

New Frontiers in the Quality of Medicines

**Plenary Session - Part 2
Action Plan for the Future
Recommendations from the Industry
15 June 2007**

EDQM International Conference

13-15 June 2007

Strasbourg, France





MISSION STATEMENT:

- **To represent the interests of pharmaceutical and chemical companies producing APIs and intermediates in Europe by being recognized experts who advance and influence the global GMP and Regulatory environment.**
- **To promote the use of safe APIs in medicinal products.**



STRATEGIC OBJECTIVES

- **Level Playing Field: to strongly advocate regulatory compliance e.g. with ICH Q7a in all global markets and its enforcement through inspection.**
- **Post approval change authorization: to put responsibility to manage change back into the hands of industry.**
- **Harmonisation: to support global harmonization in the fields of quality and regulatory affairs.**

WHAT CAN BE DONE ?



- **Effective Laws and Regulations must be implemented and enforced**
- **More API-focused inspections are needed in all markets**
- **Focus on the entire supply chain- seek out fraud and counterfeiting practices**
- **Sanctions must be tough and enforced**
- **Industry can work in partnership with regulators**
- **Report unusual labels, damaged/tampered with containers, suspected trading of illicit APIs**
- **Only use reputable brokers/traders**
- **Full transparency back to the API manufacturer**
- **Utilise analytical techniques i.e. fingerprinting**

3

ROLE OF THE AUTHORITIES



- **EDQM inspections: Many serious API issues observed in China & India. So coming authority inspection efforts should focus on producers, traders and users of APIs from such high risk regions**
- **National Authorities must collaborate across the supply chain**
- **Involve international policing agencies i.e. Interpol also in API matters**
- **Make sanctions very tough - withdraw involved MAs, prosecute and jail perpetrators**
- **Highlight those sanctioned**
- **Support and fund anti-counterfeit measures i.e. RFID**
- **Explore security checks at all borders**
- **Surveillance of integrity of API-part of supply chain**

4

RECENT DEVELOPMENTS



- **Joint Position Paper issued by US/European Industry- 'Uneven enforcement leads to sub-par drugs and National Security Risk' -EFCG/SOCMA**
- **Written Declaration tabled by MEPs**
- **Position paper submitted by CEFIC-'Impact of fraud, counterfeiting and severe non-compliance on EU Medicines'**
- **Council of Europe-Moscow Meeting/Declarations**
- **European Parliament Symposium on Counterfeit of Pharmaceuticals-co-sponsored by CEFIC-May 2007**

5

APIC SECTOR GROUP



FURTHER RECOMMENDATIONS

- **Proceed with OMCL network project- 25 APIC members signed up to date**
- **Maintain efforts towards harmonisation of different pharmacopoeia**
- **Implement ICH Q 8,9 and 10**
- **Improve framework for variations based on revision of variations regulations**

6



New frontiers in the Quality of Medicine
Action Plan for the Future:
Recommendations from the Industry

Pharmaceutical Excipients and the Future

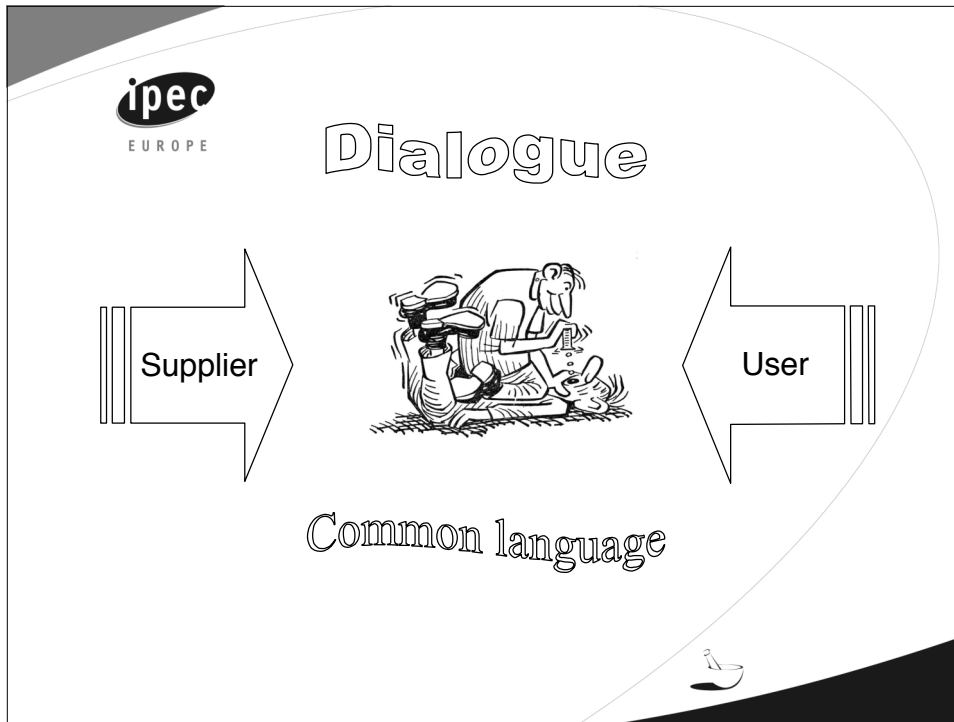
15 June 2007 - Strasbourg

Dr Patricia Rafidison
Chair, 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 and IPEC Japan (JPEC) the Council is member of TriPEC 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.





The slide features the **ipec** EUROPE logo in the top left corner. The title **IPEC Europe: main activities** is positioned to the right of the logo. Below the title, the text **To contribute to regulations, providing guidance and interpretation to ensure:** is written in a bold, italicized font. Underneath this, a bulleted list of three items is provided, also in a bold, italicized font. A small icon of a mortar and pestle is located in the bottom right corner of the slide area.

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
- Good Manufacturing Practices
- Good Distribution Practices
- Quality by Design
- Impact of regulations from associated industries
- 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, heavy metal catalyst residues
- Stakeholder relationships
- Monitor exemption of pharmaceutical excipients from other regulations (for example, REACH)





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 flag the need for legitimate and responsible business practices
- Excipient manufacturing and distribution networks cross various industry sectors
- Work collaboratively with our sister organisations (TriPEC) 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

- Influence the creation 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 protected
- 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





Regulatory Perspective on Future
Biopharmaceuticals

Karin Sewerin, PhD
Astra Zeneca
On behalf of EuropaBio



Three Areas for Consideration

Quality by Design

Biosimilars / Follow on Biologics

Biological standards

1. Quality by Design

Step wise approach:

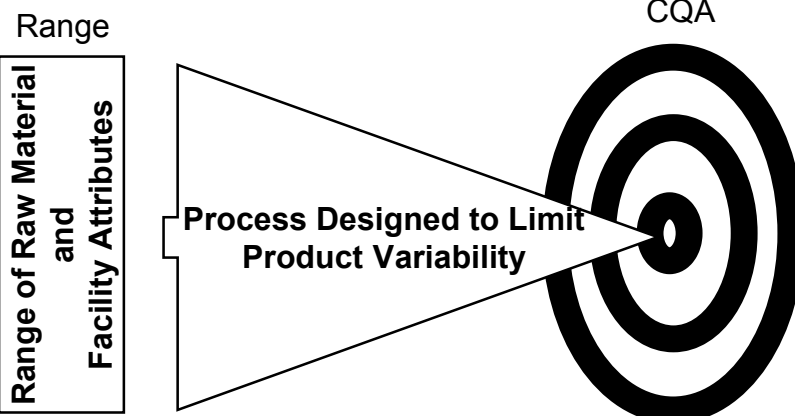
GOAL - real time release using a flexible process

FIRST STEP –

- Reduction of regulatory submissions/approvals related to process changes
 - Within design space - with no impact on product quality (scale, site etc)
- Platform approach
 - “Scale down” of process for assessment of changes



Next step: Process Design -
Target Critical Quality Attributes



After Jon Clark FDA

Control of Batch - In Process Controls vs. Specifications

Process performance parameters as IPC

- Removal of process related impurities
 - HCP, DNA,
- Control of post translational modifications
 - Glycosylation pattern, deamidation, etc

Safety and Efficacy as specification testing
on DS Bulk and Final Product



2. BioSimilarars

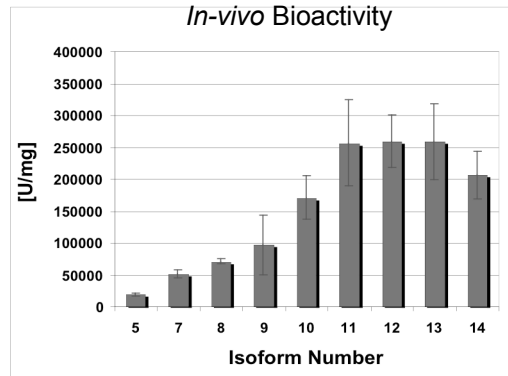
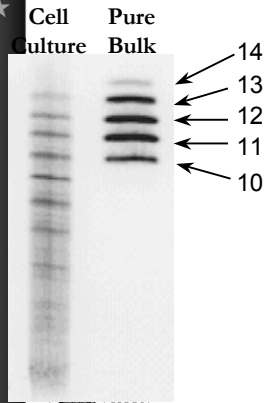
Nothing new:

- Several biological products on the market
 - rhGH, Factor VIII, Insulin, EPO etc
- Manufactured by slightly different processes
- Required to show that the alternative product is **SAFE** and **EFFICACIOUS**



Ex. EPO is not a single active ingredient it is a heterogeneous mix of similar isoforms

Isoelectric Focusing: epoetin alfa product is subtraction of cell culture isoforms



FS/0142/05/6... Critical I Biovision, April 13, 2005

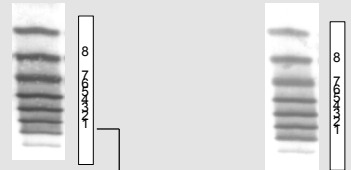
...what looks the same may be different

IEF pattern and sialic acid content of the two EPOs are very similar

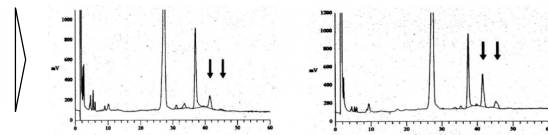
... but the biological activity is very different

The carbohydrate structures of the two EPO isoforms are different

huEPO - 1 huEPO - 2



	huEPO - 1	huEPO - 2
Sialic acid	14.0	14.2
In-vivo activity (U/mg)	226,000	400,000



Adapted from Kresse (Berg, J. et al. 1998 PCT/EP/98/07876)

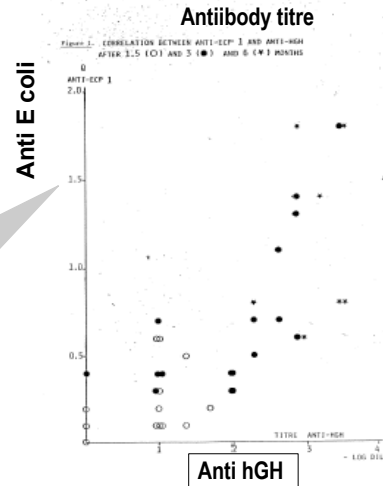
FS/0142/05/7... Critical I Biovision, April 13, 2005

Immunogenicity of methionyl recombinant growth hormone, non neutralizing

Clin Endocrinol Metab. 1986 Aug;15(3):511-35 Recombinant human growth hormone (met-hGH)

Immunogenicity evaluation by clinical trial with more than one production batch should be mandatory.

Immunogenicity of methionyl growth hormone® (Somatrem), was linked to host cell contaminants



FS/0142/05/8... Critical I Biovision, April 13, 2005

BioSimilarars are not Generica

-A different process (cell line, cell culture, purification process etc) can lead to alterations in the safety, efficacy and quality attributes.

-The impact of these subtle differences cannot be fully assessed by physico-chemical and biological characterization alone.

-A system of models (*in vivo* and *in vitro*) must be established for evaluation

FS/0142/05/9... Critical I Biovision, April 13, 2005

3. Biological Standards

- **Physicochemical tests** are not sufficient for biological products
- The **biological activity** by a biomimetic assay
 - Relative potency
 - Response is compared to a standard
 - Response is dependent on the Bioassay
- Calibration of the potency to an international standard is essential for **safe dosing** of products manufactured by multiple manufacturers



Potency / Biological Activity

- Recombinant products are often **dosed** in mass
 - mg/kg body weight
- Potency is expressed relative to a “**well defined reference material**”
- Potency is correlated to mass
 - **Specific activity** = units per mg total protein

The purity may vary

– Human FVIII/vWF plasma	- 1 IU/mL
– Human FVIII/vWF conc	- 10 IU/mg
– Human FVIII	- 2000 IU/mg
– rFVIII	- 4000 - 10 000 IU/mg
– BDD rFVIII	- 15 000 IU/mg





★ ★ International Standards for Biological Products

- **Physicochemical properties** can be described in a Pharmacopoeia Monograph
- **Purity** of a product is negotiated with regulatory agency
- **The biological activity/potency** should be correlated to an international standard, to ensure safe dosing of each product generated by alternative processes and manufacturers.



Thank you

From New Frontiers to New Horizons

Final remarks
Henk J. de Jong
Strasbourg 15 June 2007

The Conference Formulation

Ingredients:

- Academia
- Regulators
- Industry
- OMCLs

And a lot of
interactions!



Format and Frequency

- Plenary sessions
- Workshops
- One to one sessions

- At each new edition of the Ph.Eur. i.e. every 3 years

- So: « rendez vous » in 2010

Again improve communications

- Internet site of edqm
- Knowledge data base
- FAQs
- Monograph history
- Technical guides
- News

Communication

- Specific seminars/workshops
- Training courses on Ph.Eur., Certification,.....
- Consultations with industry

Actions

- Biologicals
- Traditional Medicines (TCM and)
- Updating of general methods and of monographs
- International Harmonisation

A « Thank You » to:

- All of you for coming and participating
- Staff of edqm for organising
- Services of CoE and edqm
- Our interpreters

Have a safe trip home!