will be covered in other parts of the conference)
  - GDP for APIs & new rules for import of actives
  - GMP for Excipients & a controlled traceable supply chain

Safety features

- Introduction of a unique identifier, an authenticity verification system and a data repository system for product data.
- For POM (actually white and black lists) the safety features required for each pack are a unique identifier and a tamper evident seal. Clock started on 9th Feb 2016 (Clock is ticking! complete by 9th Feb 2019)

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Chapters 3 & 5 (Equipment & Premises and Production) – effective March '15

Reason for Change

Introduction of the concept of Risk management (ICH Q9) and potential need for segregation of facilities

Reference to 2014 Safety Working Party toxicological assessment guidance (Guideline on setting health based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities.) Approach to deriving exposure limits consistent and scientifically based. Residue limits derived from Toxicological evaluation (PDE) *More detail in Annex 15 and Part III of Guide*

Significance of Change (from December 2015)

- Gives improved guidance (a harmonized approach) on prevention of cross contamination and use *of* segregated dedicated facilities.
- Requires appropriate organizational and technical control measures to address the hazard and ensure risk is controlled (R vs H vs Ex)

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Chapter 5 (Production – Starting material controls) March 2015

Reason for Change: ICH principles and Supply chain traceability

Significance of Change:

It is expected that:

- An audit of manufacturers and distributors of active substances is performed:
  - References GDP for APIs - EC guidance on API distribution requirements (a document that is based on EU GDP guide and Part 11 of EU GMP Guide)
- Following a formalized quality risk assessment appropriate controls will be put in place for excipients and excipient suppliers:
  - References EC GMP for excipients for establishing a control strategy and determining risk profiles

Clarifies expectations on manufactures regarding

- Testing of starting materials and
- Notification for restrictions in supply – (potential) shortages

Chapter 8 Complaints Quality Defects & Product Recalls – March 2015

Reason for change: Quality risk management principles incorporated. These principles to be used when investigating quality defects/complaints and when making decisions in relation to product recalls and other risk mitigating actions.

Significance of Change:

- The causes of quality defects /complaints to be investigated and determined and appropriate preventative actions are put in place to guard against a recurrence
- Also expectations and responsibilities in relation to the reporting of quality defects to the Supervisory Authority clarified

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Annex 15 (Validation) – Oct 2015

Reason for change:

Accommodates principles of ICH 8, 9, 10 & 11 and process validation and changes in manufacturing technology

Significance of change:

- Risk based targeting of qualification and validation activities with new sections (as might be expected as global supply chains become more complex) verification of transportation utilities and test methods.
- Permits "traditional" validation (validation using 3 batches) approach as well as "continuous process verification" & removal of retrospective validation
- Concern expressed about the process validation terminology i.e. allows for **continuous** process validation (different from FDA **continued** process=ongoing process verification in EMA - different regulatory systems)

Annex 16 (Certification and Batch release) Oct 2015

Reason for change: ICH 8, 9 & 10 principles introduced, changed manufacturing and supply practices (globalization of supply chain and impact of FMD), improved harmonization across EU

The significance of the change:

Requirements for *certification* spelled out:

- Entire supply chain to be fully documented
- All starting material & manufacturing sites audited and audits available to demonstrate compliance with MA.
- APIs to be compliant with GMP & GP
    - Excipients – appropriate GMP based on formalized risk assessment
    - Manufacturing sites GMP compliant & if manufacture in Third Country must comply with MA and follow GMP at least equivalent to EU GMP

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Annex 16 (Certification and Batch release) Oct 2015

Reason for change: Member States consistency improvements

The significance of the change:

Interpretation of section 3 causing concern.

" ...QP may consider confirming compliance/certifying a batch where an unexpected …deviation concerning *manufacturing process* and/or analytical control methods from details contained within the MA and or GMP has occurred..." but requires thorough investigation, correction of root cause and may require a variation to the MA .

Consistency of approach may need time - Issues:

Subjectivity when considering retrospective risk assessment,

Impact on Safety Quality and Efficacy, Stability, "unexplained" re biologicals, QP knowledge of issues earlier in manufacturing chain.

See MHRA blog – published in June 2016

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GMP for IMPs

Annex 13 to be replaced by ***Guidelines for IMPs***

Reason: Changes in line with CT regulations

-there will be cross referral to chapters and annexes of Eurdralex v4

- some items of Annex 13 will be removed

Significance:

Labeling requirements as per CT regulation annex VI already a concern

- Changes to requirements for immediate and outer packaging particulars – expiry dates to be detailed
- Labeling requirements are mandatory & can not opt out e.g. if IVRS used

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Ongoing now

Annex 17 - RTRT

Reason: ICH principles incorporated – "combination of process controls together with timely monitoring and verification of pre-established material attributes provides greater assurance of product quality" than end product testing

Significance:

- Broadens the release of terminally sterile products to align with QWP guideline on RTRT – awaiting publication, comments closed December 15

Annex 21 –Importation (Not in the PIC/S Guide)

Reason: To pull together existing GMPs for Importation into EU

Significance:

