

EDQM Conference

Quality of Medicines in a Globalised World: Dreams and Reality

14-15 October 2010
Prague, Czech Republic



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Plenary Session

-  Dr Georges France
-  Ms Suzette Kox
-  Dr Barbara Steinhoff
-  Dr Jochen Wieda
-  Dr Matthew Moran
-  Mrs Beam Suffolk
-  Dr Ilka Von Hoegen



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EDQM CONFERENCE 'QUALITY OF MEDICINES IN A GLOBALISED WORLD'

PRAGUE, OCTOBER 2010

APIC VIEW

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History of APIs and Compliance



Market Situation in the 1980s

- Europe produces > 80% of the APIs:
 - ✓ for Europe
 - ✓ for the USA
 - ✓ for much of the rest of the world inc. India & China
- Regulatory Standard determined and enforced:
 - By the US/FDA since the 1970s (US Law: API = "Drug")
 - GMP (Good Manufacturing Practice)
 - Regulatory submissions (DMF) & "post-approval changes" to those
- For EU market:
 - no substantial regulatory API submissions till 1993
 - no GMP required !

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History of APIs and Compliance



Market Situation in the 1980s

- **US/FDA is a harsh master:**
 - On-site inspections
 - Form FDA-483
 - Warning Letters
 - AIP (Application Integrity Policy)
 - Import Bans
 - Consent Decree with huge fines
 - FOI: All published in full detail in public domain!
- **European API industry dominating global API market and operating at a high compliance level**

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History of APIs and Compliance



The landslide between late 1980s and 2008

- **API manufacture moves east to India and China:**
 - Major driver: Cost (and for local Asian markets: avoiding import barriers)
- **A huge “non-GMP-API-for-export-only-industry” emerges in China:**
 - ± 3,000 “chemical” and ± 1,500 pharmaceutical API companies...
 - Initially only for ROW & EU Markets, US to join in later

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History of APIs and Compliance



The Landslide between late 1980s and 2008 (ctd)

- US market becomes main outlet for EU-manufactured APIs
- FDA compliance levels maintained in EU API manufacture
- US market: High regulatory entrance barrier (& higher API prices)
- EU API market:
 - Wide open for non-GMP APIs
 - EU APIs lose out on their home market against Asia
 - Compliance with regulatory submissions not inspected
 - In reality: same standards as ROW market

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History of APIs and Compliance



EU Directive 2004/27/EC amending 2001/83/EC:

- Transposition deadline 30 October 2005
- API GMP (ICH/Q7 = harmonized) becomes legal requirement
- API inspections possible, if triggered by suspicions or on request
- MA holder's Qualified Person to ensure API compliance
- Documents the only required proof during inspections of MA holder

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History of APIs and Compliance



EU Directive 2004/27/EC Amending 2001/83/EC:

In reality

- API inspections almost entirely within EU only (except EDQM)
- API business as usual....("90% of imported trader-APIs non-GMP")
- EU market still functions like ROW market
- But EDQM inspection findings raise concern:
Total of around 50 CEPs suspended and withdrawn by EDQM,
all either held by Asian producer or by European trader:
So unsafe APIs put in our EU medicines for years....
- But also the US/FDA is neglecting foreign inspections....
- Falsified Medicines Directive- 2008/668/EC proposed

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The cracks start to show: Some recent cases



Diethylene glycol:

- Hundreds of death in Panama (2006) after similar events in the past in e.g. Haiti, India, China

Gentamicin sulfate:

- Much counterfeit API (probably at least 33% of total) detected in EU in 2003 by analytical fingerprinting after series of deadly incidents with this API in the USA (around 2000 and earlier)



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The cracks start to show: Some recent cases



Heparin (Contract manufacture for Baxter by Changzhou SPL)

- 149 deaths reported in the USA in Q4 2007 / Q1 2008
- Deliberate counterfeit with OSCS: mimics heparin in analysis
- Detected in 11 countries, originated from 12 different sources in China
- Financial motives (OSCS \$80 vs. heparin \$1,500)
- OSCS levels in heparin 5 – 45% (profit: \$ 1 - 3 min)



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The cracks start to show: Some recent cases



Deadly Ingredients: A Worrying Pattern

<u>Product</u>	<u>Origin</u>	<u>Deliberate</u>	<u>Where Deaths</u>	<u>Comments</u>
Heparin/OSCS (Counterfeit)	China	Yes	US, not in EU	- Side effects in Germany - Mimics in analyses
Pet Food/Melamine (Counterfeit)	China	Yes	US, not in EU	- Mimics in analyses
Gentamicin sulfate (Counterfeit)	China	Yes	US, not in EU	- Only seen with special analyses - Germany reacts: Würzburg project
Glycerin/DEG (Counterfeit)	China	Yes	Not in US/EU	- But found in US/EU: In toothpaste!
L-Tryptophan (Not a counterfeit)	Japan	No	US, not in EU	- Trace impurity - Side effects in Germany

Note: Ketek® affair includes similar discrepancies between EU and US data

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Falsified pharmaceutical ingredients may kill acutely...



