EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA & Biosimilar update: Trends from marketing authorisation applications, scientific advice procedures and policies

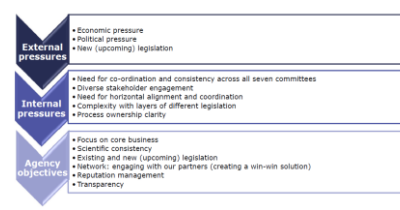
Presented by: Peter Richardson
Head of Quality Office
Specialised Scientific Disciplines Department, EMA

An agency of the European Union

EUROPEAN MEDICINES AGENCY

- **EMA - 20th Anniversary**
- **Agency Reorganisation**
  - **Review & Reconnect**
  - **Implementation**
- **New Building: 30 Churchill Place**

Triggers for re-organisation:

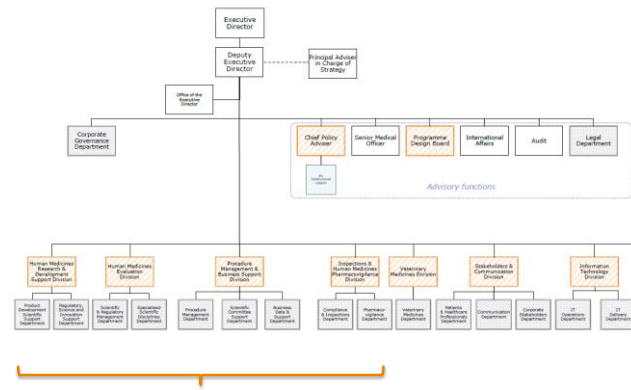


EUROPEAN MEDICINES AGENCY

Human medicines

- R&D Support
- Evaluation
- Procedures
- Inspections & Pharmacovigilance

Organisation chart 1st March 2015



4 Main Divisions

EUROPEAN MEDICINES AGENCY

- **Evaluation Div.**
  Two Departments
  6 / 3 Offices
- Therapeutic Area Offices:
  (EPL) + Labelling Stds.
- Quality Office,
  Biostatistics,
  Non-clinical and clinical p'cology

Head of Human Medicines Evaluation

Expand all items in this list

Head of Human Medicines Evaluation

Scientific and Regulatory Management

Expand all items in this list

- **Head of Anti-infectives and Vaccines**
- **Head of Central Nervous System and Ophthalmology**
- **Head of Endocrinology, Metabolism and Cardiovascular**
- **Head of Oncology, Haematology and Diagnostics**
- **Head of Rheumatology, Respiratory, Gastroenterology and Immunology**
- **Head of Labelling Review and Standards Office**

Specialised Scientific Disciplines

Expand all items in this list

- **Head of Quality**
- **Head of Biostatistics and Methodology Support**
- **Head of Clinical Pharmacology and Non-clinical Support**

EUROPEAN MEDICINES AGENCY

Primary EMA staff in the context of handling evaluation procedures

Procedure Manager (PM)

⇒ **Applicant's primary contact during the course of all evaluation procedures**

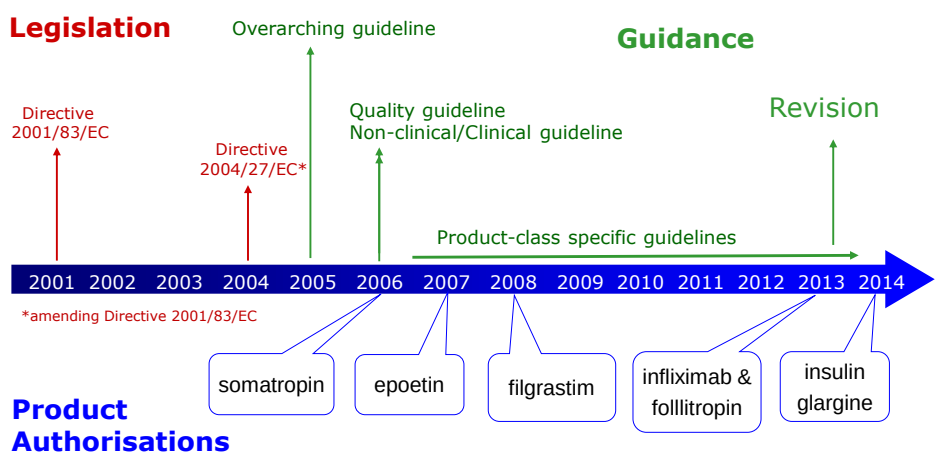
- Provision of regulatory procedural guidance
- Ensures adherence to procedural guidelines and timelines
- Regulatory scientific support in simpler procedures
- Maintains process performance metrics

