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EUROPEAN GENERIC MEDICINES ASSOCIATION

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EBG's Comments on the Draft Revised Guideline on Similar Biological Medicinal Products

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Overall comment

- The European Biosimilars Group very much appreciates this revised draft version of the guideline on biosimilar medicinal products.

  - The revision is in line with the current thinking of EU regulators as laid down in the updated "EMA's procedural advice for users of the centralised procedure for biosimilar medicinal products applications". « *March 2013 EMA / 940451/2011* »

  - The revision contains strong scientific principles to support the use of a representative reference product sourced from ICH regions outside EEA, provided that confirming information on the reference product as well as certain bridging data are submitted.

  - The revision is further extending and strengthening the pioneering role of the European regulatory and scientific framework for biosimilars.

Choice of reference product/ Scientific viewpoint

- Reference products from one original manufacturer and sourced from different jurisdictions are often not distinguishable, even though licensed under different jurisdictions.
  - Reference products authorised in different jurisdictions are often manufactured in the same facilities.
  - A reference product supplied in one jurisdiction is often manufactured in different facilities, usually no non-clinical or clinical bridging studies were required.

- Important for efficacy and safety of a product is not the legal basis of its marketing authorisation, but its quality.

- Comparability / similarity of the reference products of one original manufacturer sourced from different jurisdictions can clearly be established by stringent analytical and biological assays.

Choice of reference product/ Scientific viewpoint

- Head-to-head clinical studies comparing different biological products containing different drug substances with the same mechanism of action frequently demonstrate similar efficacy of the products.

- If clinical studies are not even able to differentiate with regards to efficacy between biological products containing different drug substances with the same mechanism of action, how should clinical studies differentiate between the “same” reference products if sourced from various jurisdictions?

- Non-clinical and clinical studies are not suitable to establish differences between the “same” reference products of one original manufacturer sourced from different jurisdictions, if any. Analytical and biological assays are much more sensitive and are, thus much more suitable.

Choice of reference product/ Legal viewpoint

- The European legal services have confirmed that the proposed revision regarding the choice of the reference product is possible on the basis of the existing legislation.

- EMA has announced this new interpretation in the updated "EMA's procedural advice for users on the centralised procedure for similar biological medicinal products applications."
  « *EMA / 940451/2011, March 2013* »

Choice of reference product/ Patient access

- The development costs are estimated to range from M€ 100 to M€ 250, depending on the product. The requirement to repeat studies by just change the jurisdiction from which the reference product is sourced would increase the development cost by M€ 100 to M€ 150, with a large share of these costs being spent for purchasing the reference product.

- The request for two or even more parallel developments of one biosimilar to achieve marketing authorisations / biological licenses in different regions is cost prohibitive, thus
  - potentially discouraging biosimilar development at all,
  - leaving the biopharmaceutical market free from price competition,
  - rendering the significant benefits of improved patient access to essential biopharmaceuticals unachievable in the EU.

Three-way pharmacokinetic study

- Scientific viewpoint

  - The factors determining pharmacokinetics of biological products are often well understood and depend, amongst others on:
  - the physicochemical properties of the active substance,
  - the formulation,
  - the receptor interactions and clearance mechanisms of the active substance.

    All relevant parameters are investigated during the comparability / similarity exercise on quality, in case of a global development, using reference products sourced from different jurisdictions.

  - If results of the comparability / similarity exercise using stringent analytical and biological assays or information available from documents demonstrate their comparability bridging pharmaco-kinetic studies of reference products sourced from different jurisdictions should not be mandatory.

Choice of reference product / Three-way pharmacokinetic study

- **Proposed change**

As a general principle a single reference product, defined on the basis of its marketing authorisation in the EEA, should be used as the comparator throughout the comparability programme for quality, ~~safety and efficacy~~ non-clinical and clinical studies during the development of a biosimilar in order to allow the generation of coherent data and conclusions on similar quality, safety and efficacy.

(…)

As a scientific matter, the type of bridging data needed will typically include data from analytical and in vitro non-clinical studies (e.g. structural and functional data) that compare all three products (the proposed biosimilar, the EEA-authorised reference product and the non EEA-authorised comparator), and, if further supportive data are needed, in certain cases, the bridging assessment may also include clinical PK and/or PD bridging studies data for all three products.

