Biosimilars

Where are we in 2017?

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Disclaimer

affiliations:

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- *The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the CHMP or reflecting the position of the CHMP or the Austrian Medicines Agency*

- *Tribute to A. Laslop and T. Lang, colleagues from AGES, who contributed & provided some slides*

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Overview of the presentation

- Introduction, definition
- EMA guidance, BSM approvals, etc.
- Where are we in the comparative assessment of:
  - Quality (EMA reflection paper)
  - Non-clinical data
  - Clinical data
  - Extrapolation of indications
  - Immunogenicity, safety
- Future challenges

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Definition

- A biosimilar is a biological medicine highly similar to another biological medicine already approved in the European Union (EU)

- The European Medicines Agency (EMA) is responsible for evaluating all applications to market biological medicines produced using biotechnology, including biosimilar medicines

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Development

- developers of biosimilars are required to demonstrate through comprehensive comparability studies that:
  - their biosimilar is highly similar to the reference medicine notwithstanding natural variability inherent to all biological medicines
  - there are no clinically meaningful differences between the biosimilar and the reference product in terms of quality, efficacy and safety
- by demonstrating biosimilarity, a biosimilar can rely on the safety and efficacy experience gained with the reference medicine → extrapolation

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Extrapolation, BSM guidelines

- BSM development/data requirements outlined a number of biosimilar guidelines:
  - Overarching GL,
  - general GLs,
  - GL on biosimilar monoclonal antibodies,
  - product specific GLs

Multidisciplinary: biosimilar

The European Medicines Agency's scientific guidelines on biosimilar medicinal products help medicine developers prepare marketing authorisation applications for human medicines.

If you have comments on a document which is open for consultation, use the form for submission of comments on scientific guidelines.

For a complete list of scientific guidelines currently open for consultation, see Public consultations.

- Overarching biosimilar guidelines
- Product-specific biosimilar guidelines
- Other guidelines relevant for biosimilars

Related content

- Scientific guidelines on biologicals
- Scientific guidelines

Overarching biosimilar guidelines

Guidelines

- Similar biological medicinal products
- Similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues
- Similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues

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EU approval of BSM

- so far, EMA approved 40 biosimilar products
- …and several others are currently under evaluation, applications for MA are increasing over the last few years
- we are moving from simpler molecules (filgrastim, insulin, epoetin) to increasingly more complex ones (monoclonal antibodies such as infliximab, adalimumab, rituximab)
- increasing complexity confers increasing challenges

Human medicines
- European public assessment reports
- Patient safety
- Pending EC decisions
- Withdrawn applications
- Paediatrics
- Rare disease designations
- Medicines under evaluation
- Medicines for use outside the EU
- Referrals
- Periodic safety update report single assessments
- Post-authorisation safety studies
- Shortages catalogue
- Recommendations on medication errors

Veterinary medicines

Herbal medicines for human use

Home ▸ Find medicine ▸ Human medicines

European public assessment reports

This page allows you to find the European public assessment reports (EPAR) for human medicines published by the European Medicines Agency (EMA).

The EMA publishes an EPAR for every medicine granted a central marketing authorisation by the European Commission following an assessment by the EMA's Committee for Medicinal Products for Human Use (CHMP). EPARs are full scientific assessment reports of medicines authorised at a European Union level.

Use this search to find information including a public-friendly summary in question-and-answer format and the package leaflet. You can also find information on medicines that have been refused a marketing authorisation or that have been suspended or withdrawn after being approved.

As of October 2016, EMA publishes the clinical data submitted by pharmaceutical companies to support their marketing applications for human medicines under the centralised procedure, allowing the public to better understand the Agency's decision-making. For more information see clinical data publication.

The Agency does not evaluate all medicines currently in use in Europe. If you cannot find the medicine you need through this search, please visit the website of your national health authority.

More information is available on the Central authorisation procedure and in EPARs: background and context.

