EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Division

Tailored Scientific Advice for biosimilar development

Report on the experience from the pilot (2017-2020)

1. Background

A similar biological medicinal product (biosimilar) contains a version of the active substance of an already authorised original biological medicinal product (reference medicinal product) in the EEA. Similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy, based on a comprehensive comparability exercise, needs to be established for the marketing authorisation of a biosimilar product.

According to the applicable guidelines (Guideline on similar biological medicinal products (CHMP/437/04 Rev 1) and Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005 Rev1) the extent and nature of the required non-clinical *in vivo* studies and clinical studies depends on the level of evidence obtained in the previous development step(s), i.e. quality and non-clinical *in vitro* characterisation, and it is recommended to discuss this in advance with regulatory authorities. Such discussions would require the Scientific Advice Working Party (SAWP)/Biologics Working Part (BWP)/Biosimilar Medicinal Products Working Party (BMWP)/Committee for Medicinal Products for Human Use (CHMP) to perform an in-depth review of data accumulated during the initial steps of development and subsequently make recommendations to applicants related to remaining uncertainties and the next steps of the development.

As regular scientific advice is intended to be prospective and would normally not include review of data, SAWP, BWP and CHMP agreed to explore the possibility of a more extensive scientific review of quality and non-clinical *in vitro* data gained from a specific development programme to allow a discussion on residual uncertainties or simplification of the development programme. Such in-depth review of analytical and functional quality comparability data could allow to further advise on the next steps of the development programme thereby further supporting the development of a biosimilar product in a targeted way.

An adaptation of the scientific advice procedure was seen as a valid instrument to adequately satisfy the concept of the stepwise approach recommended in the aforementioned guidelines. Based on the review of the quality comparability data, advice could be given on:

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- differences identified at the quality level and their potential impact on the suitability of the biosimilar approach per se or on the need for and design of additional pre-clinical or clinical investigation.
- whether a reduced, i.e. tailored/simplified clinical development programme could be granted (e.g. waiver of clinical efficacy/safety trial).

To this end, in February 2017 EMA launched a tailored scientific advice pilot to explore further in practice the stepwise approach to development support for new biosimilar developments. The pilot was open to all types of biosimilars and applicants and was decided to run until completion of six scientific advice requests. In April 2020, the pilot was completed with the finalisation of the sixth procedure. Data on the pilot and an analysis of the experience is presented below.

2. Data/Results

2.1. Characteristics of the advice requests

- The pilot covered six scientific advice procedures.
- The last of the six scientific advice procedures was finalised in April 2020.
- At the same period as the pilot was ongoing, 71 new requests for standard advices for biosimilar were given.
- The six procedures included in the pilot were submitted by four applicants, one of them requesting advice on two separate development plans and one requesting an initial and a follow-up advice for the same development plan.
- Out of the four applicants one was a small/medium-sized enterprise (SME).
- Request for information and interest to participate to the pilot was expressed by a further eight prospective applicants.
- All scientific advice requests which formed part of the pilot referred to biosimilar monoclonal antibodies.

2.2. Feedback from the applicants

A feedback questionnaire was sent to all applicants for the six scientific advice requests subject to the pilot, and responses were received for four of the requests.

All responding applicants had previous experience with scientific advice for biosimilar developments.

The applicants had learned about the pilot through the EMA website and other interactions with EMA (e.g. at conferences).

The scope of the scientific advice requests included:

- Discussion of the differences at the quality level and their potential impact on the suitability of the biosimilar approach per se;
- Possibility for waiver of pre-clinical studies;
- Appropriateness of analytical methods as well as interpretation and completeness of analytical results;

- Discussion of relevance of minor differences at quality level and their potential impact on pharmacokinetics, pharmacodynamics, safety and efficacy;
- Evaluation of data to understand any remaining gaps in the biosimilar development programme;
- Reduction of clinical development programme based on additional quality data (e.g. waiver of clinical efficacy/safety trial);
- Broadened equivalence margin based on available data as well as additional literature.

The quality of the guidance for tailored scientific advice for biosimilars available on the EMA website was rated on average 3.7 for clarity and 3.5 for comprehensiveness (on a scale from 1 = significant shortcomings, to 5 = perfect).

