Guideline

Guidelines for File Assessment for Pharmaceutical Products for Human Use.

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1. History Table

Date	Version Number	Summary of change
01/04/2021	**01/2021**	Initial Release
23/05/2024	**02/2024**	• Revision made as needed to align with current Eur. Ph and USP • Revision of limits of antioxidants in finished product specifications (Annex III) • Revision of testing of impurities (organic impurities and residual solvents) to be aligned with ICH Q6A, ICH Q3B and ICH Q3C and USP (Annex III) • Revision of method validation and verification requirements (Annex V) to be aligned with ICH Q2(R2) • Revision to formatting and other changes were made in all the document sections to provide policy clarification

2. Introduction:

The role of the NCL is integral to the oversight of the national regulatory authority, and its contribution encompasses an integrated chain of activities, throughout the lifecycle of a medical product. By virtue of its responsibility for the laboratory testing function as an NCL in the Egyptian Drug Authority, CADC's contribution is evident in the performance of various activities, including the evaluation and assessment of the quality part of product dossiers submitted to CADC, to provide technical and scientific input before marketing authorization is granted for a product, renewal of MA or re-registration, and post-approval variations.

EDA aims to strengthen its regulatory system and align itself with regulatory authorities recognized by the WHO and WLAs, to achieve harmonization with their regulatory practices, with the ultimate objective of ensuring the safety, efficacy and quality of those products To this end, and in alignment with EDA's strategic objectives, this guideline has been elaborated to regulate the technical assessment of documents included in the quality part of product dossiers, based on criteria adopted from ICH guidelines, FDA guidelines, WHO guidelines, as well as international pharmacopeias.

3. Scope

The guidelines detailed in this document apply to product files of finished pharmaceutical products for human use; both locally produced and imported, which have been submitted to CADC as part of proceedings for receiving marketing authorization (for new and generic drugs), for MA renewal/ re-registration, and for post-approval changes.

4. Abbreviations

4.1 CADC: Central Administration of Drug control.

4.2 CAO: Central Administration of Operations.

4.3 CAPP: Central Administration of Pharmaceutical Products.

4.4 EDA: Egyptian Drug Authority.

4.5 EA: Administration of Evaluation and Approval

4.6 EMA: European Medicine Agency

4.7 FDA: Food & Drug Administration.

4.8 MAH : Marketing authorization holder

4.9 PAC: Administration of Post Approval Control.

4.10 TAE: Administration of Technical Assessment and Evaluation.

5. Definitions

5.1 CADC: A Central Administration that was charged with the role of a NCL in EDA's organizational structure, and consists of: the General Administration of Technical Support, the General Administration of Quality Control Laboratories and the General Administration of Evaluation and Control

5.2 Finished Pharmaceutical Product: A finished dosage form of a pharmaceutical product is known to be the product that has undergone all production stages, including packaging in its final container and labeling.

5.3 Final report: a certificate of analysis of a pharmaceutical product that is issued from CADC, and includes the product specifications that have been approved for the marketing authorization of the product. The Final Report is attached to the product registration file archived in CADC.

5.4 Pharmacopeial product: A product that has the name of a pharmacopeia included as part of the product's trade name.

6. Main Topic

6.1 The manufacturer/ MAH is required to upload the requisite documents using the link specified on EDA's website upon application for laboratory testing.

6.2 Document review and technical assessment shall be performed by a delegated team of qualified reviewers.

6.3 The documents submitted for technical assessment fall under two categories:

6.3.1 Group I

Documents of products, which are either locally produced or imported, that have previously received MA, submitted to the Administration of Post Approval Control, for laboratory testing for purposes other than post approval changes/ variations.

6.3.2 Group II

Documents of products, which are either locally produced or imported, submitted for MA, MA renewal/re-registration or post approval variations.

6.4 Group I general rules:

6.4.1 Document review shall be carried out with reference to the Final Report previously issued by the EA for registration of the product, (or the updated specifications approved by TAE for approval of MA renewal, or the detailed final report issued by the PAC for approval of post variation changes, whichever is pertinent to the case).

6.4.1.1 In case the final report is not available, review will be according to product specifications approved by the General Administration for Stability in the CAPP.

6.4.1.2 If the stability specifications are not available, the manufacturer's specifications, coupled with a self-declaration that the submitted specifications are those approved for MA, shall be accepted.