Browse A-Z | Keyword search | Browse by therapeutic area | **Browse by type**

Browse by type:

- ○ Additional monitoring
- ○ Generics
- ◉ Biosimilars
- ○ Conditional approval
- ○ Exceptional circumstances
- ○ Orphan medicines

SUBMIT ▸

Include:

- ☑ Authorised medicine
- ☑ Withdrawn post-approval
- ☑ Suspended
- ☑ Refused

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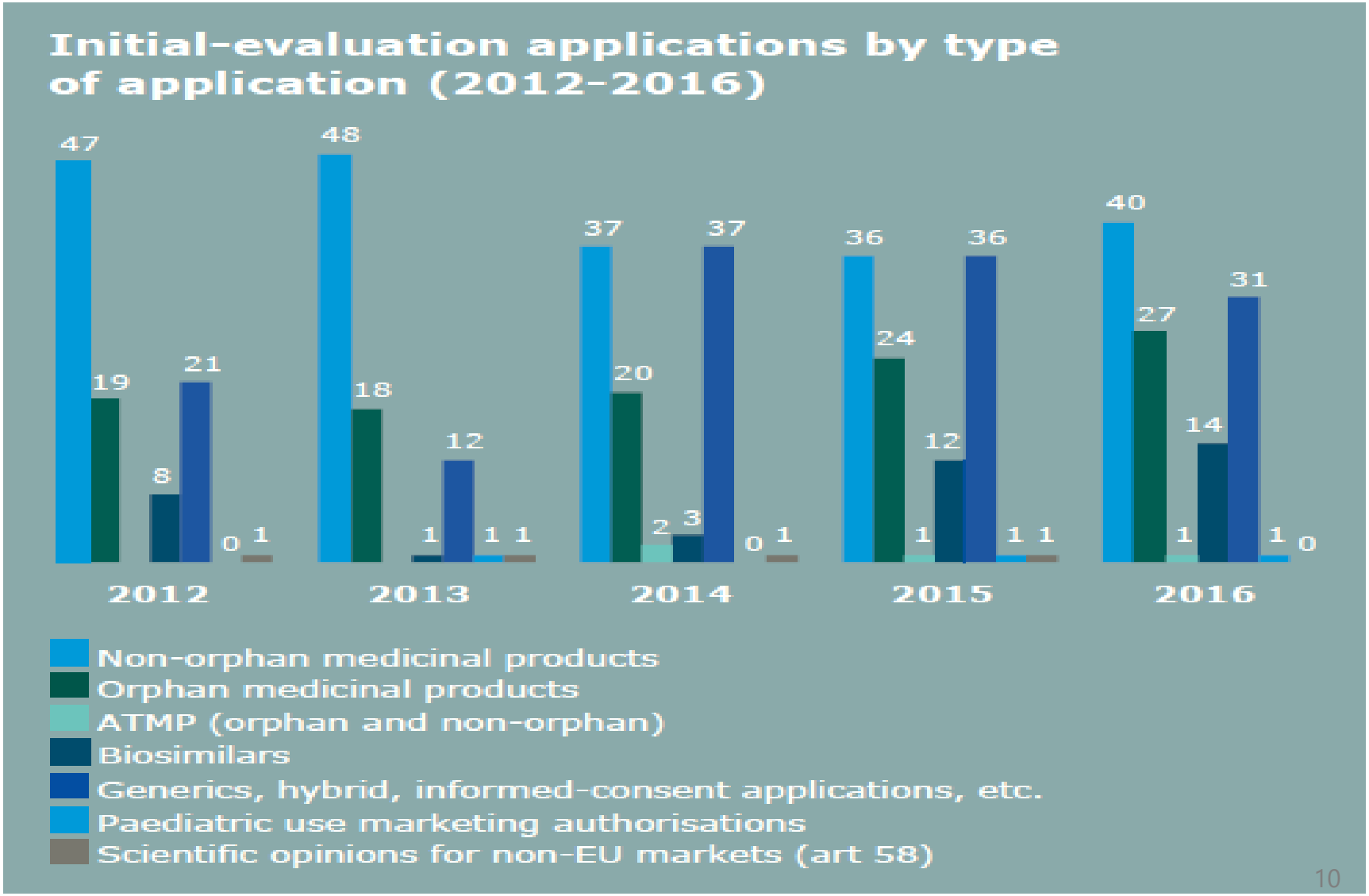
EMA statistics (annual report 2016)



