PQT/MED-specific Annotations for the ICH M9 Guideline for Biopharmaceutics Classification System (BCS)-based Biowaiver Applications

For the WHO Prequalification Unit – Medicines (PQT/MED), the relevant guideline to be considered for BCS-based biowaivers is the International Council for Harmonisation of Technical Requirements for Pharmaceutical Products for Human Use (ICH) Harmonised Guideline **'Biopharmaceutics Classification System-Based Biowaivers' M9** (2019). The ICH M9 guideline and the accompanying Questions & Answers document can be obtained from the ICH website at:

https://database.ich.org/sites/default/files/M9_Guideline_Step4_2019_1116.pdf

https://database.ich.org/sites/default/files/M9_QAs_Step4_2021_0106.pdf

To provide better clarity on PQT/MED requirements, the following PQT/MED-specific annotations to the M9 guideline 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 the M9 guideline.

Section 2.1 Solubility

As per M9, solubility data should be presented for the active pharmaceutical ingredient (API) contained in the proposed product. The API employed in the solubility experiments should be fully characterized as per PQT/MED Quality requirements.

Additional guidance on conducting solubility experiments for the purpose of BCS classification can be found in WHO Technical Report Series (TRS) 1003, Annex 6, Appendix 2 (2017) and TRS 1019, Annex 4 (2019).

PQT/MED has reviewed available solubility data and has summarized APIs invited to the programme for which data indicating high solubility has been observed. This information is summarized in Appendix 1. This information should assist manufacturers when considering whether a biowaiver approach may be possible.

Section 2.2 Permeability

As per M9, the assessment of permeability should preferentially be based on the extent of absorption derived from human pharmacokinetic studies, e.g. absolute bioavailability or mass balance. Permeability can be also assessed by validated and standardized *in vitro* methods using Caco-2 cells, as outlined in M9 Annex I.

As is stated in M9, "Human in vivo data derived from published literature (e.g., product knowledge and bioavailability studies) may be acceptable, keeping in mind that peer reviewed articles may not contain the necessary details of the testing to make a judgement regarding the quality of the results."

PQT/MED has reviewed the absorption/permeability data available to the programme and, based on this, has provided permeability classifications where possible for the APIs listed in Appendix 1. **In order to maximize opportunities to use BCS-based biowaivers, if PQT/MED has provided a permeability classification for an API in Appendix 1, manufacturers do not need to provide additional absorption/permeability data in a biowaiver application.**

Section 3 Eligibility of a Drug Product for a BCS-Based Biowaiver

"Biobatch" selection

As with all finished pharmaceutical product (FPP) applications, the consistency of the manufacturing method and the quality of the test product must be demonstrated in the relevant sections of the Quality part of the dossier.

As stated in Section 3.2 of M9, it is recommended that samples of the test product be taken from a 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 as the test product, provided the batch is the same as the intended commercial batch in manufacturing method, quality, and composition.

The API content or potency of the comparator product should be close to the label claim, and the difference in API content or potency between the test and comparator products should be not more than 5%.

Comparator product selection

Comparator products used in BCS-biowaiver applications should be selected from the current list of PQT/MED recommended comparator products, including the appropriate fixed-dose combination product.

Identification by PQT/MED of an API to be eligible for a BCS-based biowaiver application is made purely on the solubility, absorption, safety and related properties of the API (Class I or Class III). However, it does not imply that the recommended comparator product(s) will be rapidly dissolving in the case of Class I APIs or very rapidly dissolving in the case of Class III APIs, which is a requirement for BCS-based biowaiver studies. The applicant must thus ensure that the recommended comparator(s) listed on the PQT/MED website is indeed suitable for a BCS based-biowaiver application before product development.

Note that rapidly dissolving, or very rapidly dissolving, properties of a product are not required for *in vivo* bioequivalence studies. Thus, though a listed comparator product may not be suitable for BCS-based biowaiver purposes, it is still suitable for *in vivo* bioequivalence studies.

3.2 *In vitro* Dissolution

Timing of dissolution studies

For comparative dissolution studies, dissolution profiles for the test and comparator products should be generated in the same laboratory by the same staff at the same time (e.g., within 24 hours) using the same equipment, if at all possible. Compilation of 'historical' data is not acceptable.

Sampling intervals

The sampling intervals employed in dissolution studies should be short for a scientifically sound comparison of the performance of the test and comparator products. Samples should be collected at 5, 10, 15, 20, and 30 minutes. Inclusion of the 15-minute time point in the protocol is of strategic importance for profile similarity determinations.

Sample filtration

The M9 guideline states that samples should be filtered during collection, unless *in-situ* detection methods are used. For this purpose, filters should be employed in-line, at the end of the sampling probe, or both during sample collection.

pH of dissolution media

The pH of each dissolution medium should be measured at the beginning (prior to introduction of the testing unit) and at the end (as soon as possible after the collection of the 30-minute 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 dates, batch size of the test product, Certificates of Analysis (CoAs) and packaging of the batches used in the study
    b. Batch manufacturing record(s) for the batch of the test product used in the comparative dissolution study.
3. Full dissolution conditions and method, as well as the number of units (tablets, capsules, etc.; minimum 12 per product) per study. 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 reference to the quality part of the dossier.
5. Results (% API dissolved)
    a. Tabulated (individual results, mean and %CV)
    b. Graphically
    c. Similarity determination / f2 calculation if necessary and applicable
6. Conclusion/recommendation

4 Documentation

The document *Application for a Biowaiver: Biopharmaceutics Classification System (BCS)* 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 comparator product information, Certificates of Analysis, and the comparative dissolution study protocol and report should be provided as annexes to the application form.

APPENDIX 1: Provisional BCS classifications for APIs invited to PQT/MED for which data indicating high solubility have been reported.

Active pharmaceutical ingredient (API)	*Therapeutic group*	*Highest single dose [mg]*	*BCS Class*
Abacavir (as sulfate)	Antiretroviral	600	III
Cycloserine	Antituberculosis	1000	III*
Dexamethasone	Therapeutic against COVID-19	6	III*
Diethylcarbamazine	Antiparasitic	500	III*
Emtricitabine	Antiretroviral	200	I
Entecavir	Antihepatitis	1	III*
Ethambutol	Antituberculosis	400	III
Fluconazole** (Polymorphs II & III)	Antifungal	800	I
Isoniazid	Antituberculosis	300	III
Lamivudine	Antiretroviral	300	III
Levofloxacin	Antituberculosis	750	I
Linezolid	Antibacterial	600	I
Misoprostol (as 1% dispersion in HPMC)	Prostaglandin analogue	0.8	III*
Moxifloxacin (as hydrochloride)	Antituberculosis	400	I
Ofloxacin	Antituberculosis	400	I
Oseltamivir (as phosphate)	Antiinfluenza	75	III*
Primaquine (as phosphate)	Antimalarial	15	I
Pyrazinamide	Antituberculosis	500	III
Stavudine	Antiretroviral	40	I
Tenofovir disoproxil fumarate	Antiretroviral	300	III*
Zidovudine	Antiretroviral	300	I

* - Insufficient information is available to PQT/MED to determine the absorption/permeability classification of these APIs, therefore, these APIs have been assigned the provisional classification of Class III. If adequate absorption/permeability data can be provided in an application, finalization of the classification as either Class I or III can be undertaken.

** - Fluconazole polymorph I does not fulfill the requirements for BCS high solubility.