6.4.1.3 In case there are no acceptance limits for one or more of the tests specified in the Final Report previously issued from CADC, the manufacturer/MAH is required to add the test limits to the product specifications according to the specifications approved by the General Administration for Stability in the CAPP or according to the pharmacopeia limits (USP, BP or EP), with no stipulation for the manufacturer to apply to CADC for modification of the previously issued Final Report.

6.4.1.4 The following tests need to be added, or if present, the acceptance limits need to be updated, if applicable to the dosage form:

- Dissolution rate test: acceptance limits shall be as listed in Annex I and detailed in Annex II
- Bacterial endotoxin: acceptance limits shall be according to pharmacopeial limits (USP, BP or EP), or according to Annex IV (Requirements for Microbiological Analysis, section 5)
- Particulate matter: acceptance limits shall be according to pharmacopeial limits (USP, BP or EP)

6.4.1.5 If the manufacturer/MAH wishes to amend (delete - add - change limits) for one of the tests, they are directed to the Administration of Variation in CAPP and the relevant rules and regulations must be applied.

6.4.1.6 When MA is renewed for a product, with updated product or package specifications, and where laboratory testing is not stipulated by the Administration of Variation or the Variation Committee for approval, the previously issued Final Report stands, and the updated specifications shall be attached to the product registration file archived in CADC for future reference.

6.4.2 Laboratory testing is performed according to the analytical methods that have been previously approved in CADC for MA, and that are attached to the product registration file archived in CADC. In case there are changes in the analytical method/s, the applicant is required to declare such change and upload the modified method accompanied with complete validation data (or verification, if pharmacopeial) and payment receipt via the link specified on the website for method update.

6.4.3 Imported FPPs for human use that are approved by one or more of the countries listed in the Technical Committee for Drug Control's list of reference countries may be considered for the reliance pathway, at the discretion of the applicant, whereby the applicant will submit the required documents via the link for imported pre-submission assessment.

6.4.4 Files for locally produced FPPs for human use may be submitted by the applicant via the link for pre-submission assessment.

6.4.5 The product assessment requirements are defaulted to a 'fulfilled' status in the following cases:

6.4.5.1 File submission within one year after the final report issuance from the EA administration.

6.4.5.2 Document review and fulfillment of requirements through pre-submission assessment, while adhering to the pre-specified validity period of the fulfillment and the deadlines for submission of samples.

6.5 Group II general rules:

6.5.1 Approvals and decisions issued by any of the scientific and technical committees of EDA shall be taken into account in the decision-making process in CADC

6.5.2 Whenever a pharmacopeia is used as a reference, this shall always refer to the most recent version thereof.

6.5.3 If there is a monograph for the finished product, and if the monograph specifies certain tests that are not stated in this guideline, the manufacturer/MAH should add those tests, or otherwise justify waiving those tests.

6.5.4 For new pharmaceutical drug products, a complete dissolution study with scientific justification should be submitted.

6.5.5 In other cases, complete comparative dissolution study in different media may be required.

6.5.6 In the case of imported FPPs for human use that are approved by one or more of the countries listed in the Technical Committee for Drug Control's list of reference countries:

6.5.6.1 The products are assessed and analyzed according to their specifications that have been previously approved by the reference country's NRA.

6.5.6.2 The products may be considered for the reliance pathway, at the discretion of the applicant, whereby the applicant will submit the required documents via the link for pre-submission assessment.

6.5.7 If the FFP is a pharmacopeial product, the manufacturer/MAH shall adhere to the tests and acceptance criteria stated in the product's monograph.

6.5.8 The products are assessed and analyzed according to shelf-life specifications.

6.6 General Rules

6.6.1 Composition

6.6.1.1 The reference specified in the product composition (BP, USP etc.) must comply with the registration license.

6.6.1.2 The function of inactive materials in product should be clarified according to Handbook of Pharmaceutical Excipients or any other reliable reference.

6.6.1.3 For a pharmacopeial API, it should comply with the latest version of the specified pharmacopoeia.

6.6.2 Calculation sheet:

6.6.2.1 There should be a separate calculation sheet to calculate equivalency of salt to the base.

6.6.2.2 For substances for which the potency is calculated as international units, the amount of the substance will be stated in the product composition in international units and

denoted with (*) and it should be clarified in the footer below the table that the amount used depends on the potency of the raw material.