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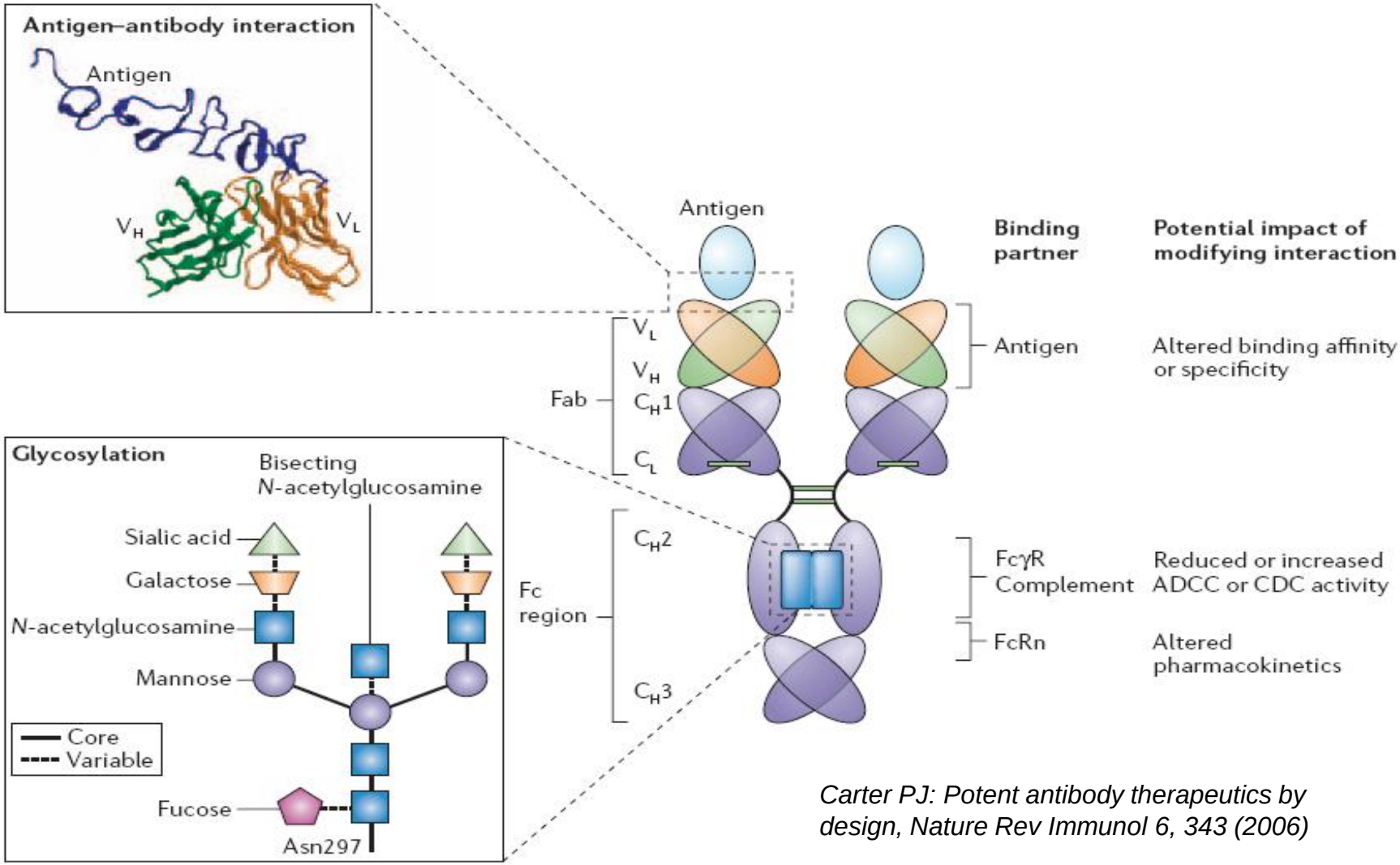
Biosimilarity for mABs



