

Legislation Update

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Current Regulatory Developments

- EU Initiatives
 - Directives and Regulations
 - GMP Guidelines
- UK Initiatives
- ICH initiatives
 - ICHQ8(R1), Q9, Q10 and Q11
- Other international initiatives
- US FDA initiatives

Directives and Regulations

Recently Revised/Implemented EU legislation

- Human Medicines Directive 2004/27/EC
 - Atypical APIs
 - “Certain Excipients”
 - GMP Certificates and EudraGMP database
- Variations system
- Advanced Therapies Regulation

EU Directive 2004/27/EC

- APIs must be made in accordance with GMP (ICH Q7a, Part 2 of EU GMP guide)
- QPs will have to declare APIs have been made in compliance with GMP
 - When MA application or Variation is submitted
 - De facto when releasing finished products

'Atypical' APIs

- Where primary use of the active substance is not in a medicinal product and the producer is not aiming to meet the specific requirements of pharmaceutical customers who represent an insignificant volume of business

'Atypical' APIs

- EMEA advice on Q&A section of website:
 - Seek alternative sources
 - In exceptional circumstances the MA holder should assess and document to what extent GMP is complied with and provide a risk-based justification for the acceptance of any derogation
 - The QP declaration should set out in detail the basis for declaring that the standards applied provide the same level of assurance as GMP

EU Directive 2004/27/EC

- 'Certain excipients' must also be made in accordance with GMP
- List of the 'certain excipients' to be published in a separate Directive

EU and Excipient GMP

- Questionnaires issued in March 2007
 - Replies were due by 30 July 2007
 - January 2008 - Independent analysis of responses showed that implementing GMP for excipients will have little or no benefit but will add cost

EU and Excipient GMP

EU Commission, June 2009:

“DG Enterprise and Industry has taken the decision not to continue with the preparation of a Commission Directive on GMP for certain excipients”

- All excipients need appropriate controls
- Use risk assessment to determine needs
- IPEC/PQG Guide provides a baseline

EU Directive 2004/27/EC

- GMP Certificates & EudraGMP

- EMEA will issue GMP certificates and keep a database, EudraGMP, of approved and non-approved manufacturers
 - Applies to all GMP inspections
 - Certificate issue and database entry to be within 90 days of inspection
 - EudraGMP database became operational Apr 2007

EU Directive 2004/27/EC - EudraGMP database

- EudraGMP version 2 went live July 2009
 - Public access to information on GMP certificates
 - Access at <http://eudragmp.emea.europa.eu>.
 - Initial limitations:
 - Not all National Competent Authorities have entered their data; e.g. UK MHRA. List of the countries providing data is on the introductory webpage
 - Due to the 3 year inspection cycle, information will not be complete until 2011.

New Variations Process: Co-decision

- Objective is to modify the legal basis of the Variations Regulations, so that **all** authorised medicinal products, **including those authorised at a purely national level**, are subject to the same criteria for the evaluation, approval and administrative handling of changes

Variations changes: Co-decision

30 June 2009

- Directive 2009/53/EC amending Directives 2001/82/EC and 2001/83/EC published
 - To be enacted by 20 January 2011
 - Makes Variations regulation apply to National Licenses unless:
 - Granted before 1 January 1998 to medicinal products authorised only in one Member State

New Variations Process: Comitology

24 Nov 2008 new Regulation 1234/2008

- Introduces “Do and Tell” for Type 1A variations
 - Do not require any prior approval and can be implemented anytime before notifying the competent authorities
 - Type 1A: submit annual report of changes made
 - Type 1A(IN): notify immediately after implementation

New Variations Regulation

Regulation 1234/2008

- Variations to be Type 1B by default; rather than Type II as at present
- Some Type 1B variations to be re-classified as Type 1A

New Variations Regulation

Regulation 1234/2008

- Other changes:
 - A new process for the classification of variations
 - Lists of Type 1A and II Variations to be published as Guidelines
 - Can ask agency for a recommendation on the classification for unforeseen variations
 - The ability to group variations
- Effective 1 January 2010

New Variations Guidelines

- Draft Guideline on classification of Variations issued 20 March 2009
- Annex contains a list of variations that should be classified as Type IA or Type II on the basis of definitions and specific examples
 - Some guidance on the scientific conditions to be fulfilled and the supporting documentation required regarding certain variations

Advanced Therapies Regulation

- Regulation on “Advanced Therapies: Tissue Engineering, Cell Therapy and Gene Therapy”
- Regulation 1394/2007 applied from 30 December 2008
- Makes provisions of Dir. 2001/83/EC apply these Advanced Therapies
 - Clinical Trials provisions
 - Marketing & Manufacturing Authorisations
 - GMP

Anti-counterfeiting Proposals

- On 10 December 2008 the Commission issued a proposed amendment to Directive 2001/83/EC on anti-counterfeit measures
- Proposals include:
 - Obligations for brokers
 - Allow Commission to make specific safety-features (such as a serialisation number or a seal) on packaging obligatory
 - The addition of **a new legal duty for Qualified Persons:**
“in the case of products intended to be placed on the market in the Community, that the safety features referred to in point (o) of Article 54 have been affixed on the packaging”.