6.6.3 Registration form

6.6.3.1 A full description of the package, concordant with the attached samples, should be stated.

6.6.3.2 The name of the manufacturer should be stated.

6.6.4 The finished product specification and certificate of analysis of production should contain the active material as stated in registration license and product composition.

6.6.5 In case of using updated method, the following shall be submitted

6.6.5.1 Full detailed method.

6.6.5.2 Complete validation or verification protocol and report.

6.6.5.3 Complete validation or verification charts.

6.6.5.4 Receipt of fees payment to change the method.

7 References

7.1 ICH Q6A - Specifications: Test procedures and acceptance criteria for new drug substances and new drug products: Chemical substances.

7.2 ICH Q2(R1) Validation of Analytical Procedures.

7.3 ICH Q3B(R2) Impurities in New Drug Products.

7.4 OMCL (Validation of Analytical Procedures PA/PH/OMCL (13) 82 2R)

7.5 Food and Drug Administration, “Methods, Method Verification and Validation”, Laboratory Manual, ORA Laboratory Procedure, Volume II, ORA-LAB.5.4.5

7.6 FDA Guidance for industry: Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances. AUGUST 2018

7.7 FDA guidance for industry: Dissolution Testing of Immediate Release Solid Oral dosage form

7.8 United States Pharmacopeial Convention Committee of Revision (Ed.), USP-NF Online (44th Ed.).

7.9 British Pharmacopoeia Commission. British Pharmacopoeia 2022.

7.10 WHO annex 6 Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part

8 Annexes

8.1 Annex I: Physical analysis

8.2 Annex II: Development for the in-house dissolution methods

8.3 Annex III: Chemical analysis

8.4 Annex IV: Microbiological analysis

8.5 Annex V: Submission of new file format in both group 1&2

Annex I

Requirements for Physical Analysis

File assessment for physical analysis of any dosage form will be performed according to the following tables:

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1. Tests performed on Aerosols (packaged under pressure):

Test	Applicability	Acceptance criteria
1. Description	All	According to manufacturer specifications
2. Net fill weight/ Minimum fill (USP) Procedure according to: USP-NF ⟨755⟩ Minimum Fill	All	USP-NF ⟨755⟩ Minimum Fill
3. Leak rate (USP) Procedure according to: USP-NF ⟨604⟩ Leak Rate	Perform this test on o Metered dose inhalation and nasal aerosols o Topical aerosols fitted with continuous valves	USP-NF ⟨604⟩ Leak Rate
4. Water content (USP) Procedure is according to: Manufacturer's method or specific monograph.	Inhalation and nasal aerosols.	According to manufacturer specifications
5. Valve delivery (shot wt test) (USP) Procedure according to: USP-NF ⟨5⟩ Inhalation and Nasal Drug Products—General Information and Product Quality Tests	Perform these tests only on inhalation and nasal aerosol (metered dose)	According to manufacturer specifications
6. No. of delivers per container (USP) Procedure according to: USP-NF ⟨603⟩ Topical Aerosol Ph. Eur. Monograph 0671	Perform this test for aerosols fitted with dose-metering valves.	According to manufacturer specifications
7. Delivery rate (USP) Procedure according to: USP-NF ⟨603⟩ Topical Aerosols	Continuous valve topical aerosols	According to manufacturer specifications
8. Delivered amount (USP) Procedure according to: USP-NF ⟨603⟩ Topical Aerosols	Continuous valve topical aerosols	According to manufacturer specifications
9. Droplet/Particle size Distribution by laser diffraction (USP) Procedure according to: USP-NF ⟨601⟩ Inhalation and Nasal Drug Products_ Aerosols, Sprays, and Powders—Performance Quality Tests	o Nasal aerosol suspension (particle size) o Nasal aerosol solution (droplet size)	According to manufacturer specifications

10. Aerodynamic particle size measurement (cascade impactor) (USP) Procedure according to: USP-NF ⟨601⟩ Inhalation and Nasal Drug Products_ Aerosols, Sprays, and Powders—Performance Quality Tests.	Inhalation aerosol	According to manufacturer specifications
11. Spray pattern/ Plume geometry (USP) **(Shape and size of evolving spray)** Procedure according to: USP-NF ⟨5⟩ Inhalation and Nasal Drug Products—General Information and Product Quality Tests	Nasal and inhalation aerosol	According to manufacturer specifications
12. Pressure test (pressure gauge) Procedure according to: USP-NF ⟨603⟩ Topical Aerosols	Continuous valve topical aerosols	According to manufacturer specifications