Carter PJ: Potent antibody therapeutics by design, Nature Rev Immunol 6, 343 (2006)

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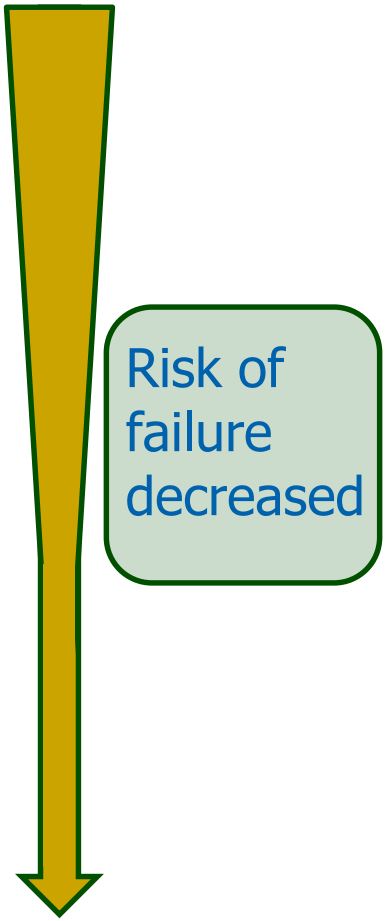
Step-wise development

1) Comparability at the quality level is key
   - Comprehensive characterisation and comparison of physicochemical and biological properties

2) Comparability at the non-clinical = functional level gives reassurance on similar effects
   - Functional *in vitro* assays to define and compare the mode(s) of action

3) Comparability at the clinical level
   - homogeneous/sensitive population, sensitive dose
   - appropriate model and statistical approach



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Comparability at the quality level

- first important milestone in stepwise development approach
- the most sensitive part of the whole comparison exercise for detecting differences
- impact of differences at quality level on clinical outcomes (efficacy/safety/immunogenicity) often hard to predict or quantify
- degree of similarity demonstrated on the quality level might determine the amount of additional evidence to be generated at later stages of development

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Quality - comparative assessment

different scenarios:

- extensive (side-by-side) comparability exercise to demonstrate "high similarity" in the quality profile between reference product and biosimilar

- due to global development: "bridging" between EU- RMP and non-EU sourced reference product

- bridging in case of changes to the manufacturing process of biosimilar candidate (might occur repeatedly during development)

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Comparative assessment of quality

- this should allow *"… firm conclusions on the physicochemical and biological similarity between the reference medicinal product (RMP) and the biosimilar …"*

