Klinikum rechts der Isar
Technische Universität München

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory perspective on comparison of quality attributes in drug development

Review of the past, current challenges and future expectations

2nd Annual Biosimilars Forum

Presented by Ina-Christine Rondak on 6 October 2017
Seconded National Expert from Klinikum rechts der Isar of TU München to European Medicines Agency

An agency of the European Union

Disclaimer

The views expressed in this presentation are the personal views of the speaker and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties nor the TU München.

Conflicts of interest: none

Review of the past and current challenges

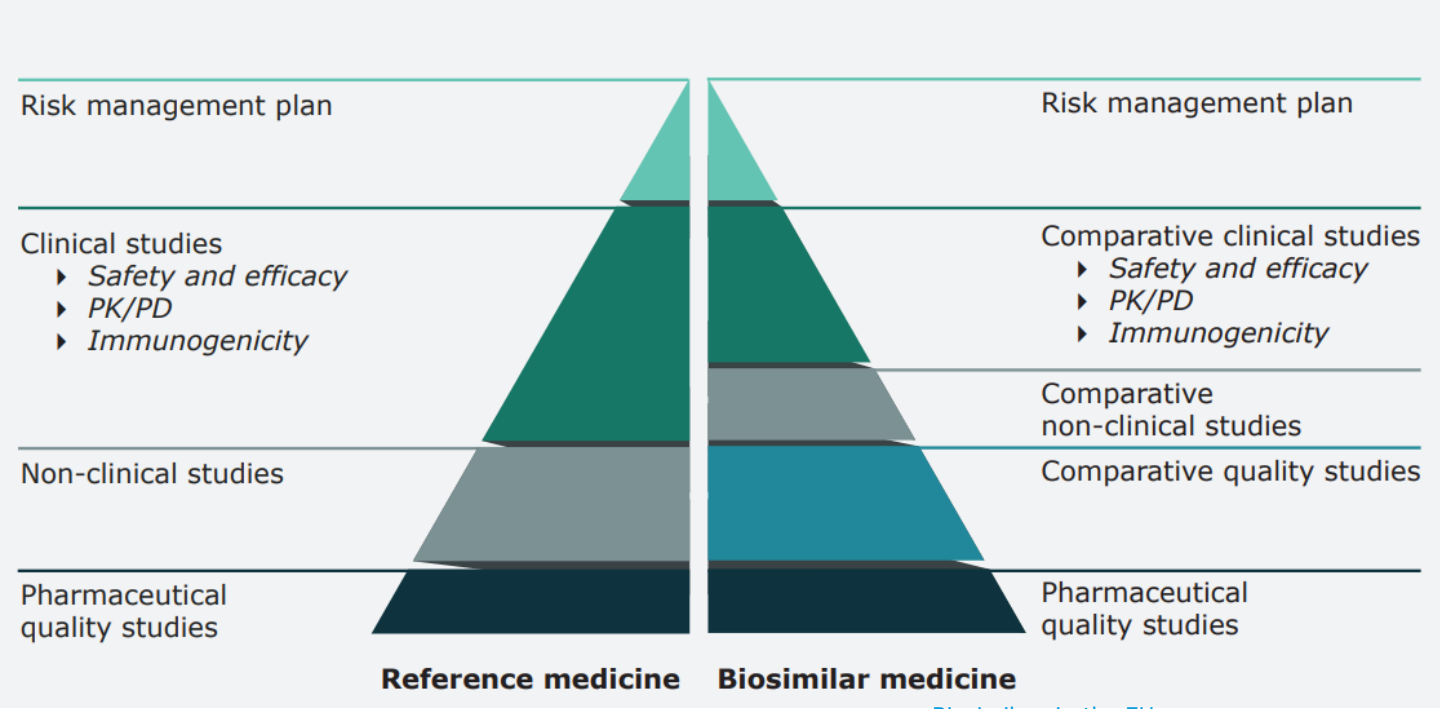
Data requirements for reference medicinal products and biosimilars