2. Tests performed on capsules:

Test	Applicability	Required Information	Acceptance criteria
1. Description: ○ **Appearance** ○ **Colour**	All	○ Capsule type: hard gelatin capsule/soft gelatin capsule ○ Capsule size ○ Colour of Cap: acc. to supplier. ○ Colour of body: acc. to supplier. ○ Colour of content (powder/pellet, liquid)	According to manufacturer specifications
2. Mass uniformity* (BP) Procedure according to: BP (Ph. Eur. method 2.9.5).	Done on capsule content. If the test for uniformity of content is prescribed or justified and authorized for all the active substances, the test for uniformity of mass is not required**.** *(Ph. Eur. monograph 0016)*		• Not more than 2 of the individual masses deviate from the average mass (actual) by more than the percentage deviation. • None deviate by more than twice that percentage. (Ph. Eur. method 2.9.5)
3. Disintegration (USP, BP) Procedure according to: USP-NF ⟨701⟩ Disintegration Ph. Eur. method 2.9.1	All		USP-NF ⟨701⟩ Disintegration Ph. Eur. method 2.9.1

4. Dissolution** Reference of method is chosen from one of the following: ○ USP or BP specific monograph. ○ FDA dissolution methods database. (submit comparative dissolution profile in the most suitable media) *** ○ In-house method Obey the dissolution method development criteria. Refer to (Annex II)	For all ○ Where a dissolution test is prescribed, a disintegration test may not be required. *(Ph. Eur. monograph 0016)* ○ Disintegration could substitute dissolution as a performance test if a justification submitted by the manufacturer that it obeys the ICH Q6A guidelines. <u>In this case, the performed dissolution method should be supplied by the manufacturer</u>.	• <u>Dissolution Parameters</u>: ○ Filter type (common types Nylon, PVDF & PTFE) ○ Media composition & pH ○ Media volume ○ Apparatus type ○ RPM ○ Temperature ○ Sinkers needed (common type: coiled sinker) ○ Sampling time ○ Q (the amount dissolved)	USP-NF ⟨711⟩ Dissolution Ph. Eur. Method 2.9.3
5. Water content (USP) Procedure is according to: Manufacturer's method or specific monograph.	If not stated by manufacturer: Needs justification to skip test		According to manufacturer specifications
6. Acid-neutralizing capacity (USP) Procedure according to: USP-NF ⟨ 301⟩ Acid neutralizing capacity	Antacids only		According to manufacturer specifications USP-NF ⟨ 301 ⟩ Acid- Neutralizing Capacity

* Average weight could be considered if needed as IPC USP-NF (1163) Quality assurance in pharmaceutical compounding.
** In case of locally acting API (not systemically absorbed), dissolution rate test may not be done and disintegration time is sufficient.
*** Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action EMA/CHMP/CVMP/QWP/336031/2017 may be referred to as guidance.

3. Tests performed for creams, gels & ointments:

Test	Applicability	Required Information	Acceptance criteria
1.Description: ○ **Appearance** ○ **Colour** ○ **Homogeneity** ○ **Visible foreign matter**	All		According to manufacturer specifications
2.Minimum fill (USP) Procedure according to USP-NF ⟨755⟩ Minimum Fill	For single and multiple dose units N.B. In case of single unit containers where the test for content uniformity is applied, the test for minimum fill is not required. *USP-NF ⟨3⟩ Topical And Transdermal Drug Products-Product Quality Tests)*		USP-NF ⟨755⟩ Minimum Fill
3.pH Procedure according to Manufacturer's method.	○ O/W cream ○ Aqueous gel ○ Hydrophilic ointment Generally: it is Formulation dependent. According to manufacturer specifications Because some topically applied drug products contain very limited quantities of water or aqueous phase, pH measurements may not always be warranted.	• Kind of product ○ Hydrophilic or ○ Lipophilic • Preparation method to perform measurement: ○ Solvent ○ Percent of dilution	According to manufacturer specifications
4. Apparent viscosity Procedure according to manufacturer's method: Viscosity–Capillary Methods USP NF ⟨911⟩, Viscosity–Rationale Methods USP-NF ⟨912⟩, and Viscosity–Rolling Ball Method USP-NF⟨913⟩	All	○ Type of device (model) ○ Device subtype ○ Spindle no. ○ RPM ○ Temperature	According to manufacturer specifications
5.Water content (USP) Procedure is according to: Manufacturer's method or specific monograph.	If not stated by manufacturer: Need justification to skip test		According to manufacturer specifications
6. Particle size (BP) Procedure is according to: (Ph.Eur.1163) using microscope.	Semi-solid ophthalmic preparations containing dispersed solid particles.		• Not more than 20 particles have a maximum dimension greater than 25 µm, and not more than 2 of these particles have a maximum dimension greater than 50 µm. • None of the particles has a maximum dimension greater than 90 µm. (Ph.Eur.1163)

