Outline

- The EU regulatory process for pharmaceuticals, in brief
- CHMP Working Parties: SAWP and SWP
- Building guidelines: drivers and procedures
- Stakeholders dialogue in the EU: Academia/Industry/Regulators
European Union
Legal Entity; Can Negotiate International Agreements on Behalf of Member States

The EU has developed a single market through a standardised system of laws that apply to all its Member States. The same rules and harmonised procedures apply to all the 28 Member States regarding the authorisation of medicines and the supervision of the safety of medicines.

Accession to the EU means a commitment to apply the "acquis communautaire" (the body of EU legislation and guidance) to ensure that all EU Member States operate to the same standards.
1965---2015

50 YEARS
EU PHARMACEUTICAL REGULATION
MILESTONES

LEGISLATIVE

1964: DECLARATION OF HELSINKI
Ethical Principles for Clinical Research

60s

1965: THALIDOMIDE DISASTER

STRUCTURED MEDICINAL REGULATIONS ESTABLISHED:
Authorization Needed for placing a medicine in the EU market

September 2012:
50Y after Thalidomide withdrawal

Thalidomide Victims Get Apology from Makers After Half a Century
August 7, 1962

**Thalidomide - Driven Actions**

- Reprotox Testing Strategy Revised (rabbit included)
- **West Germany:** Safety Testing of new drugs became compulsory

---

**1965---2015**

**50 YEARS EU PHARMACEUTICAL REGULATION MILESTONES**

**70s**

- **1975: Joint EU position for MA:**
  - Multistate Procedure;
  - Common Committee (CPMP)
<table>
<thead>
<tr>
<th><strong>1965---2015</strong></th>
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<tbody>
<tr>
<td><strong>50 YEARS</strong></td>
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<tr>
<td><strong>EU PHARMACEUTICAL REGULATION MILESTONES</strong></td>
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</table>

### 80s
- **1983:** Uniform way to summarise key characteristics of authorized products
- The rules Governing MP in the European Community (common guidelines)

- **1987:** Concertation Procedure Introduced: Opinion of EU level Committee for innovative products

- **1989:** First Guidelines on GMPs

---

### 90s
- **1990:** The ICH (Internationalization starts)

- **1993:**
  - Centralized Procedure
  - Mutual Recognition procedure
  - European Network of Medicines control Labs

- **1995:** The European Medicines Evaluation Agency (EMEA) Starts business
1965---2015

50 YEARS
EU PHARMACEUTICAL REGULATION
MILESTONES

LEGISLATIVE

THERAPEUTIC

2000: Orphan Legislation Adopted - COMP (patient representative as COMP member)

2001: Clinical Trials (CT) Directive implemented requirements for conduct of CT in the EU

2004: Rules on Traditional Herbal Medicinal products (HMPC)

2004: EU rules for biosimilars

2006: Legislation on MP for Children

2007: Regulation on ATMP

2008: Thalidomide authorized for multiple myeloma
The European System on Medicines for Human Use
EMA: A Networking Agency

- Member States have pooled their sovereignty for authorisation of medicines
- EMA is designed to coordinate the existing scientific resources of Member States (MS)
- All Agencies linked by an IT network (EudraNet)

Challenges & Achievements

- **Agency’s Remit Expanded**
  - Rare diseases (2000),

- **Patients and Healthcare Professionals Involvement (2000).**
  - Full members in most of Scientific Committees
  - Increasingly Role in Medicines Risks & Benefits Assessment

- **Increased Role in Medicines Safety Monitoring Across EU (PRAC, 2012)**

- **Publish Clinical Data behind EU medicines decision-making (2015).**
• **1995-** mostly MA issues

• **2015-** Full Medicines Life Time (A to Z)
Overview of CHMP Role
Medicines Life Time (A-Z)

• Pre Marketing
• Marketing Authorization Procedures
• Post Marketing

The EU procedures of Marketing Authorisations

CHMP

- Centralised Procedure (via EMA)

CMDh

- Mutual Recognition procedure
- Decentralised Procedure

Better Resource Utilisation
Harmonised Scientific Opinions
Harmonised Information to Doctors / Patients
In the past 20 years, the Agency has recommended the authorization of a total of 975 human medicines and 188 veterinary medicines.