Heparin



Haiti

**...or in
the
longer
term**



Panama



Gentamicin

A Domestic Food Disaster with Global Aspects:



In 2008 ca. 300,000 Chinese children were poisoned by deliberately falsified milk & milk products containing the industrial chemical melamine: >290,000 became ill, 51,900 were hospitalized, at least 6 died



How Big is the Invisible Danger of Falsified APIs?



One API batch

=>

10,000 - 200,000

Patients



Overdue oversight: Example



- After around 160 inspections worldwide at almost 130 sites in \pm 10 years EDQM has in total suspended or withdrawn around 50 CEPs.
- EDQM only inspects a small fraction of all approved API manufactures
- This implies: Large quantities of at least around 50 (but probably many more) very unsafe APIs have been administered to millions of patients in the EU for years
- From a patient safety perspective the CEPs should never have been granted
- All the CEP suspensions and withdrawals by EDQM related to API manufacture in Asia
-and until recently EDQM has been the only European entity doing API inspections* outside Europe...(*)
- CEFIC/APIC strongly supports EDQM in its overseas inspection programme

(*): *Centralised procedure APIs are inspected globally through EMEA coordination

What is needed to solve Europe's Rogue API Problem: CEFIC'S 10 points



- 1. Mandatory API GMP Certification from European inspectorate**
- 2. Global prioritization of API inspections**
- 3. Central European Unit to coordinate API inspections worldwide**
- 4. Including focus on fraud and counterfeiting within GMP inspections**
- 5. Resolve resource problems for inspections through user fees**

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What is needed to solve Europe's Rogue API Problem: CEFIC's 10 points



- 6. Use of analytical technologies by authorities and industry to detect counterfeit APIs (e.g. NIRS)**
- 7. IT System to help customs to stop importation of counterfeit APIs**
- 8. Introduction of tough sanctions and penalties for API counterfeiting**
- 9. Introduction of licensing system for traders and brokers**
- 10. Clarify legal liability of Qualified Persons**

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Thank you



Questions?



Current and new issues concerning global markets and the quality of medicines: How to face the challenges and opportunities of globalization – Europe

Pharmaceutical Excipients and the Future

*Ms Beam Suffolk
Chair, IPEC Europe
14 October 2010 - Prague*



What are excipients?

Excipients are components of medicines:

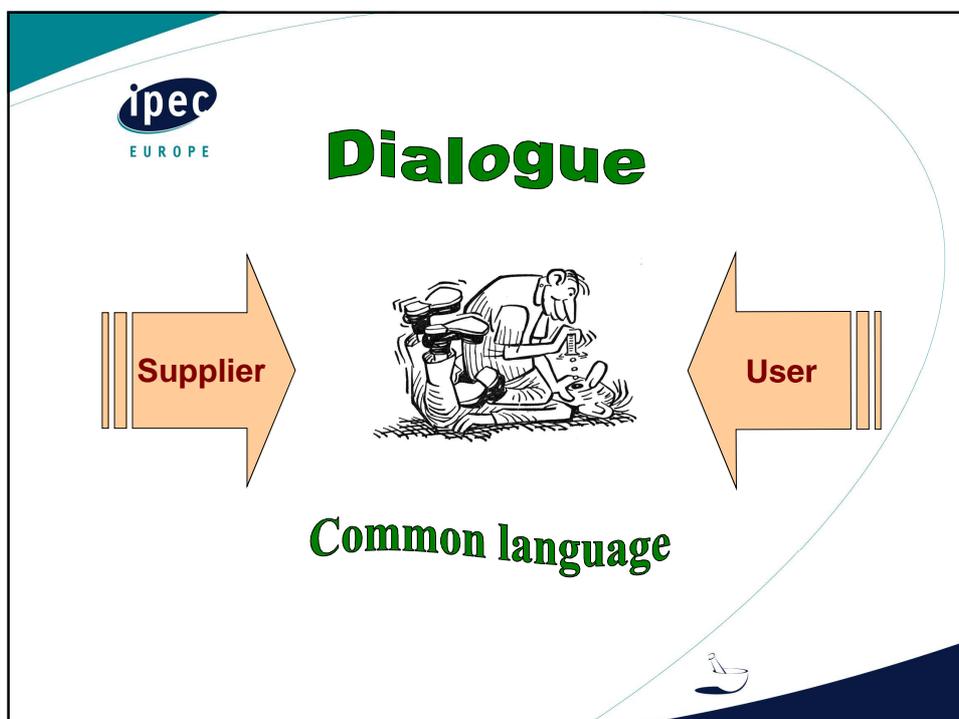
- Excipients have no therapeutic activity
- Excipients help formulate active pharmaceutical ingredients into finished drug dosage forms
- Thousands of different excipients used all dosage forms
- Excipients can influence the potency and bioavailability of an active ingredient