4. Tests performed on emulsions:

Test	Applicability	Acceptance criteria
1.Description: ○ **Appearance** ○ **Colour** ○ **Viscous or not**	All	According to manufacturer specifications
2.Minimum fill Procedure according to USP-NF ⟨755⟩ Minimum Fill	○ Vaginal emulsion, ○ Rectal emulsion, ○ Ophthalmic emulsion, ○ Otic emulsion. ○ Topical emulsion.	USP-NF ⟨755⟩ Minimum Fill
3.Deliverable volume Procedure according to: USP-NF ⟨698⟩ Deliverable Volume	Oral emulsions (labeled volume should be known)	USP-NF ⟨698⟩ Deliverable Volume
4.pH Procedure according to: Manufacturer's method.	Hydrophilic emulsions (o/w) It is formulation dependent, according to manufacturer specifications.	According to manufacturer specifications
5.Specific gravity/viscosity - Procedure of specific gravity according to USP-NF ⟨841⟩ - Procedure of viscosity according to manufacturer's method: Viscosity–Capillary Methods USP-NF⟨911⟩ Viscosity–Rationale Methods USP-NF⟨912⟩, and Viscosity–Rolling Ball Method USP-NF⟨913⟩	○ Relatively viscous emulsions ○ Ophthalmic emulsion ○ Topical emulsion ○ Otic emulsion ○ Oral emulsion	According to manufacturer specifications
6.Uniformity of mass of delivered doses from multi-dose containers (BP) Procedure is according to: Ph. Eur. Method 2.9.27	Oral emulsions which are supplied in multi-dose containers provided at manufacture with a measuring device.	• Not more than 2 of the individual masses deviate from the average mass by more than 10 per cent • None deviates by more than 20 %. (Ph. Eur. method 2.9.27)
7.Uniformity of dose of oral drops (BP) Procedure according to: Liquid Preparations for Oral Use, Ph. Eur. monograph 0672.	Oral drops only	Liquid Preparations for Oral Use, Ph. Eur. monograph 0672
8.Container content for injection (USP)/ Extractable volume (BP). Procedure is according to: USP-NF ⟨697⟩ Container Content For Injections	Parenteral emulsion	USP-NF ⟨697⟩ Container Content For Injections
9. Globule size	○ Ophthalmic emulsion ○ Parenteral emulsion	According to manufacturer specifications
10.Osmolality Procedure according to USP-NF ⟨785⟩ Osmolality and Osmolarity	○ Ophthalmic emulsion ○ Parenteral emulsion	According to manufacturer specifications
11. Container–closure integrity	Parenteral emulsions	Package Integrity Leak Test Technologies ⟨1207.2⟩, Package Seal Quality Test Technologies ⟨1207.3⟩

5. Tests performed on films:

Test	Applicability	Required Information	Acceptance criteria
1.Description: ○ **Appearance** ○ **Dimensions**	All		According to manufacturer specifications
2.Dissolution Reference of method is one of the following: ○ USP or BP specific monograph. ○ FDA dissolution methods database (submit comparative dissolution profile in the most suitable media) ○ In-house method (submit comparative dissolution profile in the most suitable media)	All	• <u>Dissolution Parameters:</u> ○ Filter type (common types Nylon, PVDF & PTFE) ○ Media composition & pH ○ Media volume ○ Apparatus type ○ RPM ○ Temperature ○ Sampling time ○ Q (the amount dissolved)	USP-NF ⟨711⟩ Dissolution Ph. Eur. method 2.9.3
3. Water content (USP) Procedure is according to manufacturer's method or specific monograph.	If not stated by manufacturer: Need justification to skip the test.		According to manufacturer specifications.

6. Tests performed on foams:

Tests	Applicability	Acceptance criteria
1.Description **Physical appearance (of the foam and of the collapsed foam) (USP)**	All	According to manufacturer specifications
2.Net fill weight/ Minimum fill (USP) Procedure according to: USP-NF ⟨755⟩ Minimum Fill	All	USP-NF ⟨ 755⟩ Minimum Fill
3.Leak rate (USP) Procedure according to: USP-NF ⟨604⟩ Leak Rate	All	USP-NF ⟨604⟩ Leak Rate
4.pH Procedure according to: Manufacturer's method.	For the collapsed foam It is a formulation dependent, according to manufacture specifications	According to manufacturer's specifications
5.Relative Foam density (USP, BP) Procedure according to: USP-NF ⟨607⟩ Pharmaceutical Foams Product Quality Tests.	Topical	According to manufacturer's specifications
6.Time to Break (USP) Procedure according to: USP-NF ⟨607⟩ Pharmaceutical Foams Product Quality Tests.	Topical	According to manufacturer's specifications
7.Delivery rate (USP) Procedure according to: USP-NF ⟨603⟩Topical Aerosols	Topical	According to manufacturer's specifications
8.Delivered amount (USP) Procedure is according to: USP-NF ⟨603⟩Topical Aerosols.	Topical	According to manufacturer's specifications
9. Water content (USP) Procedure according to: Manufacturer's method or specific monograph.	If not stated by manufacturer : Need justification to skip the test	According to manufacturer's specifications
10. Osmolality Procedure according to: USP-NF ⟨785⟩ Osmolality and Osmolarity	If applicable and the product labeled with certain tonicity	According to manufacturer's specifications
11. Pressure test (USP)	All	According to manufacturer's specifications

7. Tests performed on granules:

Test	Applicability		Required Information	Acceptance criteria
	Granule Type	Done/ Not Done		
1. Description: ○ **Appearance** ○ **Colour** ○ **Visual Clarity (for solution of granules after reconstitution).**	All		○ Colour of Granules ○ Solution or suspension after reconstitution (with certain viscosity or not)	According to manufacturer specifications
2. Deliverable volume (USP) Procedure according to: USP-NF ⟨698⟩ Deliverable Volume	Only oral granules for reconstitution (after reconstitution) in: ○ Multiple dose container ○ Single dose container Not done for granules that are administered with food or beverages**.**	 ○ Yes ○ Yes	Labeled volume	USP-NF ⟨ 698⟩ Deliverable Volume
3. Minimum fill (USP) Procedure according to: USP-NF ⟨755⟩ Minimum Fill	○ Granules for oral suspension packaged in containers (where test of deliverable volume is applicable). ○ Other multiple dose granules.	○ No ○ Yes	Labeled amount	USP-NF ⟨755⟩ Minimum Fill
4. Uniformity of Weight (Mass) of Delivered Doses from Multi-dose Containers (BP) Procedure according to: Ph. Eur. Method 2.9.27	Oral granules which are supplied in multi-dose containers provided at manufacture with a measuring device.			• Not more than 2 of the individual masses deviate from the average mass by more than 10 %. • None deviates by more than 20 %. (Ph. Eur. method 2.9.27)
5. Mass uniformity* (BP) Procedure according to: Ph. Eur. method 2.9.5	○ Uncoated single dose granules ○ Coated granules ○ Multiple dose granules If the test for uniformity of content is prescribed or justified and authorized for all the active substances, the test for uniformity of mass is not required. (*Ph. Eur. monograph 1165*)	○ Yes ○ No ○ No		• Not more than 2 of the individual masses deviate from the average mass (actual) by more than the percentage deviation. • None deviates by more than twice that percentage. (Ph. Eur. method 2.9.5)