Comparison of quality attributes in SAs from 2012 - July 2017

Tailored Scientific Advice Pilot

Emerging questions and current challenges

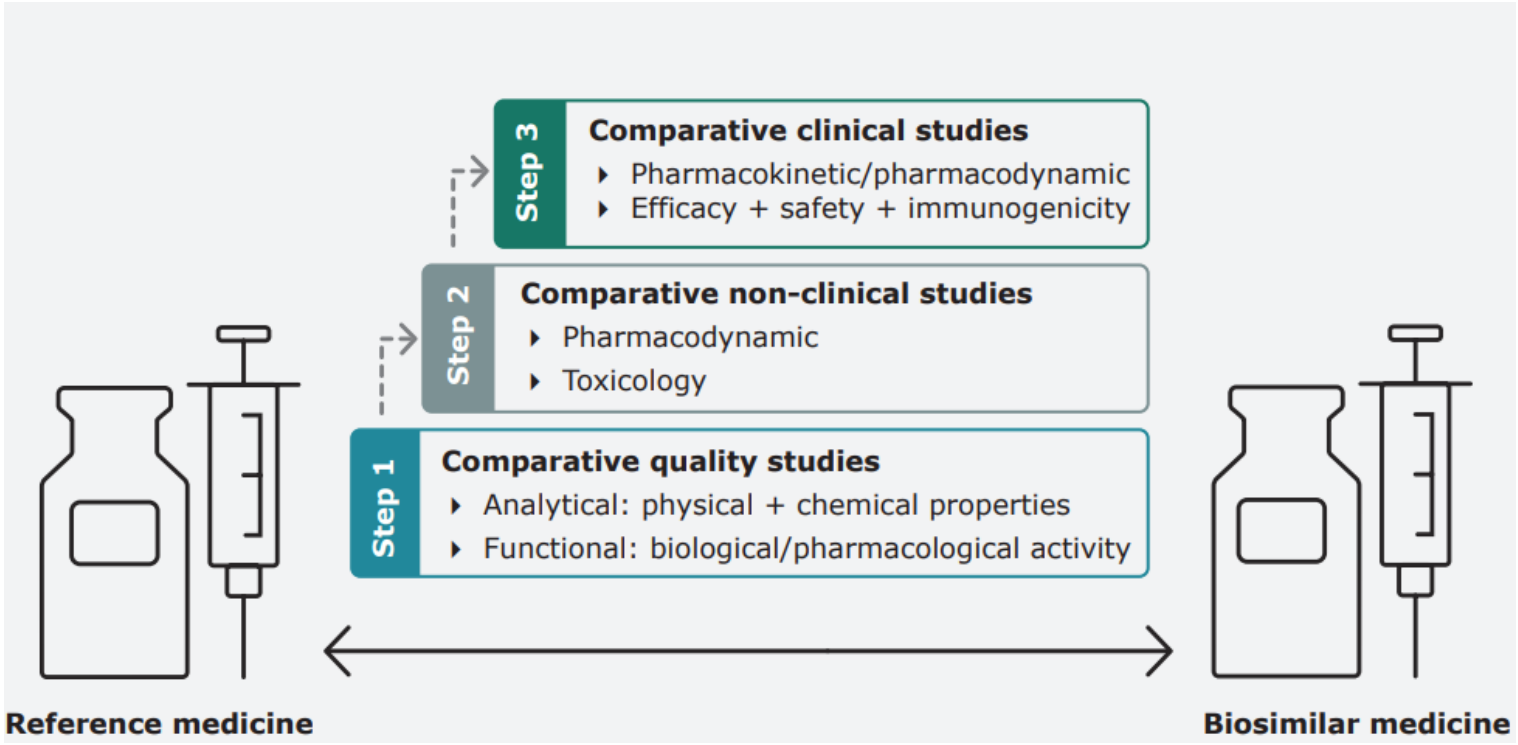
Comparison of data requirements for approval of a biosimilar versus the reference medicine