  - **How sure are we about the conclusions?**

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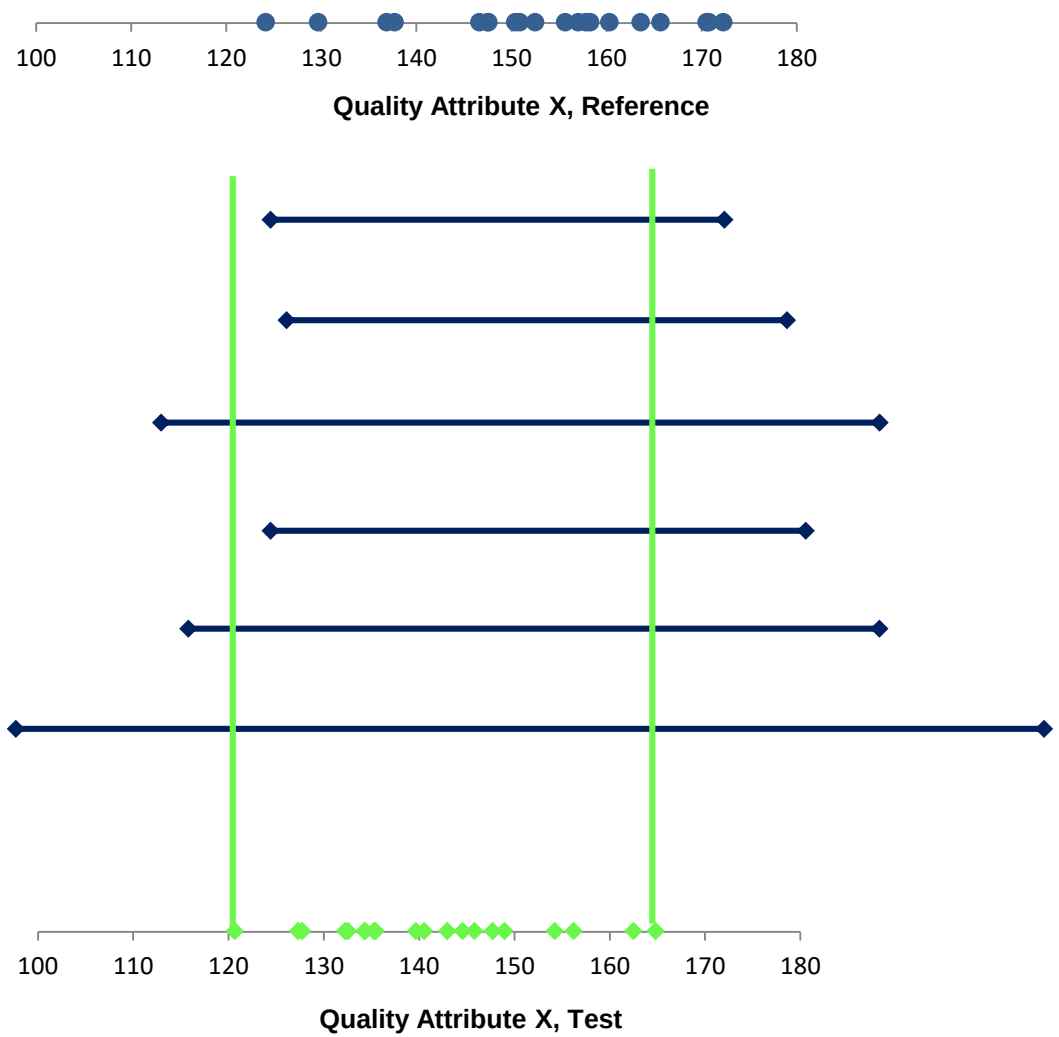
Quality assessment - Status quo

- a "similarity criterion" is defined, e.g.: *"If all test product batches fall into the min-max-range observed from the reference product batches, we conclude that 'test' is similar to 'reference'."*

- huge diversity of comparison approaches applied, using e.g.:
  - min-max range
  - 4 sigma / 6 sigma interval
  - tolerance interval
  - …
- chosen approaches often not well justified, descriptive comparisons, without robust statistical planning & testing

Status quo: possible approaches



Interval / Similarity criterion

Min-Max	x
4 sigma	x
6 sigma	✓
90/90 tolerance interval	x
95/95 tolerance interval	✓
99/99 tolerance interval	✓

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Comparative assessment of quality

- Reflection Paper on statistical methodology for the comparative assessment of quality attributes in drug development (draft) EMA/CHMP/138502/2017

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

- Reflection paper addresses:
  - Biosimilar development
  - Pre/post-manufacturing changes
  - Certain aspects of abridged MAAs for chemicals

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Reflection paper - general directions (1)

biosimilar developers should:

- plan prospectively as much as possible → protection against criticism of data-driven planning and biased post-hoc decisions
- state the objectives of comparisons and describe potential consequences of false positive conclusions on similarity
- decide upfront on (critical) QAs to be compared
- try to understand potential sources of variability as good as possible, use knowledge on variability to set up a structured sampling approach

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General direction (2)

- If pivotal evidence for similarity is expected to come from data comparisons on the quality level

→ adequate control of the risk for a false positive conclusion on (bio)similarity is of utmost importance

- limitations: sources of variability from RMP data often remain obscure; if fraction of unexplained variability is large → precision of statistical intervals low
- critical issue: shifts in important QAs of the RMP over time