- Greater clarity of what is expected (should be available Aug 2016)

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Annex 1 (the future)

Covered in conference so here simply as an example of future change:

- **Reason for change:** Questions about skill level, introduction of principles of QRM, and focus on new technology e.g. WFI & ATMPS
- **Significance:** Cohesion EU & PIC/S. It is a revision not a rewrite!
- **Expectation:** Integration of changes to Chapter 5, Annex 15

  Discussion taking place around other expected changes e.g. Media fills & small batches, clean room qualification, BFS technology & closed systems
- **Time line:** Public consultation closed, rewrite underway, draft for comment expected Q3 2016

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Drivers for change and the future

A number of drivers for change have been highlighted e.g. Scientific/Technical advancement, Global Supply Chain, Shortages and one of the biggest the incorporation of the principles of ICH 8, 9 & 10

Gives rise to the question what changes can we expect with ICH 11 & 12?

Problem statement for Q12 includes – a focus on lifecycle management and questions about industry use of anticipated flexibilities from ICH Q8 to Q11 (e.g. delays in implementing improvements)

It will be interesting to see how this translates into changes to site visits and the requirements detailed in the EU GMP guidelines

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Conclusions

- There appears to be a lot of change within EU GMP however when compared with other areas of the world there are many regulatory areas that may still require a greater focus e.g. metrics, bio similars, continuous manufacture, training etc.
- Certainly going forward further change is inevitable
- This has been a quick review of some EU GMP regulatory changes
- Hopefully it has improved your clarity about the significance of some of these changes….

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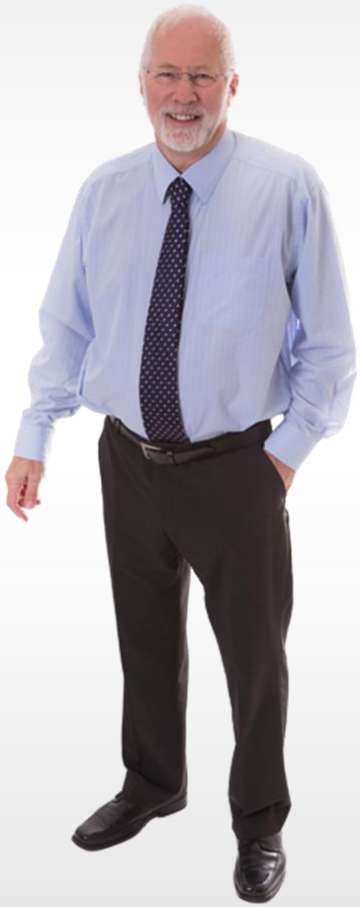
Regulatory Knowledge, Practically Applied.

Thank you for your time. Questions?



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Questions from me – for Q & A session

- What is the level of interaction between industry and your local NCA? MHRA lead in communication - is this the same with TGA? If not what do they lead on?
- Many of the changes I have talked about in the EU are being picked up by PIC/S, are they being implemented in Australia? If not now, is there a time proposal for these changes ?
- How confident are you about the MRA with the EU given these changes?
- If you were subject to an EU inspection (due to say a serious patient issue in the EU) would it present you with any problems?
- What do you intend to do (if anything) about any of the above?

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Glossary

EFPIA - European Federation of Pharmaceutical Industries and Associations
SA - Supervisory Authority
NCA – National Competent Authority
MS – Member States
MRA – Mutual Recognition Agreements
MA – Marketing Authorizations
RTRT – Real Time Release Testing
QS – Quality System
HMA – Heads of Medicines Agencies
JAP – Joint Audit Programme
IMP – Investigative Medicinal Products
POM –Prescription only Medicines
IVRS – Interactive Voice Response System
IWP – Inspectors Working Party
BEMA – Benchmarking European Medicines Agencies

Useful links

Annex 13 & ATMPs

http://ec.europa.eu/health/human-use/advanced-therapies/developments/index_en.htm

EudraGMDP

http://eudragmdp.ema.europa.eu/inspections/displayHome.do

Shortages

http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/01/WC500200296.pdf

http://www.ispe.org/drug-shortages-initiative

MHRA, MHRA Blogs, MHRA Data Integrity & MHRA Innovation office

https://www.gov.uk/guidance/good-manufacturing-practice-and-good-distribution-practice

https://mhrainspectorate.blog.gov.uk/2015/06/23/welcome/

https://www.gov.uk/government/publications/good-manufacturing-practice-data-integrity-definitions

http://www.mhra.gov.uk/Howweregulate/Innovation/

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Useful links

MHRA Consultative Committees & Inspection findings

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/483846/GMP-GDP_CC_minutes_Oct_2015_FINAL.pdf

https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/449074/BLOOD_CONSULTATIVE_COMMITTEE_newsletter_March_2015.pdf

FDA Guidance Document

https://www.federalregister.gov/articles/2015/12/23/2015-32316/draft-guidance-for-industry-on-advancement-of-emerging-technology-applications-to-modernize-the

Safety Working Party Tox Document

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/11/WC500177735.pdf

EMA (EU GMP Guide)

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

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