EMA Product Lead (EPL)

- Leads the EMA product team
- Accountable for overall product knowledge
- Provides clinical and regulatory science input
- Supports consolidation of a committee position
- Facilitates cross-committee discussions
- Reference for the defined products/ disease area

EUROPEAN MEDICINES AGENCY

Evolution of Biosimilars in the EU



EUROPEAN MEDICINES AGENCY

Biosimilar product review

32 MAAs submitted

29 MAAs reviewed

3 MAAs under review

Etanercept (1)
Insulin (1)
Enoxaparin sodium (1)

1 Negative

Interferon alfa

21 Positive

7 Withdrawn

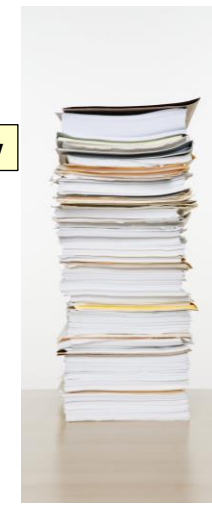
Insulin (6)
Epoetin (1)

19 Valid MAs

Somatropin (1)
Epoetin (5)
Filgrastim (8)
Infliximab (2)
Follitropin (2)
Insulin glargine (1)

2 Withdrawn

Filgrastim (1)
Somatropin (1)



6

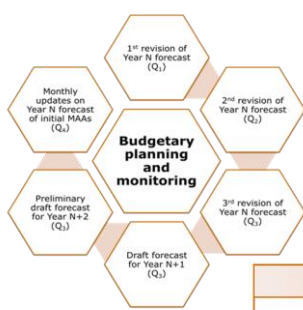
EUROPEAN MEDICINES AGENCY

Business Pipeline

Forecast and business intelligence

businesspipeline@ema.europa.eu

- BP dialogue with companies - 50+ companies actively participating in the BP activity
- Internal discussion - Contributions to the EMA planning and reporting cycle
- Business intelligence - 20/25 BP meetings per year
- Forecast - increase in biosimilar MAAs in 2015



Environmental analyses		
Business environmental analysis	- Business pipeline meetings - Pipeline e-updates	Ad hoc scientific and technical analyses

7

EUROPEAN MEDICINES AGENCY

Guidelines for biosimilars

General Guidelines:

Overarching Guideline (CHMP/437/04 Rev. 1)
"Guideline on Similar Biological Medicinal Products"

Non-clinical/clinical Guideline

Quality Guideline

Class-specific Guidelines: non-clinical/clinical aspects:

Insulin	Somatropin	G-CSF	Epoetin	IFN-α	LMWH	mAbs	IFN-β	Follitropin
2006 Rev. 2015	2006	2006 To be revised	2006 Rev. 2010	2009 To be revised	2009 Revision ongoing	2012	2013	2013

8

EUROPEAN MEDICINES AGENCY

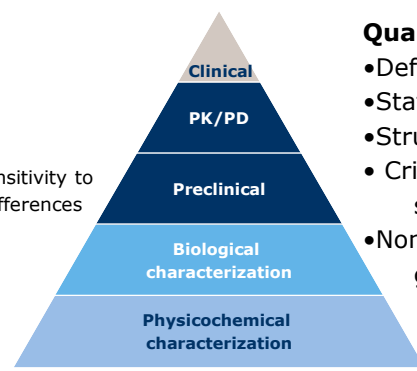
Quality – the foundation of biosimilars:

highly structured development

Lower

Higher

Sensitivity to differences



Quality

- Define Target Profile
- State of art analytical tools
- Structured development: QbD
- Critical Quality Attributes – systematically Controlled
- Non-critical attributes – greater tolerance