  (e.g.: MABS2017, VOL. 9, NO. 4, 704–714: Drifts in ADCC-related QA of Herceptin)

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Biosimilar GL: non-clinical development

step-wise and risk-based approach

- step 1 – *in vitro* studies
  always necessary, most informative, should cover most functional aspects

- step 2 – determine level of concern
  depending on qualitative/quantitative differences in critical quality attributes

- step 3 – *in vivo* studies (PK/PD and/or safety)
  may become necessary, e.g. new expression system

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Non-clinical development

- known active substance, focus on comparative assessment (sometimes new excipients require additional data)

- usually, the non-clinical package contains both, *in vitro* and *in vivo* (animal) data

- **Do we still need animal studies?**

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Comparative in vitro data

- measure biological activity of the product, in general, comparative studies of *in vitro* function, e.g.:
  - binding of ligand/receptor
  - enzymatic or cell-based assays
  - binding to target antigen(s) of mAbs
  - binding to Fc receptors and complement
  - Fab-associated functions (neutralization, receptor activation or receptor blockade)
  - Fc-associated functions (ADCC and CDC, complement activation)

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In vitro vs in vivo data

- **in EU: focus on *in vitro* studies, in most cases sufficient:**
  - much more sensitive to detect small differences
  - highly important for both, biosimilarity and extrapolation
  - using a variety of test systems to confirm results from several aspects (orthogonal methods, PD fingerprinting approach)
  - various cell types and assays (caveat: consider high sensitivity, but also physiological conditions)
- due to global development usually *in vivo* toxicity studies have been conducted/submitted

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Clinical development

- no need to establish efficacy and safety of the molecule/active substance as such, because this has been shown for the reference product (and can be extrapolated)

- comparative assessment of PK and PD, confirmatory efficacy & safety study

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PK comparability studies

usually:

- a dedicated single-dose PK/(PD) study in healthy volunteers

  study population of HV:

  - facilitates choice of a sensitive dose
  - decreases variability in exposure (e.g. via target-mediated clearance)

- limited PK/PD sampling in patient population (of efficacy trial) is expected to „qualitatively“ confirm results from HVs
  - investigation of clinical impact of variable PK and possible changes in PK over time (after repeat administration)
  - impact of ADAs

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PK comparability studies: BSM vs generics

- **for generics** we generally accept a 90% CI from 80-125%
  - within these limits we accept bioequivalence because we assume the same behaviour of the drug in the body once absorbed

- **for biosimilars** we may require a different CI for showing similarity in exposure, this should be discussed and justified
  - What if the CIs of the GMRs do not include unity? ⇨ BSM GL: may indicate an extent of dissimilarity in exposure that requires explanation and justification

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PK comparability studies: BSM vs generics

- for generics we are mainly interested in comparing the <u>absorption</u> of the test and reference products
  - usual measures AUC_{0-t} and C_{max}

- **for biosimilars** we are interested in detecting a potential difference in both, <u>absorption and elimination phase</u>
  - SC administration: both absorption and elimination are relevant

    focus on $AUC_{0-inf/0-t}$ and C_{max}, C_{min}/C_{trough}: second. parameter
  - IV administration: focus of assessment is on AUC_{0-inf}, C_{max} less important

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Clinical efficacy & safety studies

"… least sensitive part of the comparability exercise to detect differences…"

⇨ increase sensitivity:

- select population with low variability (e.g. rheumatological vs. oncological disease), homogeneous severity of disease, limited co-medication, etc.
- dose in sensitive range of the exposure/response curve, ideally steep part of dose/response (not always possible)
- appropriate endpoint, assessed at the most sensitive time
- accurate definition of equivalence margin (based on both, statistical and clinical grounds)

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Comparability at the clinical level

- Do we still need clinical efficacy & safety trials?

