2.3 Manufacturing solid orals – common issues

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Assessor

Talk points

- PQ requirements (Manufacturing related) in brief
- Common manufacturing related issues and assessment tips
- BMR review

Review of manufacturing data

- Objective
  - To establish that the applicant has sufficient understanding and control over their product and its manufacturing attributes and therefore they will be able to produce commercial batches with consistent quality as the bio and stability batches.

Applicant's role

- Applicant should support the assessment by demonstrating what has been developed, established and what is proposed for commercial batches
  - Pre-formulation studies
  - Formulation and manufacturing process development-lab scale
  - Data on pilot/submission batches
  - Scale up information for production batches
  - Strategies for continuous monitoring of the process and the product

PQ requirements in brief

- Development information (3.2.P.2)- manufacturing related aspects:
  - API characterization: at minimum pH solubility profile, crystal forms, particle size distribution, hygroscopicity, sensitivity to moisture and high temperature environment and flow properties
  - Selection of appropriate excipients, and manufacturing process
  - Risk assessment and optimization of the formulation and process parameters
  - Scale up information (scale up to submission (BE/stability) batches and further to production batches)

PQ requirements in brief

- Information on proposed production size(s), batch quantities and corresponding processes (P.3.2 and P.3.3)
  - Proposed production size(s)- discrete scale should be identified
    - could be same as the scale used for submission/pilot scale batches or
    - a scale within 10 fold compared to BE batch, if BE batch was at least 100,000 units.
    - Sizes larger than 10 fold limit compared to biobatch requires additional considerations, including BE, process validation and stability
  - Details of the proposed process including equipment, process parameters, controls should be provided (with BMR)

PQ requirements in brief

- Information on control of critical processing steps (P.3.4)
  - In process controls (process parameters or quality control tests) and where applicable, their frequency should be identified and justified
  - Intermediate product controls (e.g. for final blend) should be provided and justified
  - Hold times applied for intermediate products should be identified and when necessary supported by stability data

PQ requirements in brief

- Process validation (3.2.P.3.5)
  - either a report on at least three consecutively manufactured batches of the largest proposed scale or protocol with a commitment to prospectively validate the process should be submitted
    - In rare cases, retrospective data may be considered for established products that are being manufactured at the same site proposed for PQ.
  - as well, uniformity of the biobatch should be demonstrated
    - Data on bend uniformity or uniformity of dosage units (by content uniformity)

PQ requirements in brief

- Executed and blank Batch manufacturing records should be submitted as part of 3.2.R.1
  - Executed record for bio and/or biowaiver batches
  - Blank BMRs for each proposed production batch size
  - Summaries discussing differences between submission batches and proposed production size batches
    - Formulation
    - Equipment
    - Process parameters

- Common issues and assessment tips

development information

- The depth of submitted development information may vary:
  - Information that provides minimal discussion – prepared only to meet regulatory expectation
  - Information based on long term manufacturing and marketing experience of the specific product or related formulation
  - In-depth information that provides sufficient insight in to the product and applicant's knowledge of the product
  - Enhanced development data that may include aspects of design space
- Depth of development information appears to depend on
  - product type
  - applicant's experience with SRA submissions and
  - whether the product is new to the applicant

development information

- Example: Incomplete information on API characterization
  - Assessment considerations:
    - Information may be publicly available, .e.g., hygroscopicity or light sensitivity
    - Some information might have been discussed in other sections, e.g. a discussion on selection of wet granulation or dry granulation process may reflect on flow properties of the API
    - Some may need to be requested, e.g. pH solubility profile, hygroscopicity, stress stability data

development information

- Example: Incomplete information on selection and optimization of formulation and processes
  - Assessment considerations:
    - Usually at the stage of initial review, BE is supported by data and there is certain level of process verification and stability data on pilot batches
    - There may also be indications that the product is not new to the applicant or they are using their experience acquired on a related product