9

mAb case study – Quality Profile

EUROPEAN MEDICINES AGENCY

Quality attribute	Product	Min/max ranges	Bar diagram
G0F-GlcNac	Reference Biosim candidate	0.05 – 0.3 % 0.00 – 0.2 %	
G0	Reference Biosim candidate	1.2 – 2.1 % 1.5 – 2.0 %	
G0F	Reference Biosim candidate	20.3 – 32.1 % 25.3 – 33.0 %	
Man5	Reference Biosim candidate	0.0 – 0.9 % 0.2 – 0.5 %	
(1,6)G1F	Reference Biosim candidate	2.5 – 4.1 % 3.0 – 3.9 %	
(1,3)G1F	Reference Biosim candidate	1.6 – 2.3 % 1.7 – 2.2 %	
G2F	Reference Biosim candidate	10.5 – 25.7 % 11.0 – 24.4 %	
G2FS1	Reference Biosim candidate	35.3 – 39.1 % 36.2 – 38.5 %	
G2FS2	Reference Biosim candidate	11.4 – 13.2 % 11.4 – 13.0 %	
NGNA	Reference Biosim candidate	3.3 – 5.5 % 1.1 – 2.0 %	
Deamidation	Reference Biosim candidate	0.9 – 2.4 % 0.3 – 1.5 %	
Oxidation	Reference Biosim candidate	1.2 – 4.3 % 1.0 – 4.1 %	
Dimer	Reference Biosim candidate	0.0 – 2.1 % 0.0 – 0.8 %	
Higher aggregates	Reference Biosim candidate	0.0 – 0.8 % 0.0 – 0.2%	
Binding assay	Reference Biosim candidate	91 – 108 % 93 – 105 %	
CDA activity	Reference Biosim candidate	84 – 110 % 90 – 111 %	
ADCC activity	Reference Biosim candidate	75 – 132 % 82 – 115 %	

Quality

- QbD – Risk Analysis
- Determine CQAs
- Control Operating Ranges for CQAs
- Non-Critical attributes – less stringent control

Outcome

- Biosimilar: high level of control and similarity to originator product

10

Ref: Schiestl, et al., Biologicals 42 (2014) 128-132

EUROPEAN MEDICINES AGENCY

Insulin guideline

Revision finalised in March 2015

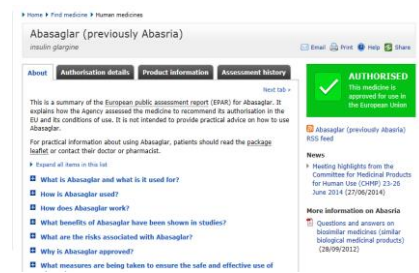
- Intermediate-, long-acting insulin preparations and insulin analogues now included
- Risk-based approach for non-clinical *in vivo* studies
- More detailed guidance on the design of the insulin clamp study
- Expectations regarding the safety study & prerequisites for waiving the safety study
  - Biosimilarity convincingly concluded from physico-chemical & functional characterisation and from PK and PD profiles
  - Impurity profile and nature of excipients of low risk / concern
  - Scientific justification always required