The expectations for the tailored scientific advice were met with an average rating of 3.7 (on a scale from 1 = not at all, to 5 = absolutely).

Respondents confirmed that tailored scientific advice was considered to add value compared to regular scientific advice for biosimilar developments. Its comprehensiveness and clarity gave the developer confidence in their development programme and strategy. The expanded room for conversations and dialogue was noted. The possibility to discuss the next development steps in light of an agreed understanding of analytical comparability data was raised as being key to designing a good biosimilar development program.

2.3. Observations in relation to the submitted data and its impact on the advice provided

Compared to standard scientific advice requests, it appeared that in the scientific advice requests for the pilot the data package on the quality part was more detailed. The possibility to review the available data allowed for more specific recommendations for further development to be given to the applicant. In terms of non-clinical and clinical information, the packages did not significantly differ from standard scientific advice in terms of level of detail.

The maturity of the quality data appeared to be the biggest challenge in reaching the goals of the pilot. The pilot brought the insight that quality and clinical development often take place in parallel rather than in a stepwise manner. Hence in some cases the quality data were rather immature (e.g. from a limited number of batches and/or not obtained with material from the proposed commercial process), which made recommendations regarding a tailored clinical development (patient size, population, efficacy margins, etc.) difficult. The only exception was the product which entered the pilot twice and for which a more mature and comprehensive data package was presented in the second submission. In this instance, more specific direction could be provided in relation to observed quality differences and a high degree of biosimilarity could be confirmed. Ultimately, the timing of obtaining the advice will need to be carefully considered.

A review of the advice provided suggests that the tailored scientific advice was not limited to recommendations on the strategy proposed by the applicants but went further to provide specific advice on the analysis of the data presented. Examples include confirmation of comparability of certain quality attributes, confirmation that observed differences were sufficiently justified based on the available data and conclusions on similarity based on the available data.

3. Discussion and conclusion

The pilot was successfully completed with the pre-specified number of scientific advice procedures finalised in order to support the analysis. The initial uptake was slower than expected. However, this is not unusual for new types of engagement opportunities. It was confirmed with industry stakeholders that the dissemination of information related to the pilot has been adequate and available guidance was also generally regarded as clear and comprehensive.

It appeared that the required maturity of the analytical data package to enter the pilot created a challenge as a mature set of quality comparability data is often achieved at later phases in the biosimilar development. The expectation to have validated/qualified methods, an established commercial manufacturing process and an adequate number of batches available at the time of the pilot was considered as a hurdle by applicants. Moreover, the stepwise approach foreseen in the regulatory guidelines is not necessarily employed in practice where clinical studies are often conducted in parallel with generation of analytical comparability data. Therefore, employing such tailored scientific advice requires adaptations in development by having a mature quality and *in vitro* non-clinical data package prior to the conduct of animal or clinical studies, in order for its utility not to be restricted to simple scientific advice "quality checks" on the available data throughout the development.

Applicants participating in the pilot appreciated the possibility to present and discuss with regulators their quality comparability data and considered the comprehensiveness of this type of advice very important to gain clarity and confidence in their programme. They consider this type of scientific advice as a valuable opportunity to decide on open questions and a tool to have more in-depth dialogue with regulators and resulting guidance.

The expectation from regulators to perform a detailed review of quality data to inform on the extent of the non-clinical and clinical data needed to be generated was in most cases limited by the lack of mature quality packages. The advice given had, in most instances, more impact on the generation of quality data per se and less impact on clinical data requirements than anticipated. It would therefore need to be seen how biosimilar development programmes can be adapted to allow potentially reduced animal and clinical study requirements to be considered.

Considering that the scientific discussions held for this type of advice have been regarded as beneficial and acknowledging the need to further mature the experience based on specific cases, the tailored scientific advice offering for biosimilar development will be continued as part of regular scientific advice operations. To account for the more in-depth review and to allow sufficient time for the scientific assessment and discussion the duration of the procedure is set to 70 days if managed without discussion meeting (100 days if a discussion meeting is needed). The number of requests is capped to a maximum of two procedures per month in order to manage the foreseen resource requirements.