Overview of CHMP Role
Marketing Authorization (MA)

**Centralised Procedure:**
- Conduct the initial assessment for EU-wide Marketing
- Post-authorization and maintenance activities (e.g., variations to MA)
- Publish the European Public Assessment Report (EPAR) + SPC+PL

**Mutual-recognition’ & ‘Decentralised’ Procedures**
- Arbitrations: if disagreement between MS on the MA
- Referrals
  - (when concerns on protection of public health)
  - or other Community interests (‘Community referral procedure’).
Overview of CHMP Role
Post-Marketing

EU Wide Pharmacovigilance
• closely monitor reports of potential safety concerns (‘ADRs)
• recommend to European Commission on changes to MA/Suspension/Withdrawal.

• Modify MA conditions
- issue an ‘urgent safety restriction’ (USR)
- Inform Healthcare Professionals of changes on to how/when medication may be used.

Overview of CHMP Role
Pre-Marketing

Assist Companies/Academia on medicines/procedures R&D
• Scientific Advice (SAWP/WPs)
• Innovation Task Force (ITF)

• Prepare scientific and regulatory guidelines

• Cooperate with international partners on harmonization of regulatory requirements for medicines (eg ICH).
### CHMP Supportive (Expert) Groups

- **Working Parties**
  - Standing
  - Temporary
- **Scientific Advisory Groups (SAGs)**
- **Drafting Groups**

### Working Parties /Expert Groups

*Experts from the EU experts list (based on specific expertise)*

**Assist CHMP on**
- Scientific issues on specific expertise fields
- Aspects of scientific evaluation of applications,
- Guideline drafting
- Identify/propose topics for consideration by the WP

<table>
<thead>
<tr>
<th>Standing WPs</th>
<th>Temporary WPs</th>
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<tbody>
<tr>
<td>Health Care Professionals (HCPWP)</td>
<td>Biosimilar Med Products</td>
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<tr>
<td>Patients&amp;Consumers WP</td>
<td>Biostatistics</td>
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<tr>
<td>Scientific Advice (SAWP)</td>
<td>Blood Products</td>
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<tr>
<td>Quality (QWP)</td>
<td>Cardiovascular</td>
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<tr>
<td>Biologics (BWP)</td>
<td>Central Nervous System</td>
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<td>Safety (SWP)</td>
<td>Infectious Disease</td>
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<td>Oncology</td>
<td>Pharmacogenomics</td>
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<td>Pharmacokinetics</td>
<td>Reumathology/Immunology</td>
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<tr>
<td>Vaccines</td>
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Scientific Advisory (SAGs) and Drafting Groups

- **Scientific advisory groups (SAGs)**
  Advice to CHMP on evaluation of specific medicinal products / treatments (MA)
  - Cardiovascular
  - Anti-infectives
  - Diabetes/Endocrinology
  - Vaccines
  - HIV/Viral diseases
  - Neurology
  - Psychiatry
  - Oncology (InterCommittee)

- **Drafting Groups (convened by CHMP/WPs)**
  - prepare proposals on specific topics
  - (CHMP / WP members/ alternates/ experts)

Scientific Advice Working Party (SAWP)

- **Coordinate (CHMP/COMP) Advice on**
  - Quality
  - Non-clinical and clinical safety and efficacy
  - Qualification on novel methodologies
  - Significant benefit of orphan medicinal products.

- **Major areas of expertise represented**
  - Nonclinical safety
  - Pharmacokinetics
  - Methodology and statistics
  - Therapeutic field with frequent requests
    - Oncology
    - diabetes
    - CNS/neurodegeneration
    - Infectious diseases (incl. HIV)

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Types of CHMP/SAWP Advice

- Scientific Advice (SA)
- Protocol Assistance (PA)
- EMA / US FDA Parallel Advice
- EMA / Joint Technology Assessment Bodies Parallel Advice

Stages of product development for SA/PA

- During the initial development of the medicinal product (before submission of the MAA)
- During the post authorisation phase.

