PQT/MED-specific Annotations for WHO Guidelines for Additional Strength Biowaiver Applications

For the WHO Prequalification Unit – Medicines (PQT/MED), the relevant guidance to be considered for an additional strength biowaiver, i.e. a biowaiver based on proportionality of formulations, can be found in Section 10.3 and Appendix 1 of WHO Technical Report Series (TRS) 1003, Annex 6 (2017). TRS 1003, Annex 6 can be obtained from the PQT/MED website at:

http://www.who.int/entity/medicines/areas/quality_safety/quality_assurance/trs1003_annex6.pdf?ua=1

To provide better clarity and highlight key differences between PQT/MED requirements and those described in Annex 6 (see in particular, the annotation for Appendix 1), the following PQT/MED-specific annotations to Section 10.3 and Appendix 1 of TRS 1003, Annex 6 should be considered by applicants when preparing data and information for a dossier for submission to the programme. The sections identified below refer to the relevant section of Annex 6.

10.3.2 Qualification for biowaivers based on dose-proportionality of formulations

The document *Application for a Biowaiver: Additional Strength* must be completed and submitted in MS Word format. The instructions for completion of the biowaiver application form are provided at the top of the form. All supporting documentation, including Certificates of Analysis, and the comparative dissolution study protocol and report, should be provided as annexes to the application form.

Section 10.3.2.1 Immediate-release tablets

Comparative *in vitro* dissolution profiles

Batch selection

It is recommended that samples of the additional strength be taken from a batch (the biowaiver batch) of commercial scale. However, when this is not possible, a batch of 1/10 or larger of the largest intended commercial batch size, or 100 000 units, whichever is greater, can also be used, provided this batch is the same as the production batch in manufacturing method, quality, and composition. The samples of the reference strength should be taken from the batch used in the BE studies (the biobatch).

Dissolution conditions

Similar *in vitro* dissolution should be demonstrated between the additional strength and reference strength in at least three different pH media considered relevant for absorption in the gastrointestinal tract. Comparative *in vitro* dissolution should be performed with 12 units[1] of each additional and reference strength batch in 900 ml or less of standard buffer media at pH 1.2, 4.5, and 6.8, at 37ºC ± 1ºC, using the paddle apparatus at 50 rpm, or the basket apparatus at 100 rpm. If the proposed dissolution medium for release of the products differs from these conditions, comparative dissolution data in the proposed release (QC) conditions should also be provided.

When high variability or coning is observed in the paddle apparatus at 50 rpm for both additional and reference strengths, the use of the basket apparatus at 100 rpm is recommended. Additionally, alternative methods may be considered to overcome issues such as coning, if scientifically substantiated. All experimental results should be provided.

Data should be collected in the absence of surfactant. Only if the lack of sink conditions is demonstrated by means of dissolution data will the use of surfactant be considered. In this case, the choice (i.e., type) and

[1] If the profiles are not similar due to the absence of sink conditions in any of the above media, dissolution profiles can be generated using the same dose per vessel (e.g., two tablets of 5 mg versus one tablet of 10 mg; in this example, a total of 2 x 12 units of the 5 mg strength are used).

minimum amount of surfactant necessary should be justified. In such cases, profiles in the absence of surfactant should also be provided.

Sample filtration

Samples should be filtered during sample collection to prevent continuation of dissolution. The filters can be in-line or at the end of the sampling probe or both.

Sampling intervals

The sampling intervals should be sufficiently short for a scientifically sound comparison of the profiles. The sampling intervals recommended by PQT/MED depend on the time taken to reach 85% dissolution (or a plateau), such point being regarded the point of completion of the dissolution for the purpose of similarity determination. Inclusion of the 15-minute time point in the protocol is of strategic importance for profile similarity determinations (except in cases of slow dissolution as in scenario 3 below).

Three scenarios have been identified:

1. The dissolution is completed within 30 minutes (very rapidly or rapidly dissolving)
    - The recommended sampling times are 5, 10, 15, 20, 30 and 45 minutes.
2. The dissolution is not rapidly dissolving (> 30 minutes), but completed within 45 minutes
    - The recommended sampling times are 10, 15, 20, 30, 45 and 60 minutes.
3. The dissolution is slow, being completed only after 45 minutes.
    - The recommended sampling times are 15, 30, 45, 60, 90, 120, … minutes.

In the first two scenarios, the relative standard deviation (RSD) up to the 10-minute time point should be ≤ 20%, with the RSD at the time points thereafter ≤ 10%.

In scenario 3 the RSD at 15 minutes should be ≤ 20%, with the RSD at the time points thereafter ≤ 10%.

If the variability in the data exceeds these RSD values, the root cause of the variability should be investigated and adjustments made. When the RSD is too high, f_2 calculation is considered inaccurate and a conclusion on similarity in dissolution cannot be made. If the investigation and adjustments are unable to address the high variability observed, PQT/MED should be contacted to discuss alternative approaches such as the use of the 90% confidence interval of f_2 using bootstrapping methodology to assess profile similarity.

pH measurement

The pH of each dissolution medium should be measured at the beginning (prior to introduction of the drug product) and end (as soon as possible after the collection of the last sample) of each dissolution experiment. These data should be reported in the dissolution study report. If the pH of the medium is not maintained over the course of the experiment, options for adjusting procedures should be discussed with PQT/MED.

Analytical method validation

Analytical methods relying on UV detection, i.e. without HPLC, should be validated for all media employed in the dissolution testing.

Format of *in vitro* dissolution study report

A study protocol should be developed prior to undertaking the dissolution study and should include sections 1 – 4 as described below for the study report. The report on a dissolution study used in the biowaiver application, created after the study has been conducted, is a separate document from the protocol and should include at least the following information:

1. Purpose of study
2. Products / batch information

a. Batch numbers, manufacturing and expiry (if available) dates, size of the additional and reference strength batches, Certificates of Analysis (CoAs), and packaging of the batches used in the study

b. Batch manufacturing record(s) for the batches used in the comparative dissolution study.

3. Full dissolution conditions and method, sampling times, and the number of units (tablets, capsules, etc.) per study should be clearly stated. It should be indicated how and when the samples were filtered. Any problems with pH-related stability of samples should be indicated and discussed in terms of preventive handling measures, analysis, and interpretation of data.

4. Analytical method, including validation or cross-reference to the quality part of the dossier.

5. Results (% API dissolved)

   a. Tabulated (individual results, mean and %CV)

   b. Graphical presentation

   c. Similarity determination / f2 calculation if necessary and applicable

6. Conclusion

Appendix 1 Recommendations for conducting and assessing comparative dissolution profiles

In PQT/MED, the following condition applies for the purpose of f_2 calculation:

• A maximum of one time point should be considered in which 85% or greater dissolution of either product has been reached.