11

EUROPEAN MEDICINES AGENCY

First biosimilar insulin approved

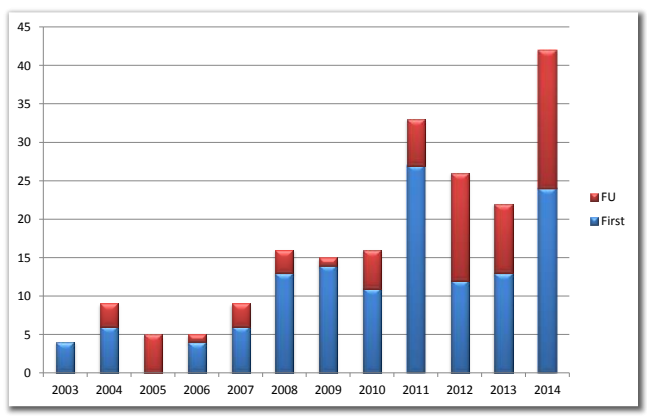
- Robust quality and non-clinical
- PK/PD clamp studies provided pivotal evidence of similar efficacy
- Two clinical studies (HBA1c) in patients with type 1 and 2 diabetes
  - Provided supportive evidence in relation to efficacy
  - Provided the required safety and immunogenicity data



12

EUROPEAN MEDICINES AGENCY

Scientific advice for biosimilars



Around 75% of scientific advice requests are for monoclonal antibodies

13

EUROPEAN MEDICINES AGENCY

Trends from scientific advice procedures

- ✓ Explore use of statistical methodology for comparative assessment of quality attributes
- ✓ Global development – increasing use of non-EU comparator
- ✓ Variety of clinical approaches proposed to demonstrate biosimilarity

14

EUROPEAN MEDICINES AGENCY

Statistical methodology for quality comparability

30 May 2013
EMA/CHMP/297149/2013 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for a reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development

Agreed by Biostatistics Working Party	March 2013
Adoption by CHMP for release for consultation	30 May 2013
Start of public consultation	28 June 2013
End of consultation (deadline for comments)	30 September 2013

Comments should be provided using this template. The completed comments form should be sent to Biostatistics@ema.europa.eu.

Keywords	*statistical methodology, quality attributes, equivalence testing, biosimilar, biological product*

15

EUROPEAN MEDICINES AGENCY

Statistical methodology for quality comparability

- Triggered by increasing number of scientific advice requests
- 25% of SA requests in 2014 for biosimilars include discussion on statistical methodology for quality aspects
- Reflection paper to cover both biosimilar developments and comparability evaluation as per ICH Q5E
  - Challenges: Limited number of batches + Diversity of critical quality attributes
  - Discuss limitations of existing methodologies and suggest alternative approaches

16

EUROPEAN MEDICINES AGENCY

Overarching Guideline

"Global Development" option:

(i.e. Reference Product from non-EU area)

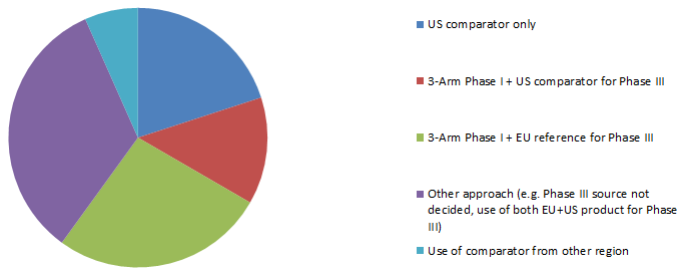
- Aim: Facilitate global development
- Reference product must be authorised in the EEA
- Comparability exercise: Non-EEA authorised comparator can be acceptable for certain clinical studies and *in-vivo* non-clinical studies, provided it is:
  - ➢ Authorised by regulatory authority with similar scientific/regulatory standards
  - ➢ Representative of the reference medicinal product (to be demonstrated by the applicant – bridging data required)

17

EUROPEAN MEDICINES AGENCY

Scientific Advice on global development

- Global development approach proposed in 75% of the scientific advice requests for biosimilars in 2014



EUROPEAN MEDICINES AGENCY

Experience from Scientific Advice requests

- Extrapolation
  - Frequently raised topic
  - More difficult with complex substances (e.g. mAb)
  - Generally: single study acceptable
  - May need additional PK/PD bridging
- Clinical Indication
  - Flexibility in clinical model can be discussed
  - Increased proposals to use oncological indications

EUROPEAN MEDICINES AGENCY

Regulatory Convergence

- EU guidelines and experience continue to be important reference for other Competent Authorities
- EU supports further development / implementation of WHO SBP guidelines
- Liaison with international partners (e.g. via International Pharmaceutical Regulators Forum – IPRF BWG, also Biosimilar Cluster EMA/FDA/HC/PMDA)
- Parallel scientific advice/ad hoc discussions with FDA

20

EUROPEAN MEDICINES AGENCY

Biosimilar identification & INN

- EMA uses INNs according to the WHO policy
- Acceptable for biosimilar to use same INN as its reference product (subject to successful demonstration of comparability)
- EMA follows closely the discussions on a WHO Biological Qualifier: uncertain value for EU

http://www.who.int/medicines/services/inn/inn_bio_bq/en/

21

EUROPEAN MEDICINES AGENCY

Pharmacovigilance/prescribing

For all biologicals:

- Brand name and batch number should be included in adverse reaction reporting (Directive 2010/84/EU)
- Brand name prescribing desirable - should be included in cross border medical prescriptions (Directive 2012/52/EU)

• Study showed good product identification for biosimilars *(Vermeer et al, Drug Saf 2013;36(8):617-25)*

• July 2016 → Implementation of ISO standards: Identification of Medicinal Products (IDMP)

22

EUROPEAN MEDICINES AGENCY

Biosimilars – product information

Information available to the healthcare professional:

- Name and INN included in the labelling
- Biosimilar: Summary of Product Characteristics (SmPC) closely follows the SmPC of the reference product
- Product identified as a biosimilar in the SmPC
- Details regarding the basis for approval (e.g. comparability studies performed) are outlined in the European Public Assessment Report (EPAR), available on the EMA website

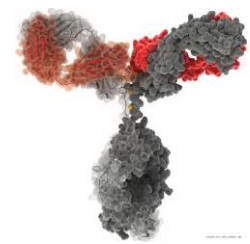
23

EUROPEAN MEDICINES AGENCY

Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins

Revision started in March 2014

- Points under discussion
  - More specific guidance for the presentation of immunogenicity data
  - Requirements of data on antibody assays
  - Role of *in-vitro* and *in-vivo* non-clinical studies
  - Risk-based approach to immunogenicity
  - Clinical data to study potential consequences of unwanted immune responses
  - Comparative immunogenicity studies
  - Post-licensing immunological studies
- Workshop planned: 4Q 2015



24

EUROPEAN MEDICINES AGENCY

BMWP info session on Biosimilars

*EMA Human Scientific Committees' Working Parties with **Patients' and Consumers'** Organisations (PCWP) and **Healthcare Professionals'** Organisations (HCPWP) joint meeting*

Conclusions from meeting:

- There is a clear need for education in this area: to resolve misconceptions and increase knowledge / awareness
- Emphasise: All biologicals are subject to thorough evaluation and surveillance
- Further discussion on substitution and interchangeability need to take place at member state level

25

EUROPEAN MEDICINES AGENCY

EMA Website - Biosimilar landing page

http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000318.jsp&mid=WC0b01ac0580281bf0

Links to:

✓Q and A for biosimilars

✓Biosimilar guidelines

✓BMWP mandate & work plan

✓Procedural guidance for biosimilars

✓Public assessment reports (EPARs) for biosimilars

26

EUROPEAN MEDICINES AGENCY

Thank you for your attention

Peter Richardson,

Specialised Scientific Disciplines Department, EMA

Head of Quality Office

peter.richardson@ema.europa.eu

Special Thanks to:

Camille Vleminckx, Scientific and Regulatory Management Department, EMA (secretary to BMWP)

Klara Tiitso, Specialised Scientific Disciplines Department, EMA (Quality Office)

Prof. Andrea Laslop, Austrian Agency for Health and Food Safety (AGES) (CHMP & SAWP member)

27