I. Rondak - Regulatory perspective on comparison of quality attributes in drug development

Biosimilars in the EU
Information guide for healthcare professionals

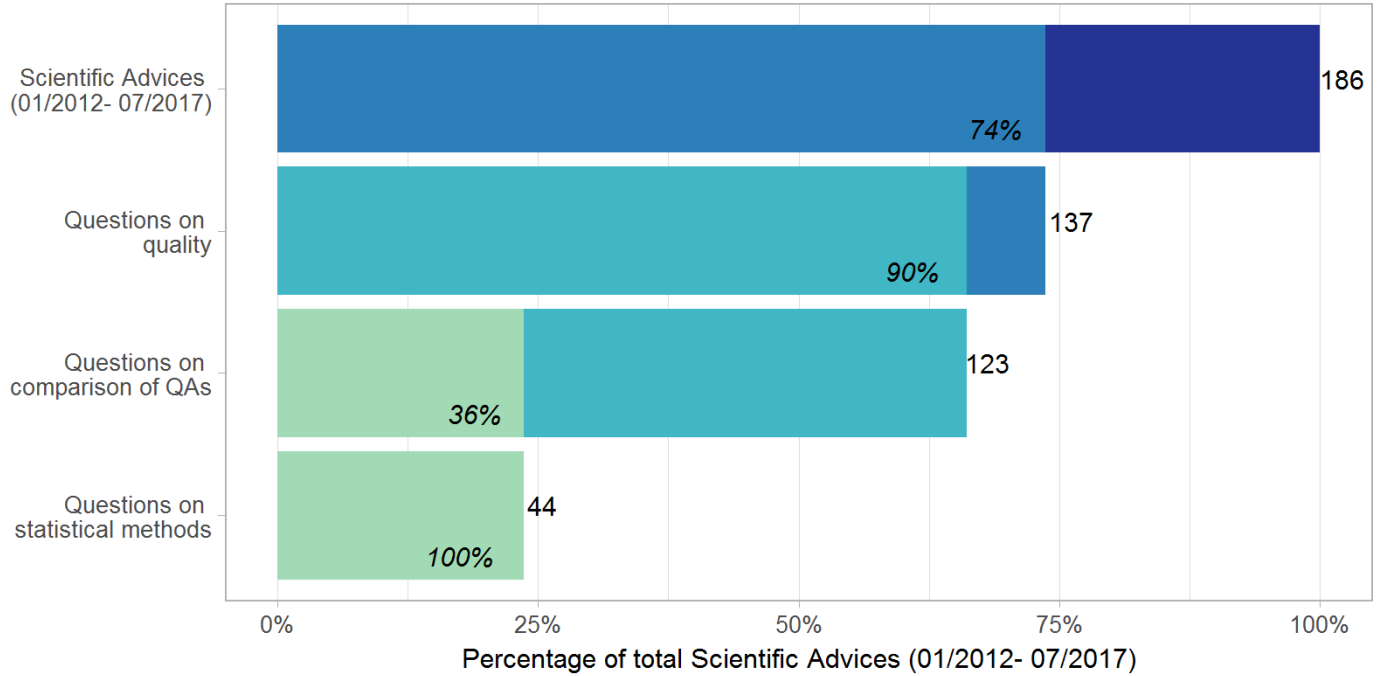
Biosimilar development: comparative and progressive



I. Rondak - Regulatory perspective on comparison of quality attributes in drug development

Biosimilars in the EU
Information guide for healthcare professionals

Comparison of quality attributes in Scientific Advices on biosimilars – an overview from January 2012 – July 2017



Tailored EMA scientific advice pilot project

- Pilot launched in February 2017 to support the development of **new biosimilars.**
- Advice to developers on the studies they should conduct, based on a **review of the quality, analytical and functional data** they already have available. Standard EMA scientific advice does not include the assessment of existing data.
- Open to **all types of biosimilars** and includes a pre-submission meeting to review the suitability of the data package. Additional month to review applications.
- Pilot shall run until **six scientific advice procedures** are completed, with maximum one scientific advice request accepted per month.
- Outcome will be analysed after completion of the pilot.
- For more information: Q&A document on EMA's biosimilar website.