Binding aspects

- NOT binding for MA
- But to be taken into account during assessment
Overview of SA/PA Procedure

NC Safety Regulatory Framework

Safety Working Party

Provides recommendations to (CHMP) on all matters relating directly or indirectly to non-clinical aspects of safety

**SWP Composition**

- Agreed by CHMP on
  - Experts selected from the European experts list
  - One member per Member State
- Chair and Vice Chair elected by CHMP
SWP Mandate and Objectives

- At request of CHMP:
  - Support to dossier evaluation on NC safety related matters
  - Scientific advice general & product matters (NC safety) to EC/CMDh/HMPC
- Assessment of NC safety findings raised post authorisation
- Contribution to SAWP Scientific Advices
- Preparation, review and update of guidelines
- Liaise with other WPs on NC safety related matters
- Focus and catalyst for training on NC assessments
- Liaison with interested parties (e.g. EFPIA, ECVAM, ABPI, ILSI)
- International cooperation on NC safety related matters (ICH)

Procedure for Drafting a Guideline

**Step 1: Concept paper**

1. Topic selection and inclusion in the relevant work programme(s)
2. Appointment of rapporteur and (if necessary) co-rapporteur
3. Development of concept paper
4. CHMP adoption and release for consultation of concept paper
   (2-3 Months)
Procedure for Drafting a Guideline

Step 2: Draft guideline

1. 5. Preparation of initial draft guideline

6. Release for consultation of draft guideline (3-6 Months)

7. Collection of comments from e.g.
   - Member States of the EEA/EFTA countries
   - Other regulatory authorities (e.g. FDA, Health Canada, Therapeutic Goods Administration, European Pharmacopoeia, other ICH partners
   - European industry associations;
   - European scientific/academic societies
   - Patients/consumer groups/health care professionals;
   - Other interested parties.

Procedure for Drafting a Guideline

Step 3: Final guideline

8. Preparation of final version of guideline

9. Adoption of final guideline for publication

10. Implementation (6 Month post adoption)
NC Safety EU Guidelines
Some drivers for their generation

Reaction to identified safety issues (product driven)
- Genotoxic impurities
- Controls Contamination in safety studies
- Strategies to mitigate the risk on First in Human CTs

Identification on uncovered areas
- NC development of Pediatric medicines
- Nonclinical and Clinical development of biosimilar Mabs
- Nanomedicines

Request by Scientific Community / Pharmaceutical Industry
- Microdosing
- Biomarker / new methodology qualification

Guideline Driver
Vfend (Voriconazole)

Approved Indications
- Treatment of invasive aspergillosis
- Treatment of candidemia in non-neutropenic patients.
- Treatment of fluconazole-resistant serious invasive Candida infections (including C. krusei)
- Treatment of serious fungal infections caused by Scedosporium spp. and Fusarium spp

sulphobutylether beta-cyclodextrin sodium (SBECDS) used in the Parenteral formulation (solubility enhancer (new excipient)).

Genotoxic 1,4 butane sultone detected in SBECDS.
- Limit for 1,4-butane sultone requested to be reduced to < 1 ppm
- or different synthesis process.
Threshold of Toxicological Concern

1.5 μg/day

theoretical 10-5 excess lifetime risk of cancer

high potency mutagenic carcinogens

Cohort of Concern:
- aflatoxin-like-
- N-nitroso-
- alkyl-azoxy compounds
INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Final Concept Paper

M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk
dated 27 November 2009

Endorsed by the ICH Steering Committee on 9 June 2010

Issues to be Resolved

- What are acceptable levels of genotoxic impurities during drug development?
- What are acceptable levels of genotoxic impurities for marketing?
- Should those impurities be regulated differently that are likely to have threshold effects?
- Should levels of genotoxic impurities be regulated using a Threshold of Toxicological Concern (TTC) approach?
- Structurally related genotoxic impurities are likely to have similar mechanisms of action. Should these be summed in calculating a TTC?
- What process of qualification testing should be followed for impurities that are metabolites?
- What additional data are needed to support having no special restrictions, or a higher acceptable daily intake than the TTC, for a genotoxic impurity?
ICH guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk

<table>
<thead>
<tr>
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<th>Event</th>
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<tr>
<td>4</td>
<td>Transmission to CHMP</td>
<td>February 2013</td>
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<tr>
<td></td>
<td>Adoption by CHMP for release for consultation</td>
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<td>30 June 2013</td>
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<td>July 2014</td>
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<td>Date for coming into effect</td>
<td>January 2016?</td>
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Guideline Driver

TGN1412

[Diagram showing the interactions between TGN1412 and TCR, CD28, and other markers, illustrating the differences between conventional and superagonistic responses.]
TGN1412 First in Human dose estimation

GLP studies in cynomologous monkey
NOAEL at 50 mg kg\(^{-1}\) week\(^{-1}\).

- HED 16 mg/Kg
- SF 100
- HED 0.16 mg/Kg

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Guideline Driver
TGN1412

13th March 2006 – 6 volunteers dosed with 0.1 mg/kg of TGN1412 at 10 min intervals developed cytokine storm

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# TGN 1412- PD component

**GLP studies in cynomologous monkey**

NOAEL at 50 mg kg\(^{-1}\) week\(^{-1}\).

- HED 16 mg/Kg
- SF 100
- HED 0.16 mg/Kg

Duff Report: Receptor Occupancy 90%
### Scope of the Guideline

**To Assist Sponsors on NIMP**

**Non-clinical Early Clinical Development**
- Identifies factors influencing risk for NIMP
- Considers aspects on
  - Quality, Nonclinical testing strategies
  - designs & conduct of FIH clinical trials
- **Gives strategies for mitigating & managing risk**
  - calculation of the initial dose to be used
  - subsequent dose escalation intervals and
  - conduct of the clinical trial

---

**FIH Estimation**

When Factors Influencing Risk are Identified

**MABEL**

- Minimal Anticipated Biological Effect Level in Humans

\[
\text{Safety factors} \\
\text{First in Human Dose}
\]

Beatriz Silva Lima, SOT, San Diego, 2015
Driver: Uncovered Areas
Nanomedicines

Falk Ehmann* et al, 2013, Next-generation nanomedicines and nanosimilars: EU regulators’ initiatives relating to the development and evaluation of nanomedicines; Nanomedicine, Vol. 8, No. 5, Pages 849-856

“...it is now important for medicines regulatory agencies to consider the mechanisms needed to ensure safe introduction of ‘follow-on’ nanomedicine products, ‘nanosimilars’.

...drug regulators need to ensure that ‘next’-generation nanomedicines enter clinical development and consequently the market in a safe and timely way for the benefit of public health.”

Nanomedicines guidance docs

Nanomedicines, including liposomal formulations, iron-based preparations and nanocrystal-based medicines, have started to come off patent.

Reflection papers on development of new nanomedicines & nanosimilars


reflection paper on the data requirements for intravenous liposomal products developed with reference to an innovator liposomal product, published in February 2013;

reflection paper on surface coatings: general issues for consideration regarding parenteral administration of coated nanomedicine products, published in August 2013

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Driver:
Scientific Community Demand

Qualification Outcomes

• Qualification Opinion
• Qualification Advice
• Letter of Support
Driver:
Scientific Community Demand

Qualification opinion ILSI/HESI submission of novel renal biomarkers for toxicity

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<td>February 2010</td>
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<tr>
<td>Adoption by CHMP for release for consultation</td>
<td>18 March 2010</td>
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<td>31 July 2010</td>
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<tr>
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<td>21 October 2010</td>
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</tbody>
</table>

Keywords: non-clinical, renal biomarkers, nephrotoxicity.

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Letter of Support for PSTC translational Drug-Induced Kidney Injury (DIKI) biomarkers

No specific urinary OPN or NGAL test system or assay validation process is endorsed by this evaluation. Strong emphasis on applying good scientific and laboratory practices for quality control of these assay test systems is imperative. Definition of the assay platform’s quantitative range and limits of detection should be established in advance of use.

EMA encourage the conduct of nonclinical and exploratory clinical analyses to evaluate the translational relevance of changes in urinary OPN and NGAL values and the magnitude of change in urinary OPN and NGAL that could be considered clinically meaningful in the determination of kidney injury when observed in an individual subject.

Beatriz Silva Lima, SOT, San Diego, 2015
Applications for Drug Biomarker Qualification
Parallel EMA/FDA Submissions

**Update: Letter of intent (December 2014)**

Joint EMA/FDA letter of intent (LOI) launched (for reducing preparation time)

The joint LOI allows the two agencies to share scientific perspectives and advice.
The agencies are also able to provide the same response to submitters.

LOIs can also be sent EMA or FDA-specific LOIs separately

Some sections of the LOI are specific for EMA or the FDA. See the template for details.

Facilitating the Dialogue:
Basic/Applied/ Regulatory Sciences

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Beatriz Silva Lima, February 2015, Bethesda
IMI Achievements:
An international, cross-sector community

- Over 6,000 researchers working for:
  - collective intelligence networks
  - improved R&D productivity
  - innovative approaches to unmet medical needs

- 650 academic teams
- 120 SMEs
- 409 EFPIA teams
- 25 patient orgs
- 17 regulators

Beatriz Silva Lima, February 2015, Bethesda
Science Regulation

THANK YOU!

Beatriz Silva Lima, SOT, San Diego, 2015

BACKUP SLIDES

Beatriz Silva Lima, SOT, San Diego, 2015
List of Abbreviations

ATMP: Advanced Therapy Medicinal Products
CAT: Committee of Advanced Therapy Medicinal Products
COMP: Committee for Orphan Medicinal Products
CHMP (new CPMP designation): Committee for Human Medicinal Products
CMDh: Coordination Group for Mutual Recognition and Decentralised Procedures - Human
CPMP: Committee for Proprietary Medicinal products
EEC: European Economic Area (EU+ Iceland, Norway, Liechtenstein)
EFPIA: European Federation of Pharmaceutical Industry Associations
HMPC: Herbal Medicinal Products Committee
ICH: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMI: Innovative Medicines Initiative
MS: Member States
MA: Marketing Authorization
PDCO: Pediatrics Committee
PRAC: Pharmacovigilance and Risk Assessment Committee
SAWP: Scientific Advice Working Party
SWP: Safety Working Party

Scope of Optional Centralized Procedure (CP)

(a) Medicinal Product (MP) contains new active substance not authorised in the EU on the date of entry into force of this Regulation
Or
(b) the MP constitutes a significant therapeutic, scientific or technical innovation
Or
the granting of the Marketing Authorization (MA) is in the interests of patients or animal health at Community level.”
Regulatory Procedures: Commonalities

Applicant submits Dossier

Day 1

Clock stop

• Questions Responses Day 120

Day 121

Clock start

• Answers

Day 210

• Commission triggers Decision Making Process – for EU-MA

• National approval in Member States

Marketing Authorisation Time Table

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Centralised Procedure Timeschedule

CHMP (B/R) and PRAC (R)

• Day 121 Submission of response to D120 LOQ

• Assessment Report of Responses (Rapp+Co-Rapp)

• ~Day 140 Teleconf with Peer Reviewers

• Day 150 Joint rapporteur/co-rapporteur Assessment of the response adopted. Discussion at CHMP.

• List of Outstanding Issues to be addressed (writing / Oral Explanation)

• Day 180 Hearing (oral presentation by the applicant Discussion. Possibly a trend vote.

• Day 210 CHMP opinion. Voting procedure. The opinion is forwarded to the European Commission

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Centralised Procedure Timeschedule

- D210: Opinion is forwarded to the European Commission

- Day 210 - Translations, Standing Committee etc.

- ~Day 300 Marketing Authorisation given by the European Commission

Re-examination of Opinion

Re-examination ("appeal")
15 days to request re-examination from receipt of the opinion

60 days to submit grounds from opinion

CHMP 60 days to consider revision of initial opinion
- No new data!
- Scientific advisory group may be consulted
- New (Co)Rapporteurs appointed

Guideline on Procedure for re-examination of CHMP Opinions (EMEA/CHMP/50745/2005)