

## Supplement 1 [for use from July 2005 (CPH25)]

Guideline on Submission of Documentation for Prequalification of  
Multi-source (Generic) Finished Pharmaceutical Products (FPPs)  
Used in the Treatment of HIV/AIDS, Malaria and Tuberculosis

### Dissolution testing

Dissolution should form an essential part of pharmaceutical development of solid oral dosage forms (and usually suspensions). The media and conditions chosen in the studies will depend on the required release characteristics of the intended product.

For immediate release products the paddle (Apparatus 2, usually at 50 to 75 rpm) and basket (apparatus 1, usually at 100 rpm) are conventional. Immediate release typically means that 75% of the API is dissolved within 45 minutes. Lately the terms rapidly dissolving (85% in 30 minutes) and very rapidly dissolving (85% in 15 minutes) became popular and important in dissolution testing.

The following media should be considered for immediate release products during development studies:

- pH 6.8 buffer (or simulated intestinal fluid without enzymes)
- pH 4.5 buffer
- pH 1.2 buffer (or simulated gastric fluid without enzymes) or 0.1 M hydrochloric acid.
- Water may be considered as an additional medium

For development purposes the generation of dissolution profiles at short intervals such as 10, 15, 20, 30 and 45 minutes in the above media are strongly recommended. This would enable:

- The selection of the formulation, by comparison of the dissolution profiles with that of the innovator product. This should be a basic strategy in pharmaceutical development to maximize the chances of bioequivalence.
- Comparison of the release properties of the pivotal batches to demonstrate *in vitro* similarity, which is considered essential for retention of efficacy and safety. Note that bioequivalence studies are done normally only once on a pivotal batch during development – it must therefore be demonstrated that the product retain the release characteristics up to and during commercial production.
- The selection of the dissolution specifications (conditions and acceptance criteria) for product release and stability study purposes. A dissolution specification should be discriminating, implying that it should be able to detect inadequate release properties of the commercial batches.
- Post-approval amendment application. If the amendment is of a major nature and requires bioequivalence studies, *in vitro* data may be acceptable, provided that (1) the profiles of the amendment batch and the current batch are similar and (2) that the dissolution study design is acceptable (preferably the three media and short interval multipoint as mentioned above).

Two scenarios for comparing the profiles obtained from multipoint dissolution are operative:

1. If both the test and reference product show more than 85% dissolution within 15

minutes, the profiles are considered similar (no calculations required). If not, see the next point.

2. Calculate the  $f_2$  value. If  $f_2 \geq 50$ , the profiles are normally regarded similar. Note that only one measurement should be considered after 85 % dissolution of both products has occurred and excluding point zero.

$$f_2 = 50 \cdot \log \left( \frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n} [\bar{R}(t) - \bar{T}(t)]^2}{n}}} \right)$$

In this equation  $f_2$  is the similarity factor,  $n$  is the number of time points,  $R(t)$  is the mean percent drug dissolved of e.g. a reference product, and  $T(t)$  is the mean percent drug dissolved of e.g. a test product.

The evaluation of similarity is based on the conditions of

- a minimum of three time points (zero excluded)
- 12 individual values for every time point for each formulation
- not more than one mean value of > 85% dissolved for each formulation
- that the standard deviation of the mean of any product should be less than 10% from second to last time point.

### 3.7 *In vitro* dissolution complementary to a bioequivalence study

(CPMP/EWP/QWP/1401/98, July 2001.)

The results of "*in vitro*" dissolution tests, obtained with the batches of test and reference products that were used in the bioequivalence study should be reported. The results should be reported as profiles of percent of labelled amount dissolved versus time.

The specifications for the *in vitro* dissolution of the product should be derived from the dissolution profile of the batch that was found to be bioequivalent to the reference product and would be expected to be similar to those of the reference product (see formula above).

For immediate release products, if the dissolution profile of the test product is dissimilar compared to that of the reference product and the *in vivo* data remain acceptable the dissolution test method should be re-evaluated and optimised. In case that no discriminatory test method can be developed which reflects *in vivo* bioequivalence a different dissolution specification for the test product could be set.

It is a requirement of the prequalification programme to submit comparative dissolution data, including profile comparison and discussion, for the biobatch and innovator biobatch (same batches as used in the bioequivalence). The data form part of the pharmaceutical development report, but can also be included in the bioequivalence study report.

For extended release products, the same dissolution strategy as for immediate release products can be followed in the development studies, though it is recommended that the analysis points

should be set according to the dissolution properties of the innovator product as determined experimentally.

For delayed release products reasonable standard conditions (acid and buffer stage), procedures and acceptance criteria are set in the USP and the BP. Multipoint analysis can be applied in the buffer stage for comparative purposes.

#### References

Guidance for Industry. Waiver of In-Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), August 2000.

CPMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence. The European Agency for the Evaluation of Medicinal Products CPMP/EWP/QWP/1401/98, July 2001.