

ADVICE TO MANUFACTURERS

The Prequalification Team: medicines (PQTm) is always available to provide prompt advice on quality and bioequivalence (BE) aspects of generic products dossiers. This note gives some examples of the type of guidance that PQTm can offer with respect to quality and BE.

The data required to prepare a dossier for submission is complex, and attention to the details of requirements is required to ensure a smooth passage through the assessment process. It is most important to ask for advice before starting any studies that will necessitate significant investment of time and/or resources.

Applicants should consult the PQTm website — since it contains extensive guidance — before requesting advice.

QUALITY

Examples of quality areas where advice may be of high importance in the preparation of product dossiers include:

- **Data to support the active pharmaceutical ingredient (API).** If options exist with respect to API data (for example, both an API master file (APIMF) and a Certificate of Suitability to the monographs of the European Pharmacopoeia (CEP) are available), or if neither an APIMF nor a CEP is available, it is recommended that applicants seek advice before dossier submission.
- **Basic criteria for the choice of biobatch.** A biobatch should be at least 100,000 units for a solid oral finished pharmaceutical product (FPP). If a smaller batch size is planned (e.g. for a product with a limited market), advice should be sought before choosing the biobatch, in order to understand the future ramifications and limitations inherent in using a smaller batch size.
- **Parameters required in the characterization of the biobatch.** The complete characterization of the biobatch (both the API and FPP) is of critical importance to the assessment. If there is any doubt as to what characteristics must be included for a particular API/FPP, advice can be sought so that the API/FPP can be characterized before expiry.
- **Use of uncommon excipient(s).** If the planned formulation contains an excipient that may be considered “novel” (as defined in TRS970 Annex 4, section 3.2.P.4.6), advice should be sought as to the excipient classification and whether reformulation will be requested.
- **Parameters required in specifications.** As above, it is important that the specifications include all relevant parameters for both the API and FPP.
- **Whether a product is considered “uncomplicated” according to the definition in the quality guideline.** Characterization as complicated or uncomplicated determines the minimum requirements with respect to the number and size of batches to be placed on stability. The “uncomplicated product” definition in the quality guideline is not comprehensive, for example mono-component ritonavir products are considered complicated, and new products are added regularly to the invitations to manufacturers to submit an expression of interest for product evaluation. Applicants may seek advice on what category a specific product falls under, in order to plan their studies.
- **When an applicant is new to PQTm, or a product is less common (suppositories, depots, etc.).** It is sometimes advisable that the applicant request that the Quality Overall Summary – Product Dossier (QOS-PD) be reviewed in brief by the team before submission of the dossier. This

is an excellent strategy to obtain general feedback from experts on the QOS-PD summary of the product.

- **Emerging issues.** When issues are encountered during development or post-prequalification, feedback may be obtained on the best way to handle the product.
- **The suitability of planned stability studies with respect to parameters tested.** This is especially important for those dosage forms for which available regulatory guidance is minimal or non-existent, such as suppositories and depot injections. (Note that for the latter, a PQTm guideline is available that deals with many of the questions that manufacturers are likely to have for this dosage form.) In particular, it is critical that the parameters tested include all those that are considered stability-indicating for the particular dosage form.
- **Requirements for stability studies.** A number of factors affect the requirements for stability studies, including the complexity of the product (see above), multiple API suppliers, the therapeutic category of the product, multiple manufacturing sites, multiple strengths and/or container closure systems, etc.

BIOEQUIVALENCE

Examples of areas for which advice on BE-related issues may be particularly valuable when preparing a product dossier:

- PQTm identifies the appropriate comparator product(s) for each invited product on the website. However, further support can be provided if obtaining the comparator product is difficult.
- If the identified comparator product is no longer available, PQTm will identify a new comparator.
- If the product is no longer available in ICH-associated country markets but is available elsewhere, PQTm will identify the best alternative market(s) for purchase of the product.
- If the applicant cannot identify a pharmaceutical distributor who can provide the comparator product, PQTm can suggest some possible distributors.
- PQTm provides advice on the most appropriate study design to be used to demonstrate the bioequivalence of a proposed product to the comparator product. Recommendations for some products are available on the PQTm website. For products not included in those recommendations, consultation with PQTm by email is encouraged.
- PQTm encourages applicants to submit a near-to-final draft of BE study protocols to PQTm for comment. This allows PQTm to comment on parameters such as sample size calculations, the posology to be used during the study, the sampling schedule, etc. The aim is to avoid studies that are not consistent with PQTm requirements.
- PQTm can provide advice on BE-related issues that arise during product development, during the conduct of BE studies, and during preparation of a dossier for submission.

For any questions or to submit a request for advice, please contact Dr Matthias Stahl, Group Lead, Medicines Assessments, Prequalification Team at: stahlm@who.int