Emerging question in relation to comparison of quality data

"Is it possible to license a biosimilar based on comparison of quality data only?"

Increased focus on comparison of quality data in biosimilar developments due to:

- Increasing knowledge & technologies to characterise biologicals
- High level of understanding of mode of action
- Sound reasoning to identify quality characteristics of importance
- Lack of sensitivity of clinical models
- Costs to run clinical trials

Comparison of quality attributes potentially (very) sensitive

Comparison of quality data - challenges

- (Statistical) methodology diverse and potentially not fit for purpose
- Clinical impact of differences hard to predict or quantify
  - Choice of critical attributes and criticality
  - Relevant differences
- Limited communication and understanding between different disciplines
  - What do we want to compare?
- Operating characteristics of methods
- What are consequences of wrong decisions

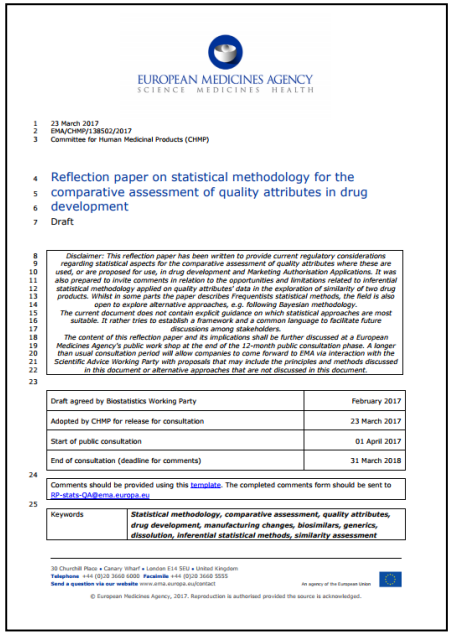
Attempts to overcome challenges

Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development (Draft)

What the future might bring

Discussion of methodological considerations

Reflection Paper on statistical methodology for the comparative assessment of quality attributes in drug development (Draft)



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2017
EMA/CHMP/138502/2017
Committee for Human Medicinal Products (CHMP)

Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development
Draft

Disclaimer: This reflection paper has been written to provide current regulatory considerations regarding statistical aspects for the comparative assessment of quality attributes where these are used, or are proposed for use, in drug development and Marketing Authorisation Applications. It was also prepared to invite comments in relation to the opportunities and limitations related to inferential statistical methodology applied on quality attributes' data in the exploration of similarity of two drug products. Whilst in some parts the paper describes Frequentists statistical methods, the field is also open to explore alternative approaches, e.g. following Bayesian methodology.
The current document does not contain explicit guidance on which statistical approaches are most suitable. It rather tries to establish a framework and a common language to facilitate future discussions among stakeholders.
The content of this reflection paper and its implications shall be further discussed at a European Medicines Agency's public work shop at the end of the 12-month public consultation phase. A longer than usual consultation period will allow companies to come forward to EMA via interaction with the Scientific Advice Working Party with proposals that may include the principles and methods discussed in this document or alternative approaches that are not discussed in this document.

Draft agreed by Biostatistics Working Party	February 2017
Adopted by CHMP for release for consultation	23 March 2017
Start of public consultation	01 April 2017
End of consultation (deadline for comments)	31 March 2018

Comments should be provided using this template. The completed comments form should be sent to RP-stats-QA@ema.europa.eu

Keywords	***Statistical methodology, comparative assessment, quality attributes, drug development, manufacturing changes, biosimilars, generics, dissolution, inferential statistical methods, similarity assessment***

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 Facsimile +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact
An agency of the European Union
© European Medicines Agency, 2017. Reproduction is authorised provided the source is acknowledged.