- the purpose of the E/S study is to rule out differences that are clinically significant
- in some cases PD data can establish comparable efficacy, but this is not yet the standard approach in many instances
- can only be considered if a validated PD surrogate endpoint exists, this is not yet the case for complex molecules with several modes of action like biosimilar monoclonal antibodies

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Comparative PD data

- examples where comparative PD data may be sufficient for showing similarity in efficacy
  - biosimilar insulin (euglycaemic clamp test)
  - low molecular-weight heparins (anti-FXa, anti-FIIa)
  - G-CSF/filgrastim (absolute neutrophil count)
  - interferons- α and -β (HCV viral load/ MRI of brain)
  - teriparatide (PK data only)

- for a primary PD endpoint
  - PD endpoint co-primary with PK endpoint(s) in PK/PD study
  - study to be powered accordingly ⇨ PD equivalence margin

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Extrapolation of indications

- once biosimilarity is established (on Q + NC + C level) can we extrapolate to all indications of the reference product?
- appropriate scientific evidence and justification needed
- important considerations:
  - are the involved receptor(s) and/or clinically relevant MoA the same in the different indications? if not or if possibly unknown, a strong scientific rationale necessary, might need additional data
  - sensitivity of the studied indication and its relevance to the other indications

→ **case to case decision** for each BSM for each indication

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Extrapolation of indications

additional data (e.g. functional assays, PD parameters and/or clinical E/S data) may be required:

- if active substance acts on several receptors, with potentially different impact in the tested/untested therapeutic indications
- if active substance itself has more than one active site, and sites may have a different impact in different indications
- if the studied therapeutic indication is not relevant for the others in terms of efficacy or safety, i.e. is not sensitive to detect the impact of potential differences in relevant aspects of efficacy and safety

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Immunogenicity

- immunogenicity differs across molecules/classes of products, prior knowledge from reference product
- immunogenic potential of small changes/differences in a QA might not be predictable or easily understood
- has potential impact on efficacy (decrease/loss of efficacy) and/or safety (hypersensitivity reactions)

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Immunogenicity conclusion

- How important are immunogenicity results?

- if a molecule is known to be highly immunogenic ⇨ very important concern

- it would be very difficult to accept higher immunogenicity, while a less immunogenic product could appear favourable

- because antibody development takes time and needs to be followed up: 12-months safety data usually required pre-authorisation (for monoclonal Abs)

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Immunogenicity testing

- methods of ADA determination increasingly sensitive, results may differ substantially from the ones obtained in the historical studies with the originator many years ago

→ How to display immunogenicity results in SmPC?

should be useful for clinicians and not misleading

→ avoid use of numbers/percentages, e.g.:

"Antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have generally been non-neutralising and transient. There appears to be no correlation between antibody development and clinical response or adverse events"

(example from SmPC of an etanercept biosimilar)

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Comparative clinical safety

- overall the biosimilar should have the same safety profile as the innovator product
  - improved safety (e.g. lower immunogenicity) may be acceptable

  → concerns of higher efficacy of the biosimilar?
    - efficacy could appear artificially increased due to lower levels of (neutralising) antibodies (ADAs)
    - might entail higher rates of other adverse events
  - comparison of efficacy profile of biosimilar and reference in patients with / without ADAs

  → acceptable if patients without ADAs show comparable efficacy

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Post-marketing - safety database for BSM

- accurate tracing of administered products is crucial, especially for further collection of immunogenicity data
  - in EU reporting according to brand name (not INN) and batch number, allows product/batch specific signal detection
  - WHO Biological Qualifyer (BQ)
    - proposal for globally recognised unique identification code, random 4 letter code complementing INN (for all biologicals)
    - currently not accepted by all regulators (voluntary)
- no globally agreed naming system yet
- cooperation of clinicians most important

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The future of biosimilars

- importance in providing affordable biological medicines of high quality at a sustainable price recognised
- regulation in Europe successively advanced
- issues still to be progressed:
  - interpretation of differences in quality attributes
  - tailoring clinical evidence of biosimilarity
  - justification of extrapolation to other indications
  - collection of safety data, naming, switching between products
  - acceptance by the public and ample use in health care
  - efforts to globally converge regulatory requirements

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Thank you for your attention!