COMMON DEFICIENCIES IN FINISHED PHARMACEUTICAL PRODUCT (FPP) DOSSIERS

Additional guidance for manufacturers

This note identifies the most common quality related deficiencies in recently assessed dossiers in the Prequalification of Medicines Programme (PQTm), and provides additional guidance to help manufacturers address these deficiencies in future submissions to PQTm. The discussions are based on solid oral dosage forms, but may also be useful for other dosage forms.

The Active Pharmaceutical Ingredient (API) supplier's vs the FPP manufacturer's API specifications

Most of the reviewed dossiers had issues concerning the FPP manufacturer's specification in relation to the API manufacturer's specification.

In general, the FPP manufacturer's specification for a given API should be in agreement with the API manufacturer's specification as accepted by PQTm (API-PQ or APIMF procedures) or EDQM (CEP).

This means:

- All test parameters and corresponding acceptance criteria (same limits or tighter) included in the API manufacturer's specification should generally be in the FPP manufacturer's specification (exceptions might include the tests chosen for identity, difference in the type of method with different associated limits e.g. HPLC assay replacing titration assay, etc.); any differences compared to the API supplier's specifications should be justified.

- Analytical methods for purity and assay should be the same as those validated by the API manufacturer or else should be fully validated and demonstrated as at least equivalent to the methods validated by the API manufacturer, or equivalent to the compendial method if compendial standard is claimed.

- The FPP manufacturer's specification should not include skip testing or periodic testing schedule except when such a proposal has been accepted via APIMF assessment (i.e. is in the accepted API manufacturer's specification). In such cases, a footnote identifying the skip tested parameters can be included. However, frequency of testing should not normally be stated in the specification since this is to be established after prequalification based on trend data on several batches tested by the FPP manufacturer, and based on the principles of vendor qualification.

Additional user specific tests such as polymorph identity and particle size distribution (PSD), as appropriate, should also be included.

Control of polymorph identity and PSD

In 35% of the reviewed dossiers missing or inadequate control of polymorph identity and/or PSD were noted.

Determination of BCS (The Biopharmaceutical Classification System) solubility is an integral part of the API data required in the dossier. All APIs of BCS low solubility[1] should be controlled for polymorph identity (when polymorphism is a factor) and should always include controls for PSD:

- Unless otherwise justified using ICH Q6A decision tree # 4, a routine polymorph ID control should be included. A discussion should be included in section 3.2.S.3 of the dossier to justify exclusion of polymorph identity for BCS low solubility APIs.

- The specification should include appropriate control for PSD. For this, the API lot used in the manufacturing of the biobatch should be tested by laser diffraction and profiles established.

Except when a limit for d90 of NMT 10µm is proposed, based on the biobatch API lot, the QC limit in all cases should include limits for d10, d50 (as a range) and d90, based on the results of the API lot(s) used in the biobatch.

In addition, APIs determined to be *critically insoluble*[2] should be monitored for change in polymorph identity, as required (see above) and PSD during stability studies. That is, the proposed retest period/shelf life for the API should also be supported by PSD and polymorph identity results. Furthermore, these parameters should be included as retest parameters.

Retest/shelf life parameters should be indicated in the API specification of the FPP manufacturer.

Control of related substances in APIs and FPPs

Other commonly identified issues (mostly with regard to FPP specifications but also in relation to the FPP manufacturer's API specifications) were proposals for unacceptably wide limits for unspecified impurities. Some applicants incorrectly assume that pharmacopoeial monograph limits for any unspecified impurities, which in some cases may be higher than the ICH Q3A/Q3B identification thresholds, are also acceptable regulatory limits.

Except for some artemisinin derivative or fermentation APIs or FPPs containing such APIs, limits for any unspecified impurities should correspond to the ICH Q3A/Q3B identification threshold. If this limit cannot be met for a particular unidentified impurity, the impurity should be identified and controlled as follows: All identified impurities should be controlled to the ICH Q3A/Q3B qualification threshold. For any impurity that cannot be controlled to this limit, a higher limit should be qualified according to the guidance provided in section 3.2.S.3.2 of the generic guide (Annex 4, TRS970).