EMA/CHMP/138502/2017

Interdisciplinary effort (BSWP, BWP, BMWP, QWP, PKWP)

Published for 1-year public consultation on 1 April 2017

Deadline for comments: **31 March 2018**

Workshop to be held on **3-4 May 2018**

Comments and expression of interest to participate in workshop to be send to RP-stats-QA@ema.europa.eu

Reflection paper - Objectives

Areas of interest

- Pre- and post-manufacturing change
- Biosimilar development
- Generic development

Scope

- Focus on methodological aspects
- Raise open issues from statistical perspective
- Address questions related to:
  - Objectives of comparisons
  - Sampling strategies
  - Sources of variability
  - Options for statistical inference and acceptance ranges

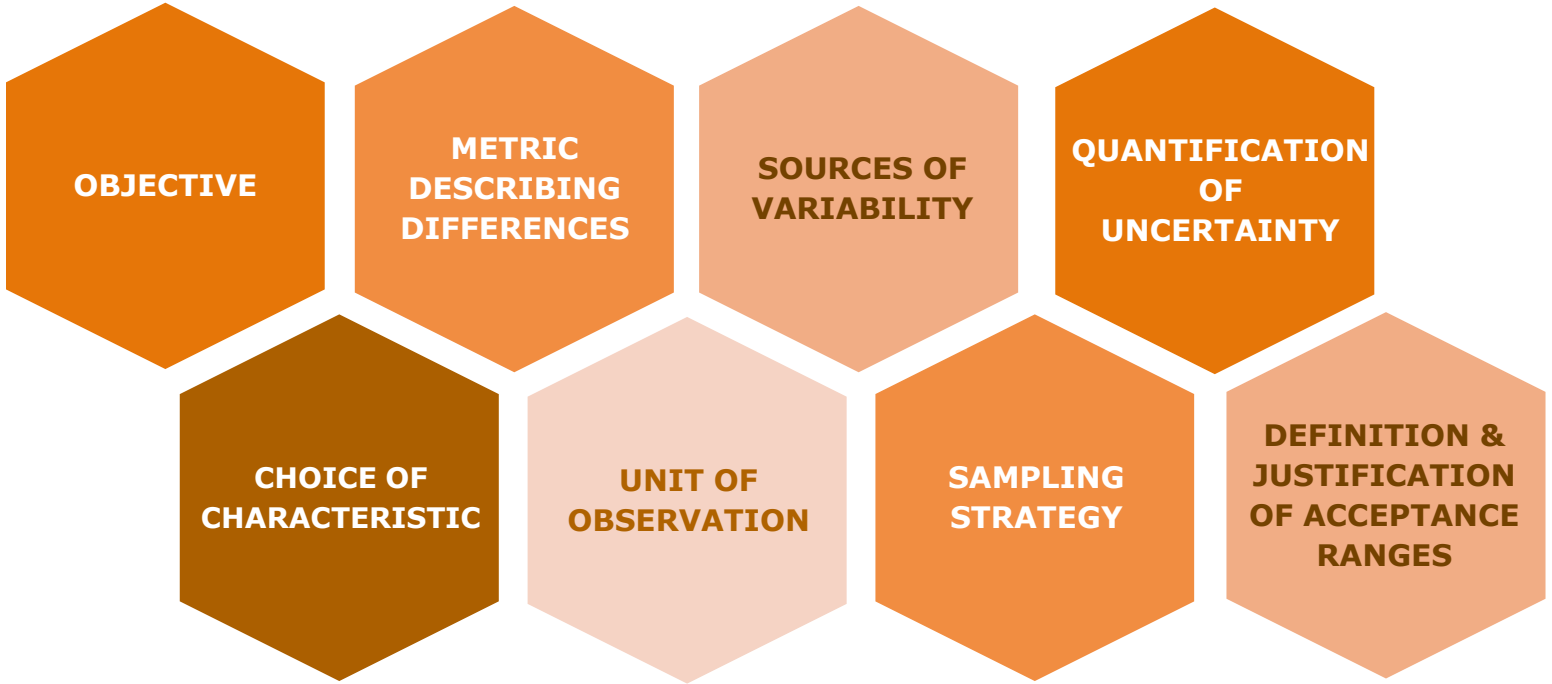
Aim

- Establish a common language
- Improve understanding among experts from various disciplines
- **Trigger discussion** vs. impose rules
- Discuss likely limitations hampering statistical inference
- Point out meaningful ways forward