Anti-counterfeiting Proposals

- Proposed Revision of 2001/83/EC:
 - Where product is obtained from the manufacturer or importer, holders of the WDA must verify that the manufacturer or importer holds a manufacturing authorisation”
- NOTE:
 - March 2009 EMEA Concept Paper on proposed revisions to replace the Guideline on Good Distribution Practice (94/C 63/03)

Anti-counterfeiting Proposals

- Proposed revision of 2001/83/EC:
 - “Active substances used as starting material shall only be imported if:
 - a. They have been manufactured by applying standards at least equivalent to EU GMP
 - b. They are accompanied by a written confirmation from the exporting third country that the standards of GMP applicable to the plant manufacturing the API are at least equivalent to those in the EU and that the plant is subject to **control and enforcement ensuring that GMP cannot be circumvented**”
 - c. This requirement shall not apply if the exporting country is listed in accordance with Article 111b

Anti-counterfeiting Proposals

- Proposed revision of 2001/83/EC:
 - Article 111b: the Commission shall, following a request from a third country, list that country by way of a Decision if for APIs its regulatory framework and control/enforcement are comparable to those in the EU. Particular account shall be taken of:
 - a. The country's rules for GMP
 - b. The regularity of inspections of GMP
 - c. The efficacy of enforcement of GMP
 - d. The regularity and rapidity of information supplied by the third country relating to non-compliant producers of APIs

Anti-counterfeiting Proposals

- Proposed revision of 2001/83/EC for anti-counterfeiting:
 - Provisions to be phased in between 18 and 48 months from date of publication of final amendment

The Rx-360 Consortium

- A group set up as an international non-profit organization including pharmaceutical manufacturers and supplier companies and trade organizations (as observers)
- Mission is to create and monitor a global quality system that meets the expectations of industry and regulators that assures patient safety by enhancing product quality and authenticity throughout the supply chain.

Patient Information Proposals

- On 10 December 2008 the Commission issued a proposed another amendment to Directive 2001/83/EC on the provision of information to patients
- Advertising of prescription-only medicines to the general public is forbidden in the EU ... **BUT**
- Different Member States interpret the current EU regulatory framework in very different ways

Pharmacovigilance Proposals

- On 10 December 2008 the Commission issued a proposed third amendment to Directive 2001/83/EC on Pharmacovigilance
- The proposals focus on but are not limited to:
 - Maintaining the current split of competences between the Member States and EMEA, while making clear the respective roles and responsibilities and minimising duplication of effort
 - Strengthening the rules on transparency relating to pharmacovigilance data, assessment and decision-making and involve stakeholders (e.g. patient and healthcare professional groups) in the processes including patient reporting

GMP Guidelines

Dedicated Facilities – Revision of Chapters 3 and 5

- EMEA drafting revisions to chapters 3 and 5 to add guidance on the need for dedicated, self-contained facilities
- Expected draft for comment early 2009
 - List of products that must have dedicated facilities?
 - Second list of products where shared facilities should not be used unless justified by Quality Risk Management?

EU GMP Guide – Revision of Chapter 5

- A separate draft revision to Chapter 5 expected soon
 - EMEA published a Concept Paper on this proposed change in April 2007
 - Will cover what is expected from MA holders with respect to the assurance of the quality of raw materials (in line with the new requirements introduced by Directives 2004/27/EC and 2004/28/EC)

EU GMP Guide – Revision of Chapter 4

- A proposed revision to Chapter 4 was published on 11 April 2008
- To accommodate the changes relating to electronic documentation, to coincide with the revision of Annex 11 on Computer Systems (see later)
- Extensive additional changes to the “Principle” and “General” sections to provide additional detail
- Comments were due by 31 October 2008

EU GMP Guide – Revision of Chapter 4

The proposed additions include:

- Need to have a Document Management System
 - With unique title and version number for each document
 - Relationships and control measures for master documents, official copies, data handling and records need to be clearly stated for both hybrid (i.e. some elements electronic and others paper based) and homogenous systems

EU GMP Guide – Revision of Chapter 4

The proposed additions include:

- Types of 'Instructions'
 - Specifications
 - Manufacturing formulae, Processing, Packaging and Testing Instructions
 - Procedures
 - Protocols
 - Technical Agreements
- Types of 'Records'
 - Records
 - Certificates of Analysis
 - Reports

Concept Paper on Revision of Chapter 7

- Published 23 October 2009
- Proposes revision to Chapter 7 to cover contracting out and “modern supply chain management”

Proposed Changes to EU GMP Annex 2 – Biological Products

- Proposals to amend Annex 2, **Biological Products**, were published in September 2007
 - One aim was to clarify the boundary between the requirements for APIs in Directives 2004/23/EC and 2004/27/EC
 - Comments due by 14 March 2008

Annex 2 – Structure

- Scope
- Principle
- Part A: General Guidance
- Part B: Specific Guidance on Selected Product Types
- Glossary

(new sections)

Annex 2 – What's New?