There should be a key below the API/FPP specifications that identifies specified impurities, at a minimum by chemical name. For any specified impurities that are also named in an officially recognized compendial monograph, this name should be included, e.g.:
Impurity A: <chemical name> = USP RC B = Ph.Eur. impurity H

[1] BCS low solubility APIs demonstrate dose solubility volume > 250 mL at one or more points across the physiological pH range (pH 1.2, 4.5, 6.8, plus the pKa if within the range of pH 1.2 to 6.8).
[2] Critically insoluble APIs demonstrate BCS low solubility (dose solubility volume > 250 mL) across the physiological pH range and require use of surfactant for dissolution testing of the FPP, e.g. lumefantrine or efavirenz.

Granulation processes

Inadequate or poorly defined end point for wet granulation process affected about 50% of the reviewed dossiers.

Regardless of the manufacturing process (direct compression, wet/dry granulation, etc.), the manufacturing process and controls proposed for production batches (detailed in the blank Batch Manufacturing Record, BMR) should be in agreement with the process and controls used in the manufacturing of the pivotal clinical batch(es) or biobatch. Differences, if any, should not normally be beyond those that can be attributed to scale differences, for example, slight changes to blending parameters.

To this end, differences should be highlighted and discussed in order to avoid further questions from the assessors. For this purpose, the table provided in section 2.3.R.2.1 of the QOS-PD should be used. Furthermore, statements such as “stop granulation when required consistency is achieved” are not acceptable as a means of end-point determination. As mentioned above, processes should be kept as close as possible to the process that was used for the clinical/biobatch.

Manufacturers are advised to use the following approaches:

1. ***When the proposed production batch size is the same as the biobatch size***

   The blank BMR for production batches should fully reflect the actual process parameters used for the biobatch, including mixing/addition amounts/times, speeds, amperage targets/limits etc. For example, if additional water and/or mixing were used for the biobatch, then the blank BMR should also require the same without statements such as “if required add additional water and mix…”. Similarly, if no additional water and/or mixing process were used then the blank BMR should not require the use of additional liquid or mixing.

2. ***When the proposed production batch size is larger than the biobatch size***

   The blank BMR instructions for manufacture of the production batches should be kept as close as possible to the process used for the biobatch. It is acknowledged that slight changes or a provision for use of additional water or mixing may be required to account for the scale difference. In this case, in addition to fully defining the parameters, manufacturers are requested to include chopper/impeller ampere or torque readings as a means of control, with provisional limits defined.

   The provisional limits should as much as possible reflect the observations recorded for the biobatch. The table provided in section 2.3.R.1.2 of the QOS-PD should be used for this purpose. Note that it is not acceptable to use the process validation of production batches as a means of establishing the parameters for scaled-up batches. Therefore, provisional settings and limits must be included in the blank BMR and it is understood that these will be validated and finalized during the process validation for production batches.

   Similarly, compression machine speeds should be defined in the BMR as *validated* or *to be validated* with ranges reflected in the process validation protocol. To this end, process validation protocols should also include a provision for machine speed challenge runs.

Hold times

Nearly all reviewed dossiers had one or more hold time related deficiencies.

Applicants should refer to the WHO guideline for *General guidance on hold-time studies* (Annex 3, TRS992). For purposes of prequalification, individual hold time of 30 days for intermediates such as final blend, core tablets and coated tablets can be proposed without submission of supporting data. Otherwise, the dossier should include data on at least one batch of the product. In addition, a cumulative hold time of not more than 90 days from dispensing to primary packaging should be set. All hold times should be specified in BMRs and section 2.3.P.3.4 of the QIS.

Proposals for a cumulative hold time of more than 90 days will need to be supported by accelerated and long-term stability data on the final product as packaged with tablets that have been held for the proposed cumulative hold time period, or a commitment should be provided to put such a batch in stability studies when manufactured. The FPP release specifications should be the measure for hold time studies, rather than the shelf life specifications.

Dissolution profiles and QC testing limits

Missing dissolution profiles and/or unacceptable limits affected nearly all the reviewed dossiers. Multimedia dissolution profile data on the biobatch is a critical reference data set that is used to support routine dissolution limits, successful process validation and future changes. Manufacturers are therefore requested to profile the biobatch in the standard three BCS pH media and in the routine medium, if the latter is different from the standard media. Dissolution profiles should be generated using the following dissolution conditions.

Media: pH 1.2, 4.5, 6.8 buffer (without surfactant), 900 ml or less, and in the routine medium (if different from the BCS media), 900 ml or less (unless justified).

Speed: Apparatus 1: 100rpm or less; Apparatus 2: 50rpm or less.

Time points: 5, 10, 15, 20, 30 for very rapid release products; 10, 15, 20, 30 and 45 minutes for rapid release products; otherwise 10, 15, 30, 45 minutes, etc.

The applicants should note that the 5-minute time point is critical for very rapidly releasing products, since this time point may be necessary to meet the three time points required for calculation of f2 values for future comparisons (for example, when future batches manufactured to support certain changes fail to achieve a release of more than 85% in 15 minutes as achieved with the biobatch). Appendix 1 of the main generic guideline (Annex 4, TRS 970) should be consulted.

Dissolution limits for QC testing should be established based on the performance of the biobatch, irrespective of limits specified in a pharmacopoeial monograph. The approach described in the EMA's reflection paper on the dissolution specification for generic oral immediate release products may be used. The acceptance criterion set based on the biobatch behaviour should then be used for stability studies. To this end, applicants are reminded to report stability results as individual (at least the range of individual values) and average values. In the case where the QC limit established based on the above approach could not be met during shelf life, stability samples can be dissolution profiled and similarity with the historical profile of the biobatch can be demonstrated. In this manner, an alternative QC limit based on the observed stability results could be proposed.

For profiles that do not achieve a mean release of 75% or more in 60 minutes, a two-tier limit is appropriate. For example, first tier limit at about 40% mean (with RSD ≤ 10%) release point, and a second-tier limit at about 75% or more release point, may be considered.

Note: Routine release and shelf life limits for products supported by BCS-based biowaiver should be as follows:

- FPPs containing BCS class 3 API (those that need to demonstrate very rapid release): NLT 80% (Q) in 15 minutes

- FPPs containing BCS class 1 API (those that need to demonstrate at least rapid release): NLT 80% (Q) in 30 minutes or tighter depending on the performance of the biowaiver test batch.

Control of moisture content in final blend and the FPP for solid oral products

Moisture content has several implications on manufacturability (e.g. smooth compression running) and on stability of the product. It should also be noted that the impact on product stability is not limited to facilitating potential degradation or microbial growth, but may also affect the product release characteristics. To this end, the following routine controls are required:

- Final blend, regardless of the method of manufacture (wet, dry granulation or blend for direct compression), should be controlled for optimal moisture content or loss on drying (LOD). The intermediate product specification for the final blend should include a limit (as a range), set based on levels recorded for the primary and/or process validation batches.

- The final product should also be tested for moisture or LOD at release and during stability studies. The test should be included in the release and shelf life specifications. The limit proposed for the shelf life specification should be based on the results observed during stability studies.

Process validation

About 60% of the reviewed applications had protocols deficient with regard to one or more of the following:

a) The protocol or signed commitment did not specify the type of validation as prospective;

b) Missing provision for monitoring/evaluation of process parameters used for the validation batches;

c) Missing provision for compression machine speed range validation;

d) Missing provision for dissolution profile comparison of each validation batch with the historical biobatch profile using the QC medium.

PQTm requires that process validation will be satisfactorily completed before any batch is released for supply (i.e. prospective validation). The process validation commitment and the proposed validation protocol should specify that validation will be completed prospectively.

Process validation protocols should also include a provision for monitoring process parameters for all critical steps, regardless of whether sampling occurs at each step. For example, although sampling at the wet granulation stage may not be required, the granulation parameters applied for the validation batches should be summarized and discussed in the protocol and the results should be captured in the validation report. Such monitoring may help in finalizing the granulation parameters for subsequent production batches.

Validation of compression/encapsulation stages should include robustness studies for the proposed machine speed range. Depending on the level of optimization performed during development pharmaceutics, a provision for validation of the proposed range for press pressure (tablet hardness range) should also be included.

A critical component of the evaluation of process validation data is comparison of the dissolution profile generated on the validation batches against the historical profile established for the biobatch. The validation batches should be profiled using 12 units in the routine medium (see also “Dissolution profiles and QC testing limits” above). The three validation batches should demonstrate similar profiles compared to the biobatch (i.e., meet similarity acceptance criteria) for the process validation to be deemed satisfactorily completed. Non-similar results should be investigated and immediately reported to WHO.

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