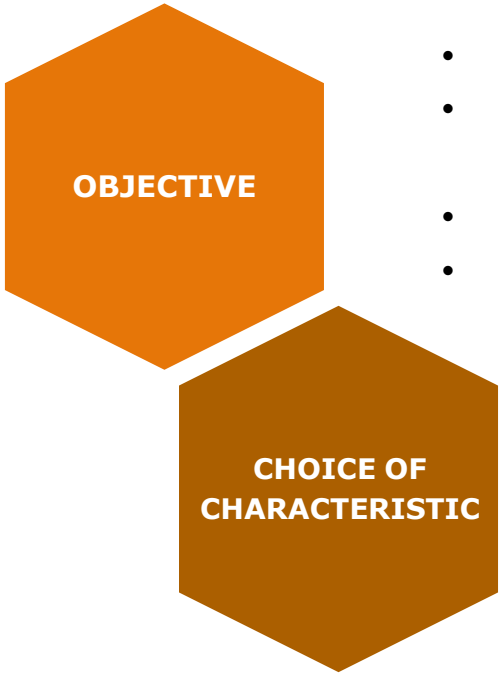
What the future might bring

- Challenges remain and will not be solved easily
  - New challenges in relation to RP such as which CQAs (relation to clinical effect) and ‘how similar’ to be discussed
- Further communication between different disciplines paramount
- Input from industry needed -> new proposals and further discussions
- Prospective planning of data analysis at quality level
  - e.g. by providing discussion on different methodological aspects

Discussion of methodological considerations



Objective and choice of characteristic



- **Within-specification**, **non-inferiority** or **equivalence** claim
- Differentiation between **inferential statistical testing** and purely **descriptive data comparison**
- Discussion of underlying **assumptions**
- **What is the contribution to "totality of evidence"?**

- Observed data to be understood as actual **realizations** of **underlying (unknown) data distributions**?
- Dedicated consideration on **choice of the distribution characteristic** to be used for comparison
- **Separate consideration** for each QA

Metric describing differences and unit of observation

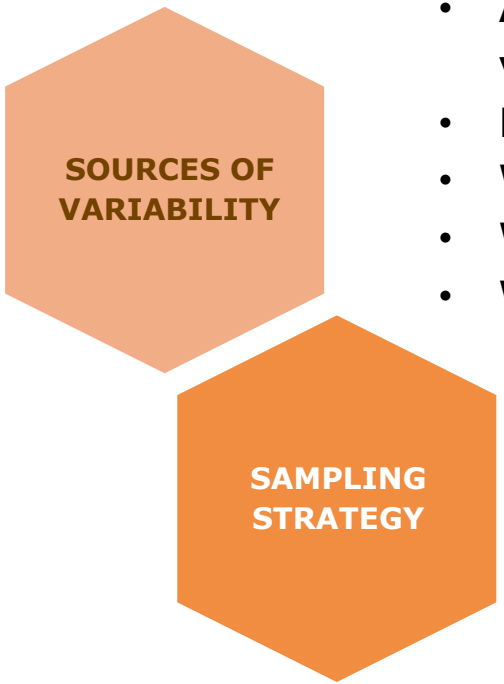
METRIC DESCRIBING DIFFERENCES

- **Discussion of choice of metric** to describe distance/difference between two unknown underlying distributions
- Fulfilment of **underlying assumptions**

UNIT OF OBSERVATION

- Not always straight forward
- Important for **sampling considerations**
- Lack of **description of data collection** might hamper **identification of potential sources of variability** and **choice of inferential statistical approach**