- Part A
 - Not a lot!
 - Increased emphasis on...
 - Contamination potential
 - Bioburden control
 - Risk assessment
 - Facility Design
 - Facility dedication/campaign working

Annex 2 – Specific Guidance

- Part B: Specific Guidance on Selected Product Types
 - Allergen Products
 - Animal Immunoserum Products
 - Vaccines
 - Recombinant Products
 - Monoclonal Antibody Products
 - Gene Therapy Products

Continued/...

Annex 2 – Specific Guidance

- Somatic and Xenogeneic Cell Therapy Products
- Transgenic Animal Products
- Transgenic Plant Products
- Tissue Engineered Products
 - Guidance under development

Revised EU GMP

Annex 3 - Radiopharmaceuticals

- Final version issued September 2008
- Effective 1 March 2009
- Provides guidance for some relatively new technology, in particular Positron Emission Tomography (PET)
 - Some of these radionuclides have a shelf life of hours and therefore the active ingredient is synthesised, made into a dosage form and administered, in less than one working day

Revised EU GMP Annex 3

- Guidance is given as to the GMP and non-GMP parts of the process; e.g.
 - Cyclotron and Reactor steps are regarded as non-GMP
 - GMP starts as soon as the chemical synthesis starts

Revised EU GMP Annex 3

- Parametric release is (still) seen as necessary
 - With systems to follow up in the event of failed result when all testing has been completed
- For sterile products QP release is still required, but there will be a two stage process:
 1. Releasing the product for administration
 2. Finally releasing the product after sterility testing

Revised EU GMP Annex 3

- The principal changes are:
 - New sections on Introduction, QA and Documentation and a glossary
 - GMP requirements for the API are given, in line with EU GMP Part II
 - The guidelines apply to materials for use in clinical trials
 - Risk assessment is strongly emphasised

Draft of Annex 6, Medicinal Gases

- Revised version issued as a draft for comment on 31 July 2007
 - Deadline for comments was 31 December 2007
 - Final version was expected 2nd half of 2008
- Major driver is the need to more clearly define what is to be considered a starting material and what is a bulk medicinal product
 - The draft includes a general rule to encourage a harmonised approach to this distinction across the EU

Revised EU GMP Guide

Annex 7 – Herbal Products

- Final version issued September 2008
- Effective 1 September 2009
- Revised to incorporate the requirements for APIs in Directive 2004/27/EC and for herbal medicines in Directive 2004/24/EC

Changes to EU GMP Guide

Annex 11 – Computer Systems

- A proposed revision to Annex 11 was published on 11 April 2008
 - A total re-write and significant expansion of this Annex
 - Much more explicit requirements
 - Comments had to be sent to EMEA by 31 October 2008

Annex 11 – Computer Systems

- Applies to the development, selection, validation and use of computer systems
- Personnel section names the key personnel
 - Users, system administrators, QA and technical staff.

Annex 11 – Computer Systems Validation

- MA holder's quality system should have policies and plans for computerised systems and up to date 'listings' of systems with their GxP functionality
- Extent of validation should depend on a documented risk assessment

Annex 11 – Computer Systems Validation

- Validation of bespoke or significantly customised systems requires formal assessment and reporting of quality and performance measures for all life cycle stages of software and system development, implementation, qualification and acceptance, operation, modification, re-qualification, maintenance, on-going support and retirement
- Supplier assessments be made available to inspectors on request

Annex 11 – Computer Systems

Electronic signatures

- E-signatures on e-records are ok
- Hand-written signatures to a printout are also ok if all meta-data is present on the printout
- Electronic signatures are expected to be legally equivalent to hand-written signatures, linked to the record and include time and date
- There may be national legislation that influences how e-signatures may be used.

