EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Scientific advice on quality aspects
Highlights from recent Scientific advice and Protocol assistance on Quality issues

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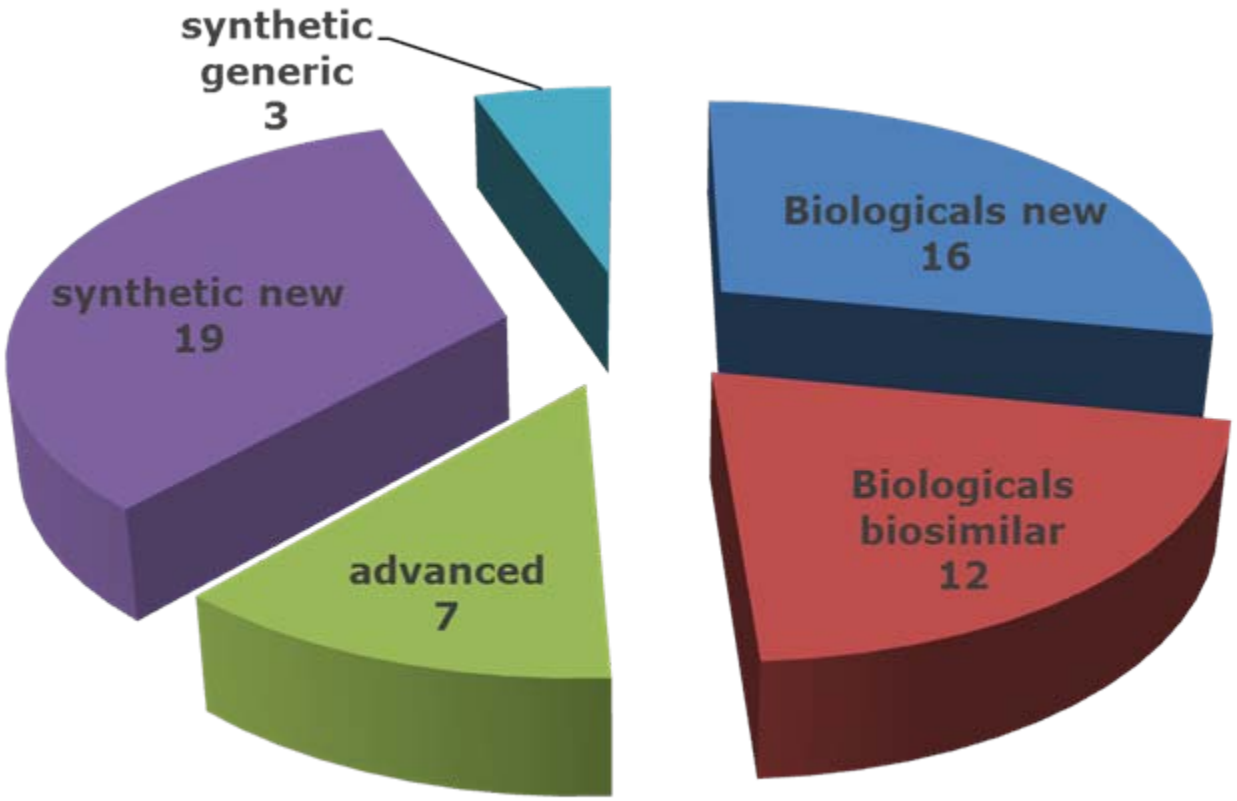
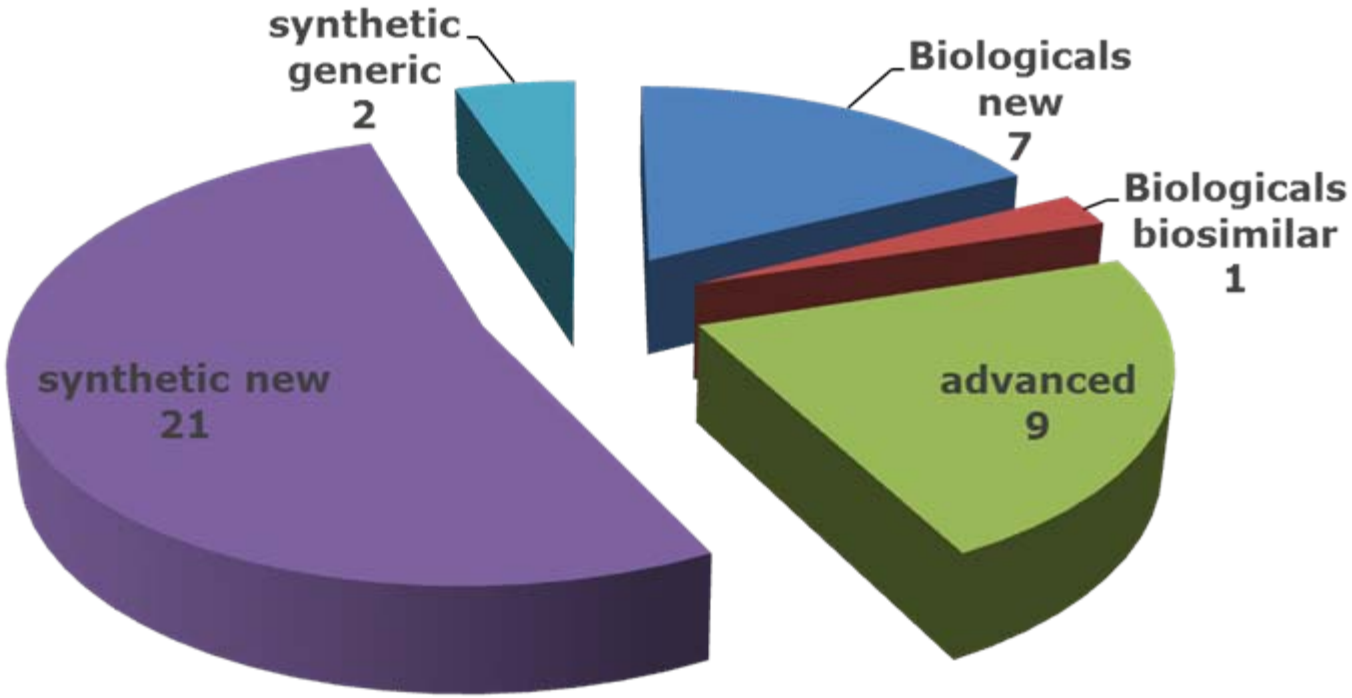
How does it work?