6. Dissolution** Reference of method is chosen from one of the following: ○ USP or BP specific monograph. ○ FDA dissolution methods database (submit comparative dissolution profile in the most suitable media). ○ In-house method (submit comparative dissolution profile in the most suitable media)	Granules that result in an oral suspension.	• Dissolution Parameters: ○ Filter type (common types Nylon, PVDF & PTFE) ○ Media composition & pH ○ Media volume ○ Apparatus type ○ RPM ○ Temp ○ Sampling time ○ Q (the amount dissolved)	Ph. Eur. method 2.9.3 USP NF ⟨1711⟩ Oral Dosage Forms- Performance Tests. USP NF ⟨711⟩ Dissolution
7. Disintegration (USP, BP) Procedure according to: USP-NF ⟨701⟩ Disintegration (Ph. Eur. method 2.9.1)	Effervescent granules		USP-NF ⟨701⟩ Disintegration Ph. Eur. method 2.9.1
8. Water content (USP) Procedure is according to manufacturer's method or specific monograph.	If not stated by manufacturer: Need justification to skip test		According to manufacturer specifications
9. pH (USP) Procedure is according to Manufacturer's method.	For reconstituted granules (after reconstitution). Except granules that are administered with food or beverages. Formulation dependent, according to manufacturer specifications		According to manufacturer specifications
10. Suspendability (USP)	For suspension after reconstitution		According to manufacturer specifications

11. Uniformity of dose of oral drops (BP) Procedure according to: Liquid Preparations for Oral Use, Ph. Eur. monograph 0672.	For granules intended to give oral drops after reconstitution.		Liquid Preparations for Oral Use, Ph. Eur. monograph 0672
12. Specific gravity/Viscosity - Procedure of specific gravity according to: USP- NF ⟨841⟩ Specific Gravity - Procedure of viscosity according to the manufacturer's method.: Viscosity-Capillary Methods USP-NF ⟨911⟩, Viscosity-Rotational Methods USP-NF⟨912⟩, and Viscosity-Rolling Ball Method USP-NF⟨913⟩	For relatively viscous reconstituted suspensions (after reconstitution) o Ophthalmic o Nasal o Inhalation o Topical o Otic o Oral		According to manufacturer specifications
13. Acid neutralizing capacity (USP) Procedure according to: USP-NF ⟨ 301 ⟩ Acid-Neutralizing Capacity	For antacids		According to manufacturer specifications

* Average weight could be considered if needed as IPC USP-NF (1163) Quality assurance in pharmaceutical compounding.

** In case of locally acting API (not systemically absorbed), dissolution rate test may not be done.

8. Tests performed on lozenges:

Test	Applicability		Information should be available	Acceptance criteria
	Lozenge type	Done/ Not Done		
1.Description: ○ **Appearance** ○ **Colour** ○ **Molded or compressed**	All		○ Lozenge shape ○ Color ○ Biconvex/flat	According to manufacturer specifications
2.Mass uniformity*	○ Molded ○ Compressed	○ Yes ○ Yes		According to manufacturer specifications
3.Water content (USP) Procedure is according to: Manufacturer's method or specific monograph.	If not stated by manufacturer: Need justification to skip test			According to monograph or manufacturer's specifications
4. Dissolution Reference of method is chosen from one of the following: ○ USP or BP specific monograph. ○ FDA dissolution methods database FDA dissolution methods database (submit comparative dissolution profile in the most suitable media). ○ In-house method (submit comparative dissolution profile in the most suitable media)	○ Molded ○ Compressed for local effect ○ Compressed for systemic effect	○ No ○ No ○ Yes	• <u>Dissolution Parameters:</u> ○ Filter type (common types Nylon, PVDF & PTFE) ○ Media composition & pH ○ Media volume ○ Apparatus type ○ RPM ○ Temp ○ Sampling time ○ Q (the amount dissolved)	USP-NF ⟨711⟩ Dissolution Ph. Eur. method 2.9.3
5.Friability (USP & BP) ** Procedure is according to: USP-NF ⟨1216⟩ Tablet Friability BP (Ph. Eur. method 2.9.7)	○ Molded ○ Compressed	○ No ○ Yes		USP-NF ⟨1216⟩ Tablet Friability BP (Ph. Eur. method 2.9.7)
6.Hardness (USP& BP)**	○ Molded ○ Compressed	○ No ○ Yes		According to manufacturer's specifications

*Average weight could be considered if needed as IPC USP-NF (1163) Quality assurance in pharmaceutical compounding.
** Not mandatory if done as in-process control

9. Tests performed on powders:

Test	Applicability		Required Information	Acceptance criteria
	Powder Type	Done/ Not Done		
1.Description: ○ **Appearance** ○ **Colour** ○ **Visual Clarity (for solution of powder after reconstitution).**	All		Colour of ