FIP Focus Group BCS & Biowaiver

Comments to the Draft Guidance: Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms based on a Biopharmaceutics Classification Scheme Guidance for industry.

General Comments:
The Focus Group “BCS and Biowaiver” of the FIP welcomes the updates made in the Draft Guidance with regard to extending the possibility to apply the Biowaiver procedure to products containing BCS Class 3 drugs and to revising the criteria for high solubility and high permeability. This will go a long way to harmonizing biowaiver guidances on a global basis.

Further, the Focus Group is pleased to note that the FDA continues to support separate guidances for application of the Biowaiver from the guidances which address pharmacokinetic proofs of bioavailability and bioequivalence. This helps to maintain clarity in the guidances.

Third, the Focus Group is of the opinion that the layout of the Guidance is very helpful in communicating the key points that must be considered when applying for a Biowaiver and maintaining clarity for all stakeholders.

Line by line Comments
Line 66: The Focus Group welcomes the addition of products containing BCS Class 3 drugs. Not only does this improve harmonization with e.g. the guidances put forth by WHO and EMA, but has also been substantiated in the literature by analyses showing that Class3 drug products are no less likely to be bioequivalent than their Class 1 counterparts.

Line 78: The Focus Group supports maintenance of using the Highest Dosage Strength for calculating the Dose to Solubility ratio. In Biowaiver Monographs to date, there has not been any evidence that changing the definition of Dose to Highest Single Dose offers any additional benefit in terms of patient safety.

Line 80: The Focus Group supports lowering the permeability criterion to 85% absorption. Again, experience with Biowaiver Monographs has been positive when...
applying the 85% criterion (e.g. to acetoaminophen) and this change will contribute greatly to harmonization.

The Focus Group also greets the maintenance of flexibility in the approach taken to determining permeability in this Guidance.

The Focus Group would like to suggest that the dose/concentration at which the permeability is measured be given some consideration in the Guidance – for example, that the sponsor should justify the dose (for human studies) or concentration(s) (in situ and in vitro studies) at which the permeability was measured.

Lines 97-102: The Focus Group supports flexibility in the rotation speed of the paddle, so that it can be increased if necessary to avoid coning.

The Focus Group would like to offer the following points for consideration regarding the restriction of the volume of the dissolution medium:

1. The dissolution test is a balance of several factors in design, including stirring speed, media composition, media volume and dissolution specification.

2. The combination Apparatus 2/50-75 rpm/900ml or less/time for 85% dissolution 15/30min has been shown to work well at FDA for Class 1 drug products and at EMA and WHO for Class 1 and Class 3 products.

3. Similar combinations have long been used in the industry to establish discriminating quality control tests.

4. For these reasons, it could be argued that there is no compelling reason to restrict the volume to 500 ml or less.

5. On the other hand, sink conditions always prevail for highly soluble drugs at a volume of 900ml. In vivo, sink conditions will also prevail for Class 1 compounds due to the rapid absorption across the mucosa. This effect is likely to also prevail for many Class 3 compounds which have modest to good permeability but fail to make the “highly permeable” cutoff. However, at very low permeabilities, sink conditions might not prevail in vitro, and in these cases it could be argued that the test volume should be decreased.

6. Reduction of the test volume would create a counterbalance to the less restrictive permeability criteria (Class 1 => Class 1 and 3) and therefore mitigate patient risks of extending the biowaiver eligibility to Class 3 drugs.

Line 104: The Focus Group would like to suggest that an additional sentence be introduced to exclude the possibility of products with <85% dissolution in 30 minutes under the test conditions to be considered for the biowaiver. This sentence could read “Products dissolving <85% in 30 minutes are considered slow dissolving, and are not eligible for biowaiver under BCS guidance”. This suggestion is intended to round out what is already written for the definition of rapidly and very rapidly dissolving drug products, so that no doubt remains about eligibility criteria.

Lines 117-138: The Focus Group would like to enquire about the basis for the determination of solubility at pKa, pKa-1 and pKa+1. Instead, the solubility of the drug should be determined at the pH at which the solubility is expected to be at a
minimum. Other than the two pH extremes i.e. 1.2 and 6.8, a minimum is only likely to occur when there is an amphoteric drug. For example, if a drug has a weak acid function with pKa of 4 and a weak base function with a pKa of 2, it would be expected that the pH of minimum solubility would lie at pH 3, this can be calculated from the Henderson-Hasselbalch equation.

The Focus Group would like to raise the issue of whether the form of the drug should be checked at the conclusion of the solubility determination e.g. salt formation with the buffer species, e.g. change of polymorph, e.g. reversion to free acid or free base from a salt form.

The Focus Group would also welcome clarification on the intent of reporting any degradation of the drug substance as a function of buffer composition or pH. Further, with respect to degradation during a solubility experiment (usually over 24 hours) we would like to raise the question of whether observed degradation is relevant for the clinic. In the case of a drug like aspirin, which degrades to a large extent during determination of equilibrium solubility but not more than 10% under simulated gastric or intestinal conditions over the relevant time-frame of residence in the upper GI tract (see Biowaiver Monograph on Aspirin) is it acceptable to merely show that the highest dosage strength can be dissolved in 250 ml over the pH range 1.2 to 6.8? A further example in this regard is capecitidine, for which observed in vitro degradation did not translate into problems with bioavailability.

Lines 163-166: Documentation of drug stability in the GI tract is required to make mass balance study results eligible for use as evidence of high permeability. An alternative approach would be to use the EMA criteria i.e. Phase I and Phase II can also be counted when present either in the urine or feces. Experience within the Focus Group has been that FDA has not accepted mass balance studies for drugs that are stable in the GI tract but which form metabolites post-absorption, and without which the drug does not achieve 85% recovery in the urine.

Lines 184-202: The Focus Group is of the opinion that the Pgp efflux is overemphasized, there are few cases where Pgp interactions have been shown to be an influence on bioavailability. We would also like to question the use of an efflux ratio of <2 as a criterion for admitting animal or in vitro test results, this seems too restrictive in light of the known overexpression of Pgp in Caco-2 cells, for example.

Line 217: At this point in the guidance it is mentioned that there should be an equal flux in both directions in in vitro permeability models to show a passive transport mechanism. This is not consistent with the requirement stated in lines 184-202 that to show a passive mechanism the efflux ratio should be less than 2. We would also like to suggest that the term “statistically significant” might be problematic in view of the fact that if results are highly variable, it will be more difficult to show statistical significance. The Focus Group would prefer that an evidence-based efflux ratio be chosen and consistently used.

Line 242: The Focus Group would like to suggest that some mention of mass balance requirements be made here. Otherwise mass balance considerations appear only at
Line 259 and there is little information to guide what is expected with regard to the mass balance in a permeability study in order for the results to be acceptable.

Line 256: The Focus Group would like to suggest a minor change in the text to read as follows: “The permeability values of the two internal standards should not differ statistically significantly between tests that are run on different occasions.”

Line 282-285: Likewise the Focus Group would like to suggest revising the text to read. “Obtaining fluids from human subjects requires intubation and may be difficult. Stability in the GI tract may therefore be documented using simulated gastric and intestinal fluids such as Gastric and Intestinal Fluids USP or, with suitable justification, Biorelevant media.”

Lines 287-291: Rather than being prescriptive about the duration of the stability study and the media, the Focus Group would like to suggest that the sponsor should justify the conditions under which the stability study should be run, both in terms of duration and media used. To illustrate, if a drug is absorbed very quickly (as determined by a PK study) then perhaps the duration of the test does not need to be as long as 1 hour in gastric fluid and 3 hours in intestinal media.

Line 310: Unless the preference for Apparatus I over apparatus II can be justified based on experimental evidence that there is less coning in a Type I than in a Type II apparatus, the Focus Group is of the opinion that this sentence should be deleted.

Line 318: Some members of the Focus Group opined that a 5 minute sampling point would be useless as the release at short time points is often driven by disintegration and therefore subject to great dosage unit to dosage unit variability. Please consider a more general statement such as “at least 4-5 samples, taken at least 5 minutes apart, over the first 30 minutes of the release test.”

Line 332: The Focus Group would like to see a clear definition of which sampling points can be used in the analysis. Our suggestion is to stop taking samples into consideration after the reference product has reached 85% dissolution.

Line 332: The Focus Group also has a query about what to do when results show CV of more than 10% - no biowaiver? Bootstrap the data?

Line 335: Likewise for very rapidly dissolving products, what is the criterion? Mean release with n=12 of 85 % or more in 15 minutes, with no greater than 10% CV? Here also, what are the ramifications if the dissolution data have a CV of more than 10%?

Line 341: Will the FDA also consider applying the biowaiver to oral suspension dosage forms, similar to the EMA?
Line 355-357: The BCS 3 requirements seem overly conservative when it comes to the composition. It makes sense to have some limitations to the amount and type of excipients where there is a suspicion of influence on absorption beyond dissolution effects. However, is there really a data-driven background supporting the current proposal of requiring the test product to be Q1 and Q2 with the reference product? Is the number of BE failures for BCS 3 drugs which meet dissolution requirements any bigger than for products containing BCS 1 substances?

Line 403: The Focus Group is of the opinion that the proposed rules for FDC products are generally very reasonable. We would like to suggest clarifying the PK interactions statement to read “provided there is no statistically significant PK interaction”

Line 433: Here a minor text change is suggested: “only if absorption from the oral cavity can be ruled out”.

Line 522: Would it be possible to propose six drugs for validation of human perfusion studies, analogously to the selection of twenty drugs tabulated for the in situ/in vitro studies?

Lines 565-566: The Focus Group comment concerning the excipients to be Q1 and Q2 for products containing BCS 3 drugs (lines 355-357) is also relevant here.