Example contd

- Assessment approaches
  - If appropriate, invite applicant to support their dossier with annual product review report, other wise
  - Focus on certain areas that must be addressed, e.g. API-excipient compatibility, justification for use of organic solvents, e.g. in film coating; tablet score lines
  - Ensure that the manufacturing process for the BE and stability batches was sufficiently detailed in BMR and the proposed scale up BMR reflects the parameters applied for the biobatch with no or little changes.

development information

- Absence of discussion on differences between the formulation and manufacturing process proposed for production batches vs biobatch (and stability batches)
  - In any case, we do the comparison by ourselves and put our summary in the report
    - Focus is on ensuring that relevant steps have been adequately described and that these are inline with what were applied for the biobatch
    - BMR review to come ahead

Development

- Use of organic solvents in FPPs
  - The use of organic solvents (class 2 or 3) in FPP processes should be justified
    - Certain binders for wet granulation such as Shellac may require use of organic solvents
    - Certain low dose insoluble APIs may need to be dissolved in organic solvents to achieve a uniform blend
    - For conversion of crystalline API to amorphous mass with excipients
    - Organic solvents may also need to be used to disperse certain insoluble polymers for modified release coating
    - When the use is justified, residual levels in the FPP should be controlled according to ICHQ3C.
  - These days it would be difficult to justify use of organic solvents in film coating- specially ICH class 2 solvents

Manufacture

- Example: Certain aspects of the FPP mfg processes may be performed at the API site or contract site, e.g. Ritonavir premix
  - Assessment considerations:
    - Full information, including BMR and process validation report/protocol for the premixing step should be submitted
    - Hold time for the premix should be established and supported by stability data
    - Applicant may be reminded the requirement that counting of expiry date starts from the date the API was first mixed with the excipients
    - Applicant should also be informed that FPP GMP requirements apply

Manufacture

- Example: proposed production size batches are not clearly identified (e.g. proposal for range of batch sizes or failure to identify largest intended batch size)
  - Assessment considerations:
    - Ask for discrete batch sizes to be identified and each to be supported by blank BMR
    - Ask for identification of the largest proposed batch size and inform requirements
      - Blank BMR and comparison with the executed biobatch record
      - Process validation protocol and commitment for prospective validation
      - Stability commitment

Example contd

- In some cases, protocol for intermediate sizes may also need to be requested
  - as this batch size may be implemented ahead of the largest intended batch size
  - certain isolated steps, such as RMG granulation or blending, may represent a different scale than the one proposed for the largest intended batch size
    - The largest proposed scale may involve use of multiple granulation lots while the intermediate scale may use a single lot of larger size than the lots for the largest scale.

Manufacture

- Example: Inadequate or vague description of processing steps, e.g.,
  - use of undefined amount of granulating fluid, addition rate and/or mixing time
  - too wide melt extrusion parameters (e.g., feed rate range, zone temperature)
  - too wide compaction parameters (e.g., feed rate, roll pressure)
    - These affect the porosity, density, shape and size of granules- potential variation in release performance and/or manufacturability
    - May also affect product stability (degradation)
  - assessment considerations:
    - Ask parameters to be set in line with those used for the biobatch
    - Check whether the development information provides adequate justification for wider processing range or ask applicant to provide justification

Melt extrusion parameters

Melting API with excipients- extrude to form granules-
Crystalline forms of the API changes to an amorphous form-
increased solubility and dissolution

Parameters	In the blank manufacturing record	In the manufacturing record of Biobatch
Feed rate	Equipment 1: 12-18kg/hr Equipment 2: 40-60kg/hr	15Kg/hr
Main feeder speed	290-400 rpm	Set parameter 296 rpm, recorded: 296-301rpm
Side feeder speed	150-210 rpm	Set parameter 200 rpm, recorded: 200-201rpm
zone temperatures (Zone 3-8)	80°C-120°C	110 -120°C