Sources of variability and sampling strategy



- **Anticipating/identifying (un)important sources of variability**
- **Between batch** (e.g. site, scale, age, starting material)
- **Within batch** (e.g. circadian effects, duration)
- **Within sample** (e.g. assay, preparation, storage)
- **Within assay** (e.g. measurement error, accuracy)

- **Description** of **prospective considerations** for the sampling of units (random sampling and deliberate selection approaches)
- **Judgment** concerning (expected) **representativeness**
- **Justification** of **'non-selected' units**

Quantification of uncertainty and definition of acceptance ranges

- **Computation of statistical intervals allows** for **quantification of uncertainty** in drawing conclusion from samples to entirety of material produced
- **Advantage** of inferential statistical methods over simple descriptive data analysis

- Should be **defined a priori** and independent of sample data
- Conceptually **different to statistical intervals** derived from actual sample data

Remaining challenges to be tackled

Major hurdles

- **How to measure the distance?**
  - Agreement on problem statement (distribution, parameters)
- **Definition of relevant differences**
  - Acceptance range/margin
- **Disentangling quantification of uncertainty from acceptance rages**
- **Definition of "similarity criterion"**
  - Conventional statistical (equivalence) test?
  - Other "test-like" criterion, i.e. interval "ranging approaches"?
  - Exploration of operation characteristics
- **Control of probability of false positive conclusion for equivalence**

Acknowledgments:

Thomas Lang

Andreas Brandt

Stephan Lehr

Biostatistics Working Party

EMA colleagues

Thank you for your attention

Further information

Ina-Christine.Rondak@ema.europa.eu

European Medicines Agency
30 Churchill Place • Canary Wharf • London E14 5EU • United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Follow us on **@EMA_News**

Back up slides

Biosimilar Product Review (September 2017)*

66 MAAs submitted

55 MAAs post-review

11 MAAs under review

2 Negative

Interferon alfa
Insulin

12 Withdrawn (pre-approval)

Insulin (6)
Epoetin (1)
Pegfilgrastim (4)
Trastuzumab (1)

3 Withdrawn (post-approval)

Filgrastim (2)
Somatropin (1)

41 Positive opinions

36 Valid MAs

Somatropin (1)
Epoetin (5)
Filgrastim (7)
Infliximab (3)
Follitropin alfa (2)
Etanercept (2)

Insulin glargine (2)
Enoxaparin (2)
Teriparatide (2)
Rituximab (6)
Adalimumab (3)
Insulin lispro (1)

