

1-6 Specifications

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Outline

- Definition
- Why are specifications important?
- Setting appropriate specifications
- PQT-medicines approach
- Selected test parameters
- Common deficiencies



References

- PQ Generic Guideline – Quality Part
- ICH Q6A Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances
- ICH Q3A - Q3D: Impurities
- Ph Int, USP, BP, EP, JP (recognized pharmacopoeias in PQ)
- Other regulatory guidelines
- PQ internal guidelines



Definition: ICH Q6A

- A specification is *a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described.*
- A specification establishes the set of criteria or quality standards to which an API or FPP should conform to be considered acceptable for its intended use
- Implication: the API or FPP when tested according to the listed analytical procedures, will meet the acceptance criteria
- Proposed and justified by applicants and approved by NMRAs

Why are specifications important?

- Part of the total control strategy for the API and FPP designed to ensure product quality and consistency: at release and during shelf life
- To confirm the quality of the API/FPP rather than to establish full characterization
- Hence should focus on those characteristics considered useful in ensuring quality as well as safety and efficacy of the API/FPP
- **Note:** Though important, a specification is not the only component/strategy to be used

Setting appropriate specifications

- Product specifications should be appropriate to the product (formulation, route of administration, API, manufacture method etc.)
- Assessors need to be aware of the available literature on the API/FPP
- Important to check if the API or FPP is compendial i.e. monograph available in a recognized pharmacopoeia
- Past experience with the API or FPP. Have there been any concerns/issues in the past?
- Applicant must declare the standard to which the product complies

Setting appropriate specifications...

- Considerations:
- Method of manufacture: Manufacturing process specific impurities
 - Residual solvents
 - Inorganic impurities e.g. from catalysts
- Formulation: solid vs liquid, dispersible, IR
 - Microbial limits
 - Dissolution
 - Degradation products e.g. interaction of Isoniazid with lactose

Setting appropriate specifications...

- Route of administration: oral vs sterile
 - Sterility/microbial limits
 - Bacterial endotoxins
 - Particulate matter

- API(s) involved
 - Degradation products
 - Polymorphism e.g. low solubility API
 - Particle size distribution
 - Chirality – presence of chiral centres

PQT approach

- QOS PD: Contains a table for the applicant/assessor to fill details on the current status of API and FPP i.e. extract

Identify available literature references for the API and FPP:

Publication(s)	Monograph exists/does not exist/exists in other combination only	Most recent edition/volume consulted
API status in pharmacopoeias and fora:		
Ph.Int.	<e.g. Monograph exists>	<e.g. Ph.Int. 4 th Edition Suppl. 4>
Draft Ph.Int. monographs not yet published (through www.who.int)	<e.g. Draft monograph available> <e.g. No revised unpublished monograph>	<e.g. www.who.int as of June 2014>
USP	<e.g. Monograph exists>	<e.g. USP 38>
Pharmacopeial Forum	<e.g. API monograph in 34 (3), change to reference now reflected in current USP monograph>	<e.g. 40 (4) July-August 2014>

PQT approach...

- The information collected will assist an applicant or assessor to be aware of current standards and literature on the API or FPP
- Specifications are required to meet the minimum pharmacopoeial standards where a monograph exists and other requirements (ICH)
- Proposed tests and limits should be fully justified
 - Residual solvents: requirements of ICH Q3C
 - Impurities: Requirements of ICH Q3A/ICH Q3B
 - Dissolution: biolot profile
- Limits proposed should also take into account biobatch/primary batch results, manufacturing capability and stability results.

Universal tests

ICH Q6A:

- Description/appearance
- Identification
- Assay
- Impurities (organic, inorganic, etc.)



Specific tests - API

- Physicochemical properties e.g. pH, melting point etc.
- Particle size
- Polymorphic forms
- Chirality
- Water content
- Inorganic impurities
- Microbial limits

Specific tests - FPP

- Dissolution
- Disintegration (e.g. for dispersible tablets)
- Hardness/friability (chewable tablets, dispersible tablets)
- Uniformity of dosage units
- Water content
- Microbial limits
- Sterility (for parenteral products)



Specific tests – FPP...

- Endotoxins/pyrogens (for parenteral products)
- Particulate matter (for parenteral products)
- Reconstitution time e.g. dry powder for injection
- Redispersibility e.g. for suspensions
- Antioxidant/antimicrobial preservative content
- Rheological properties e.g. viscosity, specific gravity
- Particle size distribution e.g. for suspensions



Selected test parameters - API

- Identification
- Assay
- Polymorphism and particle size: for low solubility APIs
- Related substances
- Residual solvents

Identification test

- Identification should be specific to the API i.e. should be able to discriminate between compounds of closely related structure e.g. IR spectroscopy for the API, whenever possible.
- A single HPLC retention time is not regarded as being specific. Two chromatographic procedures, where the separation is based on different principles (HPLC + TLC) or combination of tests into a single procedure is generally acceptable, such as HPLC/MS, or GC/MS.
- Identification test for the salt, where applicable e.g. test for sulfate
- A test for optical rotation for chiral APIs