Applicant was requested to revise the BMR or justify the wide range

Manufacture

- Common issues related to critical process controls, e.g.
  - Wide limits and frequency for in process controls
    - IPQC frequency should reflect the shortest run time expected- to ensure that at least at start, middle and end of run sampling is performed. Av wt /individual wt should be performed more frequently (typically every 30 minutes)
  - Absence of control of final blend moisture (or proposal to monitor an upper limit only)
    - Important to avoid flow and compressibility problems during compression/filling as well as for stability of the final product
  - Absence of routine test for blend uniformity for low active load products
    - Critical for low load products containing 5mg of the API or where the API constitutes less than 5% of the tablet/capsule fill wt.
  - Failure to declare hold times or proposing hold time with out relevant supporting stability data

Hold time

- Generally time taken for processing a solid product from first date of API-excipient mixing to primary packaging should not exceed 30 days, other wise
  - Hold time of more than 30 days for intermediates should be supported by stability data
    - Blends/granules: appearance, moisture content, assay and depending on the formulation, blend uniformity, MLT and on a case by case basis related substances
    - Core/coated tablets/Capsules: above tests plus dissolution /FPP release spec
    - Cumulative processing time until primary packaging should not exceed 90days

Manufacture

- Common issues related to process validation:
  - Proposal for concurrent validation protocol (or failure to identify the type of validation)
    - Validation on the three batches should be completed before batches are released for marketing (i.e., prospective validation)
  - Not all steps are monitored
    - e.g., wet granulation steps:- though the wet mass may not necessarily need to be sampled, the process parameters applied for the validation batches should be summarized and discussed
  - Insufficient sampling, e.g. during compression and capsule filling
    - Sampling points above and over the normal IPQC sampling should be set
  - Absence of speed challenge runs
    - Unless the impact of machine speed was verified on pilot batches

Process validation issues-contd

- Failure to subject final tablets for dissolution profile comparison against historical biobatch profile
  - One critical aspect of validation is to verify that the validation batches (and so future production batches) perform in similar way as the biobatch
- Failure to make necessary improvements to process parameters following completion of process validation
  - Post validation process parameters should be finalized, e.g. wet granulation parameters or blending parameters

More on BMR review- assessment focus

- Environmental controls (humidity and temperature) - whether these are specified in the BMR and whether they reflect the nature of the product manufactured
  - generally 20°C/ 40-60%RH; hygroscopic materials and capsules require lower RH% (usually around 40%)
- Standard batch quantities and dispensing records, whether they reflect the unit composition and actual biobatch quantities; whether formulae for compensating API quantities are correct
- Processing sequence, e.g. whether binder is added to the mix or separately prepared and whether this is inline with the biobatch record
- Process descriptions- are they clear and adequate to the production staff and to the assessor?

BMR review- assessment focus

- Major equipment are clearly identified at minimum by type, (e.g. octagonal blender) capacity, and ID in the BMR

- In process controls and their frequency are identified and whether these are acceptable.
  - Sometimes the BMR may refer to SOPs. In this case the summary of the tests, limits and frequency should at least be provided in the dossier section 3.2.P.3.3 or 3.2.P.3.4

BMR review- assessment focus

- How does the manufacturing process proposed for production batches compare with the process used for the biobatch (as well as stability batches)?
  - For this, we compare the blank and executed record for the biobatch
  - Comparison is mainly in terms of equipment (make, model, capacity) process descriptions and parameters as well as in process controls applied.
    - For the biobatch, actual applied parameters, as seen earlier, should be checked

BMR review- assessment focus

- Example of common issues that may be identified on comparing BMRs
  - Differences in equipment
  - Differing blending and lubrication parameters
  - Wide processing range compared to the actual parameter used for biobatch, as seen earlier
  - Unsolicited changes compared to previous reviewed BMR version (on reviewing response submission)

Differences should be explained and their impact understood. Note that since usually production batches are yet to be manufactured there may not be sufficient experience to justify differences

Lubrication/blending parameters

Biobatch	**Blank BMR**
Octagonal blender (400Lt)	Bin blender (1500Lt)
Blending: 15 minutes at 10rpm	Blending: 38 minutes at 04 rpm
Lubrication: 5 minutes at 10rpm	Lubrication: 13 minutes at 04rpm

What is the impact of the above differences on performance of Production batches relative to the biobatch?

- Thank you for your attention