IPEC Europe

- IPEC Europe, the International Pharmaceutical Excipients Council Europe, is an association which serves the interests of producers, distributors and users of pharmaceutical excipients.
- Together with its sister associations IPEC Americas, IPEC Japan and IPEC China. It is a member of IPEC Federation whose global membership extends to more than 200 companies.
- IPEC Europe represents the views of its members to appropriate regulatory bodies and aims to be recognized by government agencies around the world as the voice of European producers, distributors and users of pharmaceutical excipients.
- For this it develops position papers and it contributes to global harmonization efforts in the fields of regulations, regulatory standards and pharmacopoeial monographs for excipients.





IPEC Europe: main activities

To contribute to regulations, providing guidance and interpretation to ensure:

- ✓ excipients do not compromise patient safety
- ✓ their sources of supply are secured
- ✓ the unique nature of excipients is recognised through the inter-relationships between our areas of focus



IPEC Europe: our focus

- Harmonisation of monographs
- Harmonisation of standards
 - ✓ Good Manufacturing Practices
 - ✓ Good Distribution Practices
 - ✓ Excipient Information Packages
 - ✓ Quality Agreements
- Quality by Design
- Protection of intellectual property





IPEC Europe: regulation

Voice proactively that excipients must be adequately regulated but recognising that relevant criteria are not the same as for drug products/APIs:

- GMP for certain excipients
- Harmonisation of monographs
- Composition/impurities
- Emerging guidelines, for example potential genotoxic impurities and heavy metal catalyst residues
- Stakeholder relationships



IPEC Europe strategy: supply

Proactive promotion of good business practices which mitigate supply chain risks

- Counterfeiting and illegal supply of medicines still proliferate
- Recent events continue to emphasize the need for legitimate and responsible business practices
- Excipient manufacturing and distribution networks cross various industry sectors
- Work collaboratively with our sister organisations (IPEC Federation) and regulators (*GMP* (EC), *GDP* (WHO)) by influencing the “What’s” and providing the “How to’s” (*GMP* and *GDP* guides and audit guides)





**IPEC Europe strategy:
innovation**

Enable innovation and protection of proprietary information

- Promote and encourage the creation of the Excipient drug master files scheme in EU
- Facilitate more rapid adoption of monographs for new excipients



**IPEC Europe strategy:
the future**

- **Need *regulation***: balanced legislation to permit self regulation
- **Need *harmonisation***: immediate globalisation and simplification
- **Need *recognition***: excipient sources and uses must be ensured
- **Need *innovation***: development and use of new excipients must be stimulated
- **Need *supply chain control***: sources must be secure
- **Need *Stakeholders cooperation***: access and partnership must be possible





IPEC Europe
one of our key commitments





Excipact

Project commenced in May 2008 with EFCG and IPEC Europe, now comprises 5 trade associations

- EFCG - European Fine Chemicals Group
- FECC – European Association of Chemical Distributors
- IPEC-Americas
- IPEC Europe
- PQG - Pharmaceutical Quality Group (UK)










Excipact

Motivation

- Safety of medicines for patients – recent tragedies
- Drug producers have to qualify their suppliers
 - Traditionally by a mixture of paper and physical audits
 - Now a regulatory expectation of physical audits on ALL suppliers – no current alternative to physical audits
- Armies of auditors and auditees
 - A familiar story?
- Transparent certification schemes for all components of a drug benefit the entire industry including patients



Excipact

Why Certification?

- Absence of regulations for excipients
- Certification Scheme for self-regulation
- Ability for supplier to initiate process
- Applicability to manufacturers and distributors of excipients
- Well developed and accepted assessment model





Excipact

Certification & 3rd Party Audits

- Provides information on Supplier's GMP practices from experienced auditors with knowledge of excipient manufacturing & GMPs
- Allow companies to focus resources on excipients with highest risk
- Reduces audit load for suppliers and users
- Can allow a level playing field for all
- Help smaller companies (both users and suppliers) and those with limited budgets
- Makes 100% audit verification of suppliers practical



Excipact

Goals

- Acceptance by all stakeholders
- International: certificates accepted globally
- Inclusive: applicable to as many excipients as possible
- Certification assessable for as many accredited 3rd party organizations as possible
- Evolutionary: builds on existing guides and standards
- Simple: easy to understand and apply for all stakeholders

Minimize Risks – Maximize Benefits




Excipact

Excipient GMP focus on both Safety (as food) and Consistent quality (as API)

- Specifications, Process Capability (validation for Excipient), and Change Control with customer notification form the basis of difference between food and excipient GMP
- Starting point of full GMPs, degree of documentation & oversight form the basis of difference between API and excipient GMP
- Raw materials for excipient manufacturing are consumed by the process as compared to ingredients (excipients) for drug products that are consumed by the patient
- Failure of an excipient may result in rejection of a drug batch or decrease in effectiveness or stability of a drug product





Excipact

Good Distribution Practices

- Annex to ISO 9001 containing specific requirements for GDP – Certificate as Annex to ISO 9001 – same model as EFfCI
- Suitable for excipient suppliers (e.g. distributors)
- Allowance for different distributor/trader operations (trading, warehousing, re-packaging, bulk transport etc.)
- Harmonised requirements with IPEC GDP Guide for Pharmaceutical Excipients
- In-line with SQAS ESAD Section F&G
- Where there is overlap, GMP- and GDP-Annexes contain same requirements



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Excipact

Quality of auditors is critical

- Competency framework defined using ISO 19011
- Alternative starting routes to qualification possible i.e. experienced in ISO 9001, GMP or GDP
- Considered best practices e.g. SQA and Qualified Person assessment processes
- Training Guide included
- Training programme for auditors to be developed



Excipact

Certification Scheme

Website

- List of Third Party Certification Providers
- Directory of certified excipients suppliers
- List of certifications suspended and withdrawn
- Program Procedures
 - Appeals
 - Complaints
 - Requirements of Third Party Certification Provides
 - Study Guide for Excipient GMP Certification Auditors





Excipact

Certification Scheme

Participation

- Legal Agreement between Excipact and 3rd Party Assessment Body
- Confirmation of certification held by 3rd party assessment body
- Confirmation of auditor competency and qualifications to the requirements of the scheme

Delivery of Scheme

- Target is 2011



The International Pharmaceutical Excipients Council Europe

"Helping To Shape The Future Of Excipients"

Thank you for your attention!

Beam Suffolk
IPEC Europe Chair





Plasma Protein Therapies

Ilka von Hoegen
Plasma Protein Therapeutics Association
Prague 14 – 15 October 2010



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PPTA Members



Plasma derived therapies and Recombinant therapies; Manufacturing sites in USA, Austria, Belgium, Switzerland, and Italy



Plasma derived therapies; Manufacturing sites in Austria, France, Germany and Sweden



Plasma derived therapies; Manufacturing site in Germany



Plasma derived therapies; Manufacturing sites in USA



Plasma derived therapies; Manufacturing sites in Spain and USA



Plasma derived and Recombinant therapies; Manufacturing sites in USA, Switzerland, and Germany



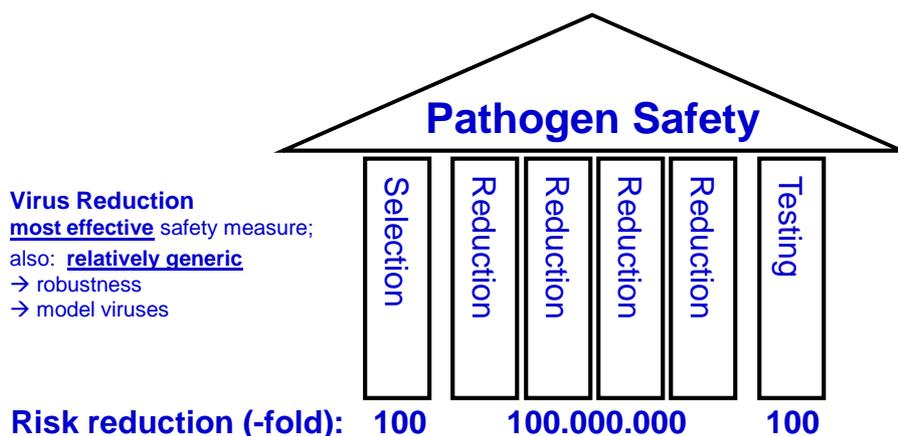
Plasma derived therapies; Manufacturing sites in Italy