Polymorphism

- Important for low aqueous solubility APIs (DSV > 250 ml at any pH over the physiological pH range 1.2-6.8) e.g. Nevirapine, Efavirenz etc. with > 1 crystalline forms
- Necessary to ensure that polymorph of API batch used to manufacture the clinical batches is consistently manufactured/supplied
- Test should be in the specifications
- Polymorphic form should be monitored during stability and included as a retest parameter: ensure no polymorph changes
- Consult ICH 6A, Decision tree #4

Case study 1

- Nevirapine API: 3 polymorphs known – I, II, III
- Polymorphic form of API lot used in BE study – Form I, confirmed by XPRD
- Nevirapine has poor aqueous solubility
- Is polymorphic form control necessary in the specifications?
- Answer:
- Yes, Form I needs to be produced/supplied consistently

Ritonavir case

- Ritonavir was registered in 1996.
- After about two years, batches of FPP started failing their dissolution tests.
- Discovered that the polymorph had changed – Form II instead of Form I (metastable)
- Form II was the more stable form, hence had lower solubility
- Product had to be temporarily withdrawn until problem was solved

Particle size

- Important for low aqueous solubility APIs (DSV > 250 ml at any pH across physiological pH range) e.g. Efavirenz, Nevirapine, Artemether
- For these APIs, particle size can have a significant effect on dissolution rates, bioavailability, and / or stability.
- Appropriate test and limits included in the specifications based on results observed for API lot used to manufacture the biolot
- Micronized APIs: limits at d10, d50 & d90
- PSD should be monitored during stability. Also included as a retest parameter when insoluble over the entire physiological pH range
- Consult ICH 6A, Decision tree #3

Case study 2

- Nevirapine 200mg tablets
- BE study was done with batch manufactured with API lot with PSD results of D10: 1 μm ; D50: 5 μm ; D90: 17 μm
- Applicant proposes PSD limits only at D90 of NMT 25 μm ?
- Question: Is this approach satisfactory?
- Answer: No, you need limits also at d10 & d50 (as a range) as well

Related substances - API

- Process related or degradation products
- Appropriate test and limits should be included for
 - Specified (identified / unidentified)
 - Unspecified (individual unknowns)
 - Total related substances
- All the limits should be appropriately justified/qualified
- Take cognizance of ICH Q3A reporting, identification and qualification thresholds when setting limits
- Consult ICH Q6A, Decision tree #1

API impurity thresholds

- Based on maximum daily dose

Maximum Daily Dose ¹	Reporting Threshold ^{2,3}	Identification Threshold ³	Qualification Threshold ³
≤ 2g/day	0.05%	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
> 2g/day	0.03%	0.05%	0.05%

- Must be aware of the Total daily intake thresholds in addition to the % thresholds (the lower of the two)

Selected test parameters - FPP

- Assay
- Uniformity of dosage units
- Dissolution
- Related substances
- Residual solvents
- Water content
- Microbiological quality: sterility, microbial limits

Assay

- Specific, stability-indicating assay test in the specifications
- Non-specific assay methods (when justified) should be used with suitable test for impurities to achieve overall specificity e.g. titration for assay, HPLC for related substances.
- Tighter limits at release e.g. 95.0-105.0%.
- Wider limits may be accepted during shelf life e.g. 90.0-110.0%
- Monitored during stability



Uniformity of dosage units

- Critical especially for low dose formulations.
- PQP requirements aligned with those of the Ph. Int.
 - Content uniformity(CU): a test and limit for CU is required for each API present in the FPP at $< 5 \text{ mg}$ or $< 5\%$ of the weight of the dosage unit.
 - Mass uniformity: a test and limit for weight variation for API(s) present at $\geq 5 \text{ mg}$ and $\geq 5\%$ of the weight of the dosage unit
- Pharmacopoeial tests/limits would be accepted e.g. USP <905>
- Scored tablets: CU must also be demonstrated for half-tablets (one-time study) if CU is required for whole tablets and if half-tablet contains $< 5\text{mg}$ of the API. CU may be required for half-tablets for paediatric use even if $\geq 5 \text{ mg}$.



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Case study 3

- Ondansetron 8mg tablets, scored. Tablet weight 80mg
- CU in specifications? **No, API > 5% of tablet weight**
- One time CU for half tablet? **Yes, < 5mg**



Related substances - FPP

- Requirements for APIs also apply
- Take cognizance of ICH Q3B reporting, identification and qualification thresholds when setting limits
- API process impurities need not be controlled unless also a degradation product
- Should be monitored during stability
- Consult ICH Q6A, Decision tree #2



FPP impurity thresholds

- Based on maximum daily dose

Reporting Thresholds

<u>Maximum Daily Dose</u> ¹	<u>Threshold</u> ^{2,3}
≤ 1 g	0.1%
> 1 g	0.05%

Identification Thresholds

<u>Maximum Daily Dose</u> ¹	<u>Threshold</u> ^{2,3}
< 1 mg	1.0% or 5 µg TDI, whichever is lower
1 mg - 10 mg	0.5% or 20 µg TDI, whichever is lower
>10 mg - 2 g	0.2% or 2 mg TDI, whichever is lower
> 2 g	0.10%

Qualification Thresholds

<u>Maximum Daily Dose</u> ¹	<u>Threshold</u> ^{2,3}
< 10 mg	1.0% or 50 µg TDI, whichever is lower
10 mg - 100 mg	0.5% or 200 µg TDI, whichever is lower
>100 mg - 2 g	0.2% or 3 mg TDI, whichever is lower
> 2 g	0.15%

- Note: Total daily intake thresholds in addition to the % thresholds

What this means

Any impurity:

- > reporting threshold should be reported
- > Identification Threshold (IT) should be specified
- > Qualification Threshold (QT) should be qualified
- Unspecified (individual unknowns) \leq Identification threshold
- Critical to correctly establish thresholds

Qualification of impurity limits

Options: - adopt limit \leq QT or qualify, for specified impurities:

- Level present in a product used in safety and/or clinical studies (ICH Q3)
- Impurity known/confirmed to be a significant metabolite of the API (e.g. WHOPAR, EPAR, SmPC).
- Literature i.e. pharmacopoeial limits for specified related compounds are considered qualified; an unspecified/unknown limit in a monograph is not qualified.
- Limit supported by levels found in unstressed innovator product

Case study 4

- Ph. int. limits: Zidovudine 300 mg capsules, MDD 600 mg
- Ph. Int. Related substances statement: Impurity C NMT 3.0%....The area of **any other peak**, apart from the principal peak, is not greater than twice the area of the principal peak in the chromatogram obtained with solution (2) (**1.0%**)...Total NMT **4.0%**.
- Is limit of NMT 1.0% acceptable for any individual unknowns based on this Ph. Int. statement?

Case study 4

- No, limit of NMT 1.0% is not in line with ICH Q3B
- Acceptable limit is NMT 0.2%.
- Limit of NMT 3.0% for impurity C would be considered as qualified
- Total impurity limit: should be based on actual results observed
- Is NMT 1.0% appropriate for other impurities?
- Yes, for impurities A & B specified in this monograph

Dissolution

- Dissolution is considered product-specific: method and limits should be appropriate for the proposed product.
- Dissolution limits at release and shelf-life should be identical - provide confidence about release properties of the FPP
 - Expressed in terms of 'Q' – allows for 3 stage testing S1, S2 & S3
- Limits proposed should be meaningful – reflect dissolution profile results observed for biolot; must be in line with basis of biowaiver acceptance; not too wide as to be irrelevant
- May have limits at > 1 time points e.g. Artemether dissolution limits NLT 40% in 1 hour and NLT 60% in 3 hours

Dissolution....

- Limits appropriate to the formulation i.e. immediate release, delayed release, extended release etc.
- Test monitored during stability



Dissolution....

- Additional considerations required when there is a BCS-based biowaiver:
 - BCS Class 1 (e.g. emtricitabine, stavudine, zidovudine, levofloxacin, linezolid, ofloxacin): The test and comparator products must be at least rapidly dissolving (NLT 85% in 30 minutes)
 - BCS Class 3 (e.g. abacavir sulfate, lamivudine, ethambutol, isoniazid, pyrazinamide): The test and comparator products must be very rapidly dissolving (NLT 85% in 15 minutes).
- Dissolution limits must meet conditions for granting biowaiver.
- Consult ICH Q6A, Decision tree #7

Case study 5

- Pyrazinamide 500mg tablets. The applicant claimed USP standard for the product. API known to be BCS class III
- Product granted BCS-based biowaiver
- The applicant proposes the following dissolution limits:
 - Release NLT 80% in 45 minutes at release
 - Shelf life NLT 75% (Q) in 45 minutes
- Question: Would you consider limits acceptable?
- Why Yes/No?

Case study 5

- No. Because:
- BCS class 3 biowaiver condition: NLT 85% released in 15 minutes
- Q is missing from release limits: Q implies 3 stage testing
- Limits at release and shelf life not the same
- Hence limits should be NLT 80% (Q) in 15 minutes at release and during shelf life
- Note: USP limit: NLT 75% (Q) in 45 minutes

Other tests

- Residual solvents: Only a concern if organic solvents are used in the manufacturing process
 - Limits should be set in line with ICH Q3C requirements
- Water content or LOD: Test and limit when appropriate e.g. hygroscopic APIs, if film-coated. Monitored also during stability.
- Microbiological quality (sterility, microbial limits): Tests and limits should be established as appropriate based on formulation and route of administration (ICH Q6A Decision tree #8)

Common deficiencies

- Specification not version-controlled, not dated, not signed and no standard claimed/declared
- Tests and limits proposed not appropriate e.g. missing PSD limits for low solubility API, limits too wide etc.
- Officially recognized compendial standard exists and the proposed IH tests/limits do not meet minimum compendial standards
- Pharmacopoeial standard claimed not met by proposed tests/limits or equivalence of test methods not demonstrated
- References to test methods missing from the specifications



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- Thank you!

Questions?