



Making Medicines Affordable

4th International Forum on Business Development in APIs & GMP Fine Chemicals

Latest EU GMP Developments Affecting Starting Materials

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Making Medicines Affordable

Outline of Presentation

- EU Commission (EC) survey & EMEA Inspectorate Action Plan (API GMP)
- EU Commission legislative proposal (Anti-counterfeit)
- Revision of the EU GMP Guide
- Impact of ICH Quality related topics



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API GMP (EC & EMEA) (1/4)

- Dir. 2001/83/EC, as amended (Oct 2005)
 - Article 46(f) and 47
 - “The holder of a manufacturing authorisation shall at least be obliged to [...] **use as starting materials only active substances**, which have been manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials.”
- GMP Guide Part II + Compilation of Community Procedures on Inspections and Exchange of Information

API GMP (EC & EMEA) (2/4)

■ Key legal responsibility:

- Ensuring API GMP compliance lies with the Manufacturing Authorisation Holder

■ « self-regulation »: inspection of non-EU manufacturers may happen on request but is not mandatory

■ Inspections will encompass:

- API audit reports (internal or 3rd party)
- API & Finished Products in & out-side Europe

API GMP (EC & EMEA) (3/4)

- 2006 → EMEA Inspectorate collaborative initiative: survey on API GMP inspections findings (all MSs)
- 2007 → 2 years of implementation of the legal requirements (Dir. 2001/83 as amended)
- EMEA prepared a single community-wide report

API GMP (EC & EMEA) (4/4)

- 2008: Creation of a drafting group on API GMP (EMEA GMP Inspection work programme):
 - Role → development of action plan in response to survey findings
- Expected report publication: mid-2008 along with a proposed action plan

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Anti-counterfeit (EC): Background

- **European Parliament:**
- **Resolution on counterfeit medicinal products (06 Sept 2006)**
 - Strengthening of EU regulatory and quality control systems
 - Enhanced cooperation at national , EU & international level
- **Declaration on Active Substances (04 Sept 2006)**
 - GMP Inspections for manufacturers & importers

Anti-counterfeit (EC) Background

- Change in extent of the issue of counterfeit medicines in Europe
 - Or increased awareness and enforcement ?

2006	2007
Lifestyle medicines	Life- <u>saving</u> medicines
Illegal Supply Chain	<u>Legal</u> Supply Chain
<1% in Regulated Markets (EU)*	+ <u>384% increase</u> in seizures of counterfeit medicines at EU customs borders from 2005-2006**

* WHO estimate 2006

** DG TAXUD 2007

Anti-counterfeit (EC) Legal proposal March 2008

■ Scope of EC proposal:

- Counterfeit medicines for human use
- Active substances (ie, substandard)

■ In cases of API, EC refers to:

- EMEA report on API GMP inspections (not yet public)
- Major non compliance / lack of transparency of local control

■ Timelines: Contributions by 9 May 2008

Anti-counterfeit (EC) Legal proposal

- Key Issue → supply chain integrity
- Proposed action points:
 - Tightening of requirements, supervision & enforcement for the manufacturing, trading and distribution of medicines and active substances
 - Amendments Dir. 2001/83/EC & 2003/94/EC, GMP, GDP and EMEA Community Procedures on Inspections guidelines
 - Enhance international cooperation and awareness

EGA Supply Chain Integrity Pact (PACT)



- Aims to elaborate solutions to improve supply chain integrity



EGA Supply Chain Integrity Pact (PACT)

- GIRP - Wholesalers Association
- PGEU - Pharmacists Association
- EGA - Generic Medicines Association

- Focusing on:
 - GDP & Licensing (eg, wholesalers' licenses)
 - GPP (Good Pharmacist Practices)
 - Enhancing awareness, information and training

Anti-Counterfeit (EC) API specific measures (1/2)

- API GMP principles to be included in a 'Legal Act of Community Law'
→ to enhance enforceability
 - eg, Commission Directive,
- Extension GMP/GDP requirements to the entire supply chain (art. 46a 2001/83/EC)
 - eg, agents, wholesalers
- Increased API control by recipient
 - ie, manufacturers

Anti-Counterfeit (EC) API specific measures (2/2)

- **Transparency & Traceability measures**
 - Eg, extension of EudraGMP database (eg, GDP certificates for wholesalers), mandatory notification of manufacturing / import of API
- **Third party auditing**
- **Increase inspections in 3rd countries**
 - Especially where standards, supervision or inspections are not equivalent to EU

Anti-Counterfeit (EC) Interim Conclusions

- High on the agenda of the EC, but also WHO (IMPACT) and EDQM (ad hoc group)
 - Act fast to prevent MSs from starting unilateral actions
- In line with earlier industry initiatives
- Public consultation will be followed by:
 - Stakeholders contributions analysis
 - Overall impact assessment: social, economic, environmental consequences



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EMA GMP Work Programme - 2007 / 2008

- **Joint Audit Programme (JAP) (03-2007)**
 - ensure consistency of GMP standards and a harmonised approach throughout Europe
 - JAP, PIC/S & MRA audit programmes → COMMON Evaluation Guides developed by Health Canada
- **Launched in May 2007, EudraGMP access becomes public by mid-2008**
- **Good Distribution Practice Guidance to be reviewed for improvements 2008**

Revision of the EU GMP Guide - 2008

■ Public consultation Early 2008

- Chap.5 Production:
 - Qualification of Suppliers
 - *Include the new obligations of manufacturing authorisation holders to only use active substances manufactured under GMP*
 - Testing of Starting Materials
 - *Common approach on what is expected from manufacturing authorisation holders with respect to the assurance of the quality of raw materials used*