Changes to EU GMP Guide

Annex 11 – Computer Systems

- MHRA inspectors have expressed concerns with the wording proposed:
 - Particularly section 15 (Back up, Migration, Archiving, Retrieval)
 - Danger of over interpretation by both regulators and industry
 - Particularly with Modern PAT applications collect large amounts of data

Changes to EU GMP Guide

Annex 13 – IMPs

- Draft revision published in April 2008
 - Comments were due by 31 October 2008
- The following changes are proposed:
 - Minor change to section 3 to reinforce independence between production and QC functions in cases where the number of personnel involved is small.
 - Changes to sections 36 and 37 to supplement, for IMPs the guidance for reference and retention samples given in Annex 19
 - Section 44 reworded to enhance understanding of the two-step release procedure that applies to IMPs
 - A change control process for the PSF that is defined in a Technical Agreement between the QP and the Sponsor

Changes to EU GMP Guide – Annex 14

Human Blood and Plasma Products

- Draft revision published January 2009
 - Comments due by 31 July 2009
- Incorporates references to 2002/98/EC, “The Blood Directive”, 2005/61 EC and 2005/62/EC, the extensions to the blood directive

EMEA QP Discretion – 2006/9

- EMEA March 2006 Ref:
EMEA/INS/GM71188/2006
 - “Reflection paper on a proposed solution for dealing with minor deviations from the detail described in the Marketing Authorisation for Human and Veterinary Medicinal Products (including biological products)”
- Revision published January 2009
 - Reduced the scope and added provisos

EMEA QP Discretion – 2007

- Meeting held in September 2007 at EMEA, between the EU Inspectors Working Party (IWP) and industry 'interested parties'

QP Discretion – Industry Position

- Reflection Paper welcomed as a step forward
- The Scope should be extended to include:
 - Recurrent unplanned minor deviations due to:
 - An issue prior to implementation of corrective actions to address the first occurrence
 - An issue where an incorrect root cause and/or corrective action was initially assigned
 - Pending approval of a variation
 - One-off ‘Planned Deviations’
 - OOS deviations or attributes determined to have no impact on safety, quality or efficiency

QP Discretion – Moving forward?

- The 2009 paper states:
“A number of feedback comments were received that cannot be taken forward at this time but may be addressed in the forthcoming revision of the Variations legislation”
 - Some minor recurring deviations may be type 1A ‘do and tell’ variations
- Still wide differences in interpretation across Member States
 - UK and Ireland are the most dogmatic

EMEA QP Discretion – 2006/9

- Any deviation, which may materially affect the Safety or Efficacy of a batch of product quality, must result in a QP decision not to release that batch
- SOPs and details on makes and models of equipment submitted with a Marketing Authorisation application are not considered as particulars that define the requirements of that marketing authorisation

EMEA QP Discretion – 2006/9

- Recurrent deviations from the manufacturing process and/or analytical control methods as approved in the MA, even though judged minor, are changes and variations to the affected MAs are necessary
- Planned deviations are therefore also outside the scope of this paper.

EMEA QP Discretion – 2009

- A batch can be considered to continue to meet the requirements of the MA when:
 1. The deviation is minor, one-off and unplanned in nature and relates only to the manufacturing process and/or the analytical control methods of either the starting materials or the medicinal product as described in the MA or CTA and has no influence on the analytical results
 2. The active substance/antigen and finished produce specifications in the MA or CTA are complied with

EMEA QP Discretion – 2009

3. An Assessment is performed using **an appropriate approach such as** described in ICH Q9, Quality Risk Management, to support a conclusion that the occurrence is a minor quality deviation that does not affect the safety and efficacy of the product
4. The risk assessment should assess the need for inclusion of the affected batches in the ongoing stability programme as required by Chapter 6 of the GMP Guide

EMEA QP Discretion – 2009

5. The risk assessment for biological medicinal products should consider in particular that even minor changes to the process can have an unexpected impact on safety or efficacy
6. The Quality Risk Management Process is integrated into the manufacturer's quality assurance system, notably the documentation system established to comply with GMP, and records are available for inspection by the competent Authorities