- 2 coordinators from Scientific Advice WP
  - Internal and external experts
- Involvement of:
  - Committee for Advanced Therapies
    - Gene Therapy WP
    - Cell based Products WP
  - Quality WP
  - Biologics WP
  - Vaccine WP
  - Biosimilar Medicinal products WP
  - Herbal Medicinal Products Committee
- Possibility for Discussion Meeting
- Discussion in SAWP and CHMP

Advice procedures with Q last 6 months



Advice procedures with Q last 18 months FROM SMEs



General Comments

- in depth assessment of data is outside the scope of a scientific advice procedure.
- Is Drug Substance (Product) specification acceptable for use in phase I (or subsequent):
  - has to be decided by the **NATIONAL competent authority** that assesses the Investigational Medicinal Product Dossier. EMA Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Product in Clinical Trials

Synthetic New Products

- 7 with Q on Starting Materials
  - *should be a significant **non-complex** structural fragment of the drug substance.*
  - *synthetic process should include **multiple steps** (covering steps in which the skeleton of the API is formed), especially steps regarding the formation and breaking of covalent bonds (stereochemical resolution if relevant)*
  - *description and control of **isolated intermediates** should be given for each step.*
  - *Control of **impurities** arising from the starting material and subsequent synthetic steps should be demonstrated.*

Synthetic New Products

- 7 with Q on Starting Materials
  - Examples:
    - as far as XXXX is concerned, this is **considered to be a complex** molecule that represents a significant component of the final active substance. In view of this, it is **not considered** to be acceptable as a starting material.
    - XXXX as API starting material is **not endorsed** even acknowledging the fact that it is well characterized. XXXX is a relatively **late stage intermediate, comprising already the two main structural elements**