Revision of the EU GMP Guide - 2008

■ Late 2008

- Dedicated facilities (Chap. 3 & 5)
 - Include the concepts of ICH Q9 Quality Risk Management

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Impact of ICH Quality Related Topics (1/4)

- **Guideline Trio** (*www.ich.org*)
 - ICH Q8 Pharmaceutical Development (2005)
 - ICH Q8 Annex (public consultation)
 - ICH Q9 Quality Risk Management (2005)
 - ICH Q10 Quality Systems (topic acc. 2005)
- **“Science-based” and “Risk-based”
concepts & principles**
- **Apply to the entire Life-Cycle
(direct link to patient’s risk)**

Impact of ICH Quality Related Topics (2/4)

Quality

Degree to which a set of inherent properties of a product, system or process fulfills requirements

Risk

Combination of the probability of occurrence of harm and the severity of that harm

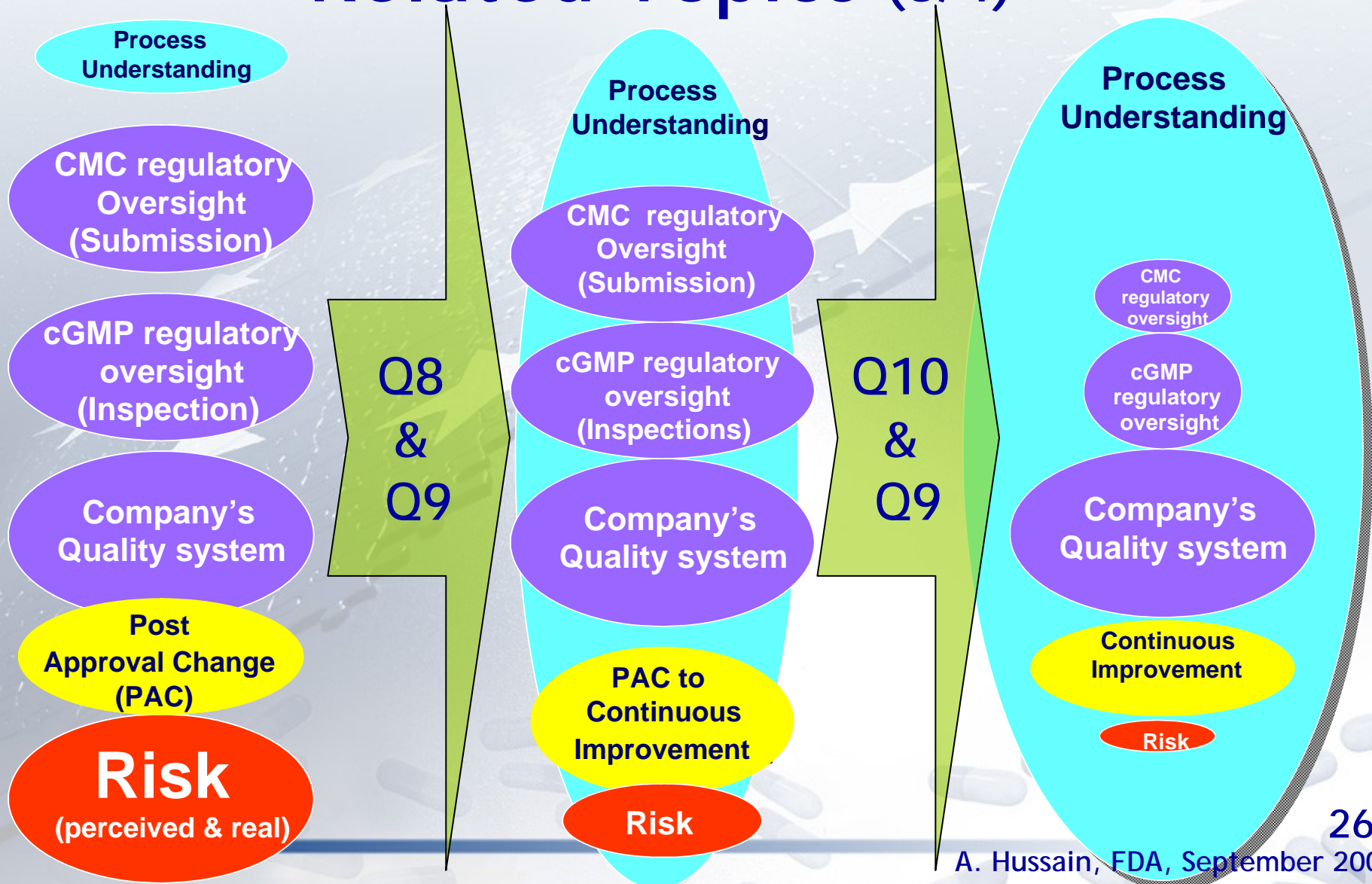
Management

Systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle



QRM

Impact of ICH Quality Related Topics (3/4)



Impact of ICH Quality Related Topics (4/4)

- **Annex 20 Quality Risk Management (=Q9)**
 - Inventory of tools and methods
 - List of potential applications
 - No additional regulatory expectations
- **Update of the GMP Guide:**
 - Part I: Quality Management (1), Dedicated facilities (3, 5)
 - Part II → to be updated at the next occasion
- **Compilation of Community Procedure & Quality Guidelines → update foreseen**



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**Thank you
for your attention !**

Any Questions ?

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