EMEA QP Discretion – 2009

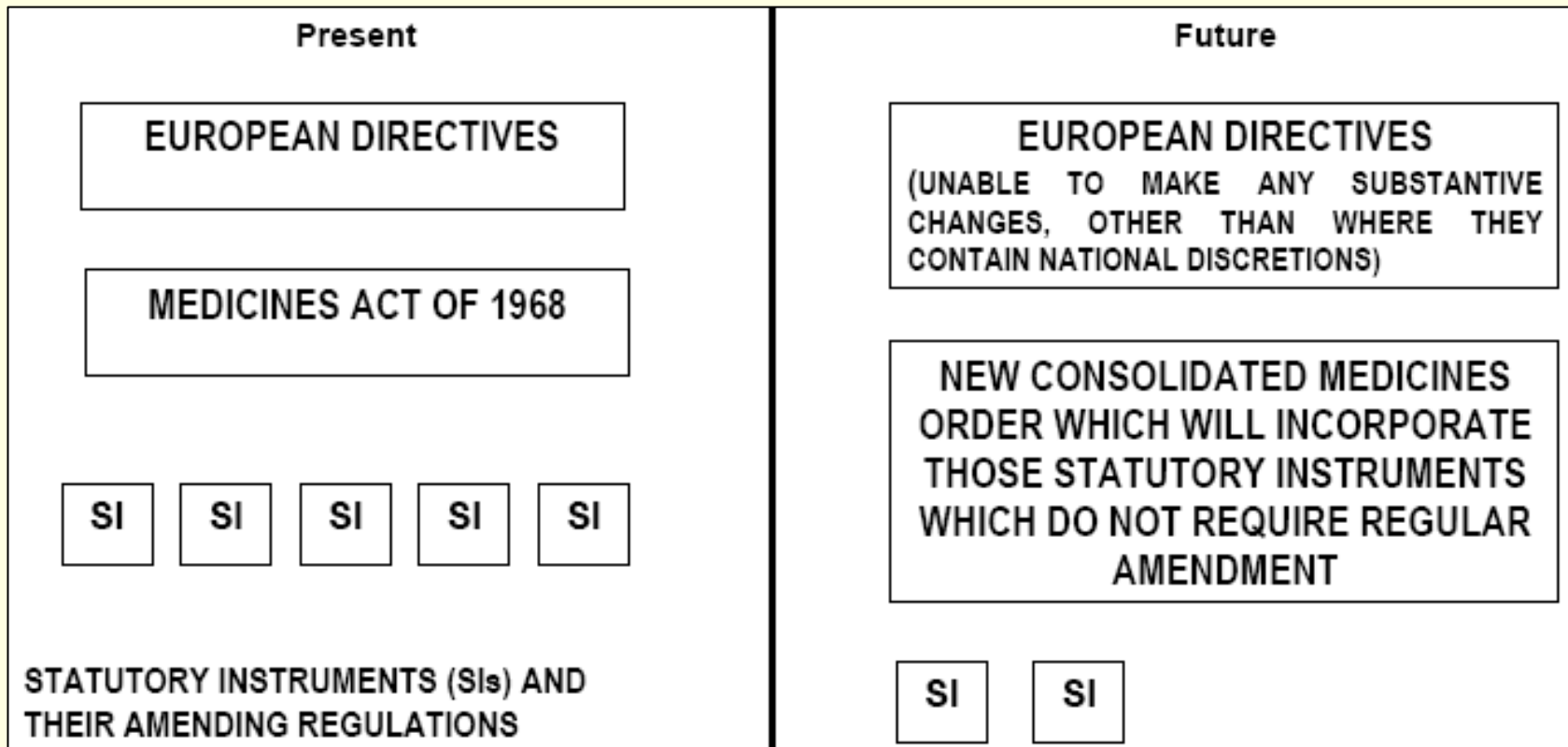
7. Deviations must be properly recorded in the relevant batch documentation in accordance with GMP. All such deviations must be reviewed as part of the annual product quality review as required by Chapter 1 of the GMP Guide

UK Developments

Consolidation & Review of UK Medicines Legislation

- Concept Paper published by MHRA January 2009
- Current situation is very complex and fragmented
 - Huge number of Statutory Instruments (SIs)
- Project with two strands:
 1. Consolidation of existing legislation
 - Using a Legislative Reform Order (LRO)
 2. Simplification

Present and Future Structure of UK Medicines Legislation



Consolidation & Review of UK Medicines Legislation

- Consolidation
 - MHRA hope to have draft Order by Spring 2010
- Simplification
 - Consultation will continue “well into 2010”

UK Herbals certification mark

- The Traditional Herbal Registration (THR) certification mark is a type of trade mark.
- It indicates that the herbal medicine has been registered with the MHRA under the Traditional Herbal Registration (THR) scheme



MLX 357 – Supply Chain and Counterfeit Medicines

- Published in December 2008
- Main proposals are to:
 - Require an applicant for a Wholesale Dealer's licence to demonstrate that he/she is a "fit and proper person" to undertake such a role, with minimum requirements to be set out in guidance;
 - Require disclosure by applicants of criminal records;
 - Empower MHRA to decline a Wholesale Dealer's licence if an applicant discloses a relevant criminal conviction;
 - Require payment in advance of fees for the licence and for inspection;

MLX 357 – Supply Chain and Counterfeit Medicines

- Proposals continued ...
 - Introduce a “due diligence” obligation into the legislation, with a requirement to notify the MHRA of suspicious events;
 - Introduce a requirement that each “body corporate” at a Wholesale Dealer’s site must have its own Wholesale Dealer’s licence which cannot be transferred to another part of the business;
 - Clarify MHRA powers to refuse to grant/suspend/revoke Wholesale Dealers’ licences if service fees or other fees are not paid;

MLX 357 – Supply Chain and Counterfeit Medicines

- Proposals continued ...
 - Remove the £35,000 turnover reduced fees concession.
 - Strengthen the role of the Responsible Person (RP) by:
 - Specifying a minimum qualification for RP
 - Requiring RP membership of a professional body
 - Having a Code of Practice for RPs
 - Having a Register of RPs
 - Requiring continuous presence of RP at each site and qualified deputy RPs
 - Nominated RPs for multi-site wholesalers
- Comments were due by 13 March 2009

MLX 357 – Supply Chain and Counterfeit Medicines

- Comments re. proposal were:
 - Supportive of changes to WDL application process; except the loss of £35,000 concession
 - Supportive strengthening RP role; except continuously on-site provision
- MHRA response:
 - Will conduct a further consultation in autumn 2009.
 - Expect to implement by April 2010

MHRA API Supply Concerns

MHRA has 4 main concerns:

- Variability of starting materials to manufacture APIs which are derived from a natural source
- A lack of both upstream and downstream supply chain traceability for APIs
- Inadequate auditing of API manufacturers by finished product manufacturers
- Deliberate adulteration and fraudulent activities

MHRA API Supply Proposals

Introduce an API “Pedigree”

- “Pedigree” will require all APIs to be able to demonstrate:
 - full upstream traceability for all “critical” starting materials
 - downstream traceability of the finished API from site of manufacture to the finished product Manufacturer’s site.
- “Pedigree” documents will need to be more than just a simple flow chart and have proof that the sourcing/supply routes have been confirmed
- The QP will be responsible for assuring the accuracy of the “Pedigree” document as an extension of the QP declaration of GMP conformity

MHRA API Supply Proposals

Other suggestions being considered:

- Automatically remove from MA API suppliers that have not been used for 5 years
- Require formal risk assessment of new API sources that are not based in the EU, USA or countries with an MRA
 - May later be expanded to excipients as well
- Auditing (by MHRA) all registered API manufacturers in China over the next 2-3 years

MHRA API Supply Actions

- MHRA GMP inspections to increase their focus on API Supplier Audit Programmes
 - Assurance of the total supply chain
 - Adequacy of supplier audits is a major concern
 - QPs must be able to demonstrate clearly the basis any GMP declarations that they sign.
 - MHRA will applying sanctions and disciplinary actions against the manufacturer and/or the QP where they find deficiencies.

MHRA API Supply Actions

- If a regulatory body GMP inspection of an API manufacturer results in the removal of or failure to issue a GMP certificate:
 - All the manufacturers who have the API supplier named on a MA will be contacted to inform them they are no longer considered to be of the required standard and cannot be used.
 - All QP declarations that have been generated relating to that API manufacturer will be challenged and legal action may be taken against the approving QP and their employer

ICH Initiatives

Quality/GMP initiatives at the

International **C**onference on
Harmonisation of Technical
Requirements for Registration of
Pharmaceuticals for Human Use

ICH Q4B, Pharmacopoeial Harmonisation, Annexes

- Several Annexes approved in 2007 & 2008:
 - Annex 1, **Sulphated Ash**, Step 4 in Nov. 2007
 - Annex 2, **Extractable Volume of Parenteral Preparations**, Step 4 in Jun 2008
 - Annex 3, **Particulate Contamination: Sub-Visible Particles**, Step 4 in Jun 2008
 - Annex 4A, **Microbiological Examination of Non-Sterile Products: Microbial Enumeration Tests**, Step 4 in Nov 2008
 - Annex 4B, **Microbiological Examination of Non-Sterile Products: Tests for Specified Micro-Organisms**, Step 4 in Nov 2008

ICH Q4B, Pharmacopoeial Harmonisation, Annexes

- Recently approved annexes continued ...
 - Annex 4C, **Microbiological Examination of Non-Sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use**, Step 4 in Nov 2008
 - Annex 5, **Disintegration** test, Step 4 in Jun 2009
 - Annex 6, **Uniformity of Dosage Units** test, Step 2 in November 2008
 - Annex 7, **Dissolution** test, Step 2 in Nov 2008
 - Annex 8, **Sterility** test, Step 4 in November 2009

ICH Q4B, Pharmacopoeial Harmonisation, Annexes

- Annex 9, **Tablet Friability**, received Step 2 approval in June 2009
- Annex 10, **Polyacrylamide gel electrophoresis (PAGE)**, received Step 2 approval in June 2009

Q8 (R1) – Annex to Q8

- Received Step 4 approval in November 2008
- Published in EU as CHMG NfG in February 2009
 - Effective June 2009
- Q8(R2) published in August 2009 to correct typos
 - Effective in EU in October 2009

Q8 (R2) – Annex to Q8

- Annex elaborates the elements of pharmaceutical development as:
 - Target Product Profile
 - Critical Quality Attributes (CQA)
 - Linking material attributes and process parameters to CQAs by risk assessment
 - Design Space
 - Control Strategy
 - Product lifecycle management and continual improvement

Q8 (R2) – Design Space

- Concept of 'Design Space' is elaborated upon with guidance on:
 - Selection of variables
 - Defining and describing a design space in a submission
 - Unit operation design space(s)
 - Relationship of Design Space to scale and equipment
 - Design Space versus proven acceptable ranges
 - Design Space and edge of failure

Q8 (R2) – Overall Development

Minimal Approach	QbD Approach
<p>Mainly empirical</p> <p>Developmental research often conducted one variable at a time</p>	<p>Systematic, relating mechanistic understanding of input material attributes and process parameters to drug product CQAs</p> <p>Multivariate experiments to understand product and process</p> <p>Establishment of design space</p> <p>PAT tools utilised</p>

Q8 (R2) – Appendix 2

Appendix 2 provides illustrative examples of the following:

- Use of risk assessment
- Depiction of interactions
- Presentation of Design Space

ICH Q10 – Pharmaceutical Quality Systems

- Received Step 4 approval in June 2008
- Implemented in USA in April 2009
- Expected to be implemented in EU as another Annex to the EU GMP Guide with changes to Chapters 1, 2 and 7

Q10 - Structure

1. **Pharmaceutical Quality System**
 2. **Management Responsibility**
 3. **Continual Improvement of Process Performance and Product Quality**
 4. **Continual Improvement of Pharmaceutical Quality System**
 5. **Glossary**
- Annex 1:** Potential Opportunities to Enhance Science and Risk Based Regulatory Approaches
- Annex 2:** Diagram of the ICH Q10 Pharmaceutical Quality System Model

ICH Q10 – Pharmaceutical Quality System

Q10 will:

- Augment existing GMPs
- Provide a bridge between different regional regulations
- Establish and maintain a state of control
- Facilitate continual improvement

Q10 – Management Responsibility

- Management **commitment**, management **review** and **communication** are of particular importance
- Senior Management
 - Establish a PQS appropriate for the organisation and compliant with regulations
 - Ensure that PQS responsibilities and authorities are defined and communicated
 - Ultimate responsibility to foster a company-wide commitment to quality and for the successful functioning of the PQS

Q11 – API Development

- New expert working, Q11, started at ICH meeting in June 2008 to write a guideline on “Drug Substance Development”.
- Q11 will aim to define the development process for APIs similar to those contained in Q8 for medicinal products
 - Detail for the 3.2.S.2 section of CTD

Implementation Working Group (IWG)

- Will cover implementation issues for Q8, 9 & 10
 - Technical Issues & Related Documentation
 - Technical examples and case studies
 - Level of detail to include in dossier
 - Common understanding of terminology
 - Inter-relationship between Q8, Q9, Q10
 - Application to both review and inspection
 - Communication and Training
 - Updating of existing ICH guidelines

Implementation Working Group (IWG)

- Formal Question and Answer document published in April 2009 covering the following topics:
 - Quality By Design:
 - Design Space
 - Real Time Release Testing
 - Control Strategy
 - Pharmaceutical Quality System
 - ICH New Quality Guidelines' Impact On GMP Inspection Practices
 - Knowledge Management
 - Software Solutions

EMA/FDA GCP Initiative

- EMA & FDA (CDER) have launched a bilateral GCP Initiative
- Designed to ensure that CTs submitted in marketing applications in EU and USA are conducted uniformly, appropriately and ethically.
- Began an 18-month pilot phase on September 1, 2009
- Will focus on collaborative efforts to inspect CT sites and studies.

Revised Canadian GMP



- Issued on 8 May 2009; becomes effective on 8 November 2009
 - Supersedes the 2002 edition
- Includes measures that introduces expectations similar to those for EU QPs:
 - Expectations for the individuals in charge of QC
 - “No lot or batch of drug shall be made available for sale unless the sale of that lot or batch is approved by the person in charge of the quality control department.”

FDA Initiatives



U.S. Department of Health and Human Services

Food and Drug Administration

15 day limit for 483 responses

- FDA would like to see a response to 483's within 15 working days.
- If FDA decides to issue a warning letter:
 - If the firm's response is received by FDA within 15 business days, the letter will acknowledge the response and provide comment as to FDA's perceived adequacy of the firm's response.
 - If the firm's response is received more than 15 working days after the FDA 483, FDA will not comment on the response in the warning letter and they will evaluate the response to the FDA 483 along with the response to the warning letter.
- FDA will review this program, which began on 15 September, 2009, after 18 months.