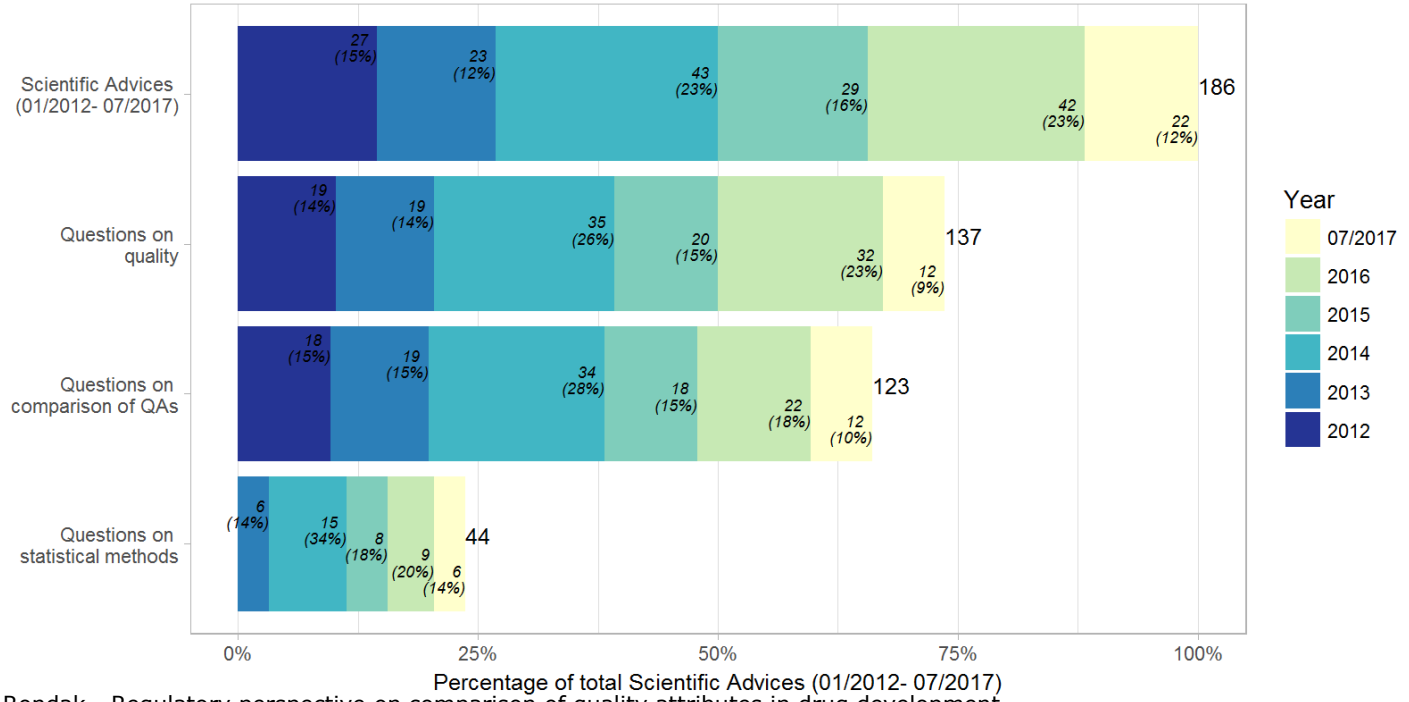
Adalimumab (2)
Bevacizumab (2)
Infliximab (1)
Insulin glargine (1)
Pegfilgrastim (2)
Trastuzumab (3)

2 Awaiting EC decision

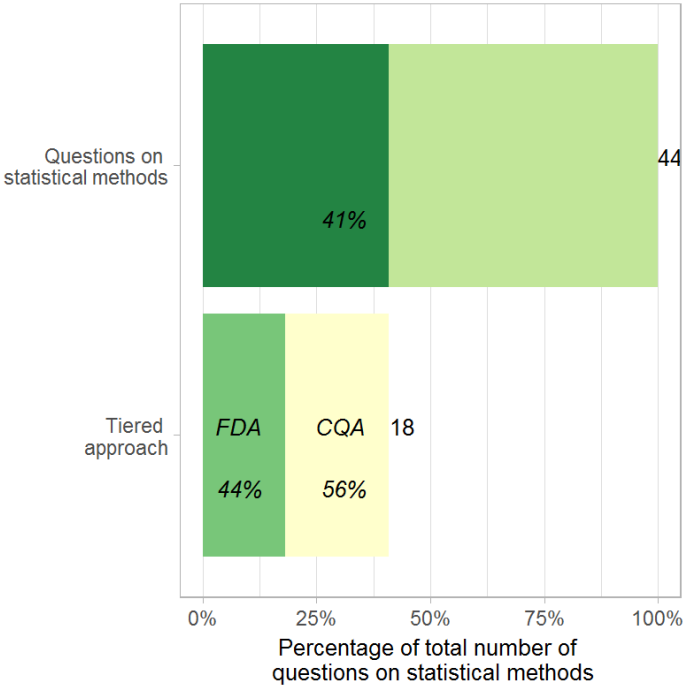
Adalimumab (1)
Trastuzumab (1)

* Information on EMA website

Comparison of quality attributes in Scientific Advices on biosimilars – per year



Tiered approaches used for comparison of quality attributes in Scientific Advices on biosimilars



- Of the 44 SA which posed questions on statistical/methodological aspects:
- **18/44 (41%)** discussed a tiered approach while
- **8/44 (18%)** mentioned the FDA tiered approach and
- **10/44 (22%)** mentioned CQAs with different rigour.