Synthetic New Products

- Starting Materials con'd

  - Owing to the **one-step manufacturing process**, it is the duty and responsibility of the manufacturer to identify substances which could be carried-over from the proposed starting materials. **Therefore, the knowledge on the quality of the starting materials is essential.**
  - **GMP is currently not required for the synthesis of starting materials**. This has the consequence that potential **suppliers** of the starting material **can change** the specifications of the previous structural units, specifications of solvents and reagents or the way of synthesis - all operations that could influence the purity of the active substance - **without informing** the active substance manufacturer.

Synthetic New Products

- 5 with Q on stability package
  - Amount of data needed at time of submission:
    - **Guideline on Stability Testing**: Stability Testing of Existing Active Substances and Related Finished Product,
    - *at the time of submission* ***at least 6 months*** *data should be available on at least* ***three primary batches*** *are required;* ***two of these batches should be at least of pilot scale.***
  - Excipients:
    - according to current guidelines **excipients** and **degradation products of excipients** need **not to** be included in the drug product specifications (release and shelf life).

Synthetic New Products

- Other Q and A
  - Submission of **validation data** for the manufacturing of three commercial scale lots of the DP after MAA submission but during review process
    - Acceptable
  - **Comparability** after change in manufacture
    - Try to minimize and anticipate
  - **Peptides synthesized** solely by solid phase peptide synthesis are not biologics.
    - agreed

Biologic New Products

- All but one advice
  - **Comparabilty**
    - Changes prior to phase III
    - phase III to commercial product
    - Testing of **quality attributes is sufficient** according to the ICH Q5E guideline but:
    - When a relationship between specific quality attributes and safety and efficacy cannot be established, and in the case that differences between quality attributes of the pre- and post-change product are observed, the inclusion of a combination of quality, non-clinical, and/or clinical studies in the comparability exercise, should be considered.

Biologic New Products

- Other Q and A

  - … is proposing two identity assays (Western blotting and isoelectric focusing), but according to ICH Q6B guideline (section 6.1.1.a), the amino acid sequence should also be determined to the extent possible.
    - demonstrate the **amino acid sequence** at the level of cell banks,
    - add **peptide mapping** to the active substance specifications
  - … proposes bioburden testing following to **USP 61** and **USP 62**; consider performing bioburden testing according to **Ph. Eur**
  - **setting of specifications**: guideline **ICH Q6B**. In addition requirements set in the **Ph. Eur. monographs** for parenteral preparations, injections, should be fulfilled.

Biologic New Products

- Other Q and A

  - **Reprocessing** is not encouraged and should be exceptional. In general due to technical problem, e.g. filter integrity testing failure, re-processing of filtration steps might be acceptable. **Re-filtration** in order **to remove contaminates or an impurity** is **not acceptable**

Biosimilars

- comparability data submitted for demonstration of biosimilarity should be obtained using a specified EU licensed product. Any data obtained with reference medicinal product sourced outside the EU can only be considered supportive.

Comparability

- During the development:
  - to identify the differences generated by the change
  - To keep record (filiation) of the evolution of the product(s) tested at different stages of the (non) clinical development
- After the Marketing authorisation
  - to determine to what extent additional clinical data (or PMS studies) would be warranted
- For biosimilar products
  - head to head comparison in an attempt to detect any "differences“ (structure, purity, potency, …) between the originator product and the biosimilar counterpart

Recommendations

- **The Sc Ad procedure is NOT:**
  - a pre-evaluation of the dossier to be submitted
  - For getting an approval or assessment of the quality of a product for clinical trials => National competences
- **The Sc Ad procedure is aimed at:**
  - Providing advice and recommendations on difficult technical issues where guidelines may be differently interpreted
  - Providing an opportunity to raise questions which are not covered in the Quality guidelines
- **Quality of the responses** provided is largely dependent upon
  - the relevance and quality of the question(s) put
  - and the documentation provided to support the Company position