FDA speed up Enforcement

- 15 day time limit for 483 responses is part of a wider initiative to increase effectiveness
- Five other steps are:
 - Take responsible steps to speed the warning letter process.
 - Work more closely with the FDA's regulatory partners.
 - Prioritise follow-up on warning letters and other enforcement actions.
 - Be prepared to take immediate action in response to public-health risks.
 - Develop and implement a formal warning letter “close-out” process”

21 CFR 210 & 211, cGMP, Revision

- In September 2008 a revised 'final rule' was issued
 - Changes became effective 8 Dec. 2008

21 CFR 210 & 211, cGMP, Revision

- Main changes effective Dec. 2008:
 - Written procedures designed to prevent microbiological contamination of sterile drug products must include procedures on the validation of all aseptic processes in addition to sterilisation processes.
 - Use of filters containing asbestos prohibited
 - A person is not required to repeat by hand calculations performed by automated equipment

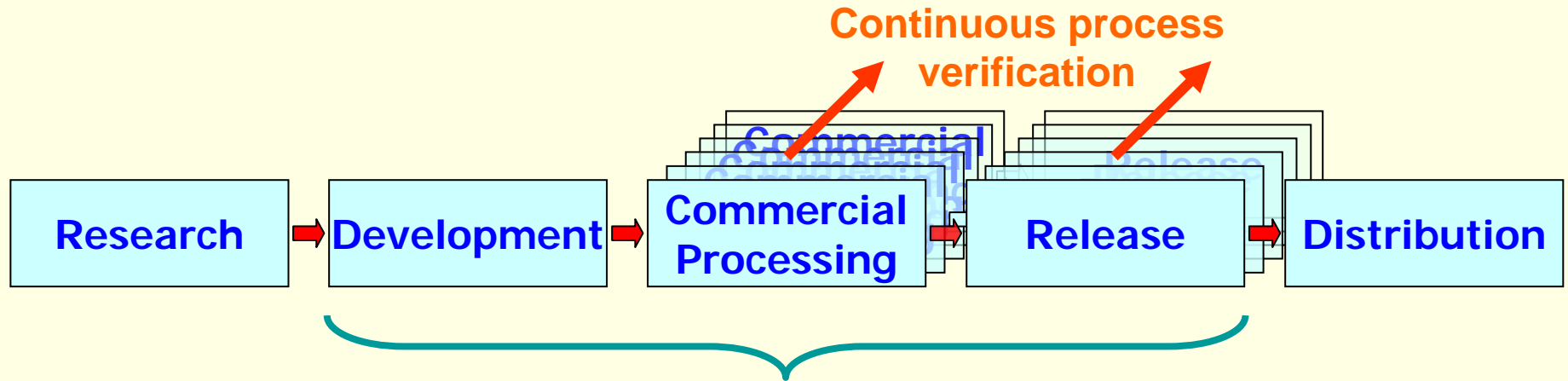
FDA GMP for Phase 1 IMPs

- FDA issued a final rule to exempted investigational drugs in Phase I testing from certain GMP regulations
 - Published in US Federal Register in July 2008.
- Took effect on Sept. 15 2008
- Applies to small-molecule drugs and biologics
 - Inc. vaccines and gene therapy products
 - Excludes products from human tissue or cells

FDA GMP for Phase 1 IMPs

- FDA also issued document 'Guidance for Industry: cGMP for Phase 1 Investigational Drugs ' giving GMP requirements for Phase 1 IMPs
 - This Guidance includes standards for:
 - facilities and equipment,
 - control of components, testing,
 - stability, packaging, labelling, distribution, and recordkeeping
- that are all still absolute requirements

Process Validation



Process Validation

A journey, not an event

Process Validation – The Stages



- Defines the commercial process based on knowledge gained through development and scale-up

- Confirms the process design as being capable of reproducible commercial manufacturing

- Ongoing assurance that during routine production the process remains in a state of control

How much Process Understanding do I need

- “Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the product

3 batches really is dead!



Securing the Supply Chain

- FDA has numerous initiatives aimed at securing the supply chain:
 - Good Importer Practices
 - Standardised Numerical Id.
 - Voluntary Third-Party Certification Programs
 - Physical-chemical identifiers (PCIDs)

Testing for Melamine contamination

- Guidance issued on 6 August 2009
- Certain pharmaceutical ingredients should be tested for melamine.
 - Due to recent events involving pet and livestock food products in the United States, and milk products for infants in China
- List of ingredients in the guidance that are recommended to be screened includes
 - Lactose, Povidone and Crospovidone.
- Recommends the use of FDA-published test methods
- FDA are developing a sampling & testing program for ingredients at risk for melamine contamination.

Conclusion

- The rules keep changing!
- The rate of change is currently at an unprecedented level
- QPs, in particular, must keep up with these changes
 - Take the time
 - It is a GMP expectation

Thank you

DBA

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