Definition of “biosimilar product”

- New definition

- The new wording of the definition of a biosimilar product “…contains a version of the active substance” is clear, concise and, from a scientific standpoint, well chosen.

- However, in the updated “EMA’s procedural advice for users of the centralised procedure for similar biological medicinal products applications” the following definition is given: “The active substance of a similar biological product is a known biological active substance and similar to the one of the reference medicinal product.” *« EMA / 940451/2011, March 2013 »*

- From a scientific viewpoint the term “version of a known biological active substance” is most suitable and justified because according to the EU requirements the critical quality attributes of a biosimilar have to be within the variability of the reference product.

The biosimilar approach

- **Proposed change**

"A biosimilar is a biological medicinal product that contains a version of a known biological active substance of an already authorised original biological medicinal product (reference medicinal product)."

Summary

- The European Biosimilars Group (EBG), Sector Group of the EGA, considers the revised draft version of the guideline on biosimilar medicinal products as an important step forward encouraging the development of biosimilars, thus enhancing patient access to effective modern biological therapeutic alternatives.
- Most important are the scientific principles to support the use of representative reference product material sourced from ICH regions outside EEA if stringent analytical and biological assays have demonstrated comparable quality of such reference product to its counterpart sourced from within the EEA.

- EBG appreciates very much the revised guideline on biosimilar medicinal products being adopted near-term considering the changes proposed by EBG to support continued development of biosimilar products at a global level.

Back up

Interchangeability

- **EU consensus definitions published by the European Commission in the** « ***Consensus Information Paper 2013 "What you need to know about Biosimilar Medicinal Products"*** »

- **Interchangeability: The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber.**

- **Substitution: Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.**

- **Switching: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.**

- **Please note: The US definitions are partially different.**

Interchangeability

- How to assess interchangeability
  - In the EU, the decision whether a biosimilar could be used interchangeably with its reference product is within the remit of the treating physician.
  - In the EU, a biosimilar will only be approved once it is proven that it is highly similar to the reference product in physicochemical and biological terms and that clinically meaningful differences between the biosimilar and the reference product can be ruled out.
  - The reasoning for the biosimilarity designation is based on the thorough and comprehensive assessment conducted by the agency and described in detail in the European Public Assessment Report.
  - To decide whether a biosimilar medicinal product can be used interchangeably with its reference product, the thorough assessment undertaken by the agency, which is published in the EPAR, should be consulted.

Interchangeability

- **Proposed change**

The EMA evaluates biosimilar medicines for authorisation purposes. ~~The Agency's evaluations do not include recommendations on whether a biosimilar should be used interchangeably with its reference medicine~~ The results of these thorough scientific evaluations as performed by the EMA are described in the EPAR which is published on the Agency's website upon approval. The publically accessible EPAR should be consulted in order to substantiate the decision whether to use a biosimilar instead of its reference medicine.

Identification

- Identifiers

  - The trade name of the specific medicinal product and the batch number are the most sensitive and most important information allowing the unambiguous identification of the finished medicinal product which is on the market in an EU member state.
  - A clear identification of the concerned product is requested to support pharmacovigilance monitoring and to ensure correct prescription and dispensing.
  - The trade name is the most suitable and an unambiguous identifier of a biological medicinal product for prescription and dispensing, as stipulated in the “COMMISSION IMPLEMENTING DIRECTIVE 2012/52/EU” laying down measures to facilitate the recognition of medical prescriptions issues in another member state.
  - Trade name and batch number are the essential identifiers to follow-up serious adverse events.

Identification

- Proposed change

- In line with the COMMISSION IMPLEMENTING DIRECTIVE 2012/52/EU of 20 December 2012 laying down measures to facilitate the recognition of medical prescriptions issues in another member state we suggest to add a final bullet point after line 120:

  In order to support clear identification of prescribed and dispensed biological medicinal products, brand names should be used for biological medicines in accordance with the Commission Implementing Directive 2012/50/EU laying down measures to facilitate the recognition of medical prescriptions issued in another member state.