Canadian Based (North America Regional Member Only)

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- The starting material is human plasma
 - Individual product classes (IG, clotting factors) are separated in a complex manufacturing process
 - They are stable products with a defined shelf life of several years
 - They are global, i.e. distributed throughout the world
- Plasma protein therapies are different from labile components for transfusion
- They are among the most highly regulated medicinal products
 - Many governments recognise the unique cost structure by specific reimbursement policies



Viral Inactivation and Removal:

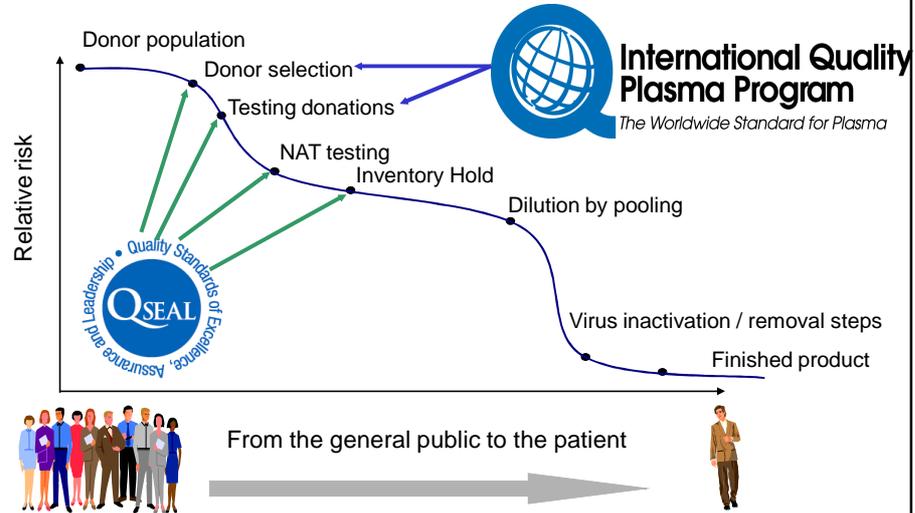
- Effective in eliminating HIV, HBV, HCV and other blood-borne infectious agents

Validation:

- Provide evidence that selected steps of the manufacturing process effectively inactivate/remove viruses
- Provide indirect evidence that the manufacturing process will inactivate/ remove a wide range of viruses including (emerging) enveloped and non-enveloped viruses of diverse physico-chemical characteristics

The model virus concept, i.e. using a wide range of physicochemically diverse viruses for the validation of virus reduction steps, has also been verified, in that the behaviour of a virus of interest, such as WNV, SARS has been adequately predicted !

Today, plasma protein therapies have a excellent safety record with regards to known and emerging pathogens



www.pptaglobal.org

EDQM takes a vital part in assuring the safety and efficacy of plasma protein therapies, for example:

- OMCL network
- OCABR (Official Control Authority Batch Release)
- Mutual recognition of OCABR
- Assays and International standards
- Guide to the preparation, use and quality assurance of blood components
- Participation of non-EU countries

Diagnosis and treatment of all patients

Even in developed countries many patients are not diagnosed or treated

Provision of sufficient and safe plasma for fractionation for treatment of all patients

Recognition of the global nature of plasma protein therapies

More international harmonisation of regulatory requirements

Ilka von Hoegen
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For more information, please visit:

www.pptaglobal.org
www.donatingplasma.org

Quality Standards of Excellence, Assurance and Leadership (QSEAL) Standards

- Qualified Donor Standard – to ensure a committed, healthy donor population
- Viral Marker Standard – to demonstrate the quality of the donor population
- NAT Testing Standard – to allow for the detection of certain viruses even earlier than current licensed serological screening technology
- Inventory Hold Standard – to allow for the retrieval of plasma prior to use if new post-donation information becomes available regarding the donor's health status
- Parvovirus B-19 – to assure that manufacturing pools do not exceed 105 IU Parvovirus B-19 DNA per ml.
- Intermediates Standards – to assure that intermediates are of the highest quality and safety.

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Treatment With Plasma Protein Therapies

Number of plasma donations needed to treat one adult for one year

Alpha-1 Antitrypsin Deficiency	943
Primary Immunodeficiency Disease	130
Hemophilia A**	1,237

Source: PPTA, The Marketing Research Bureau, selected package inserts.
Based on 150 lb. patient over the course of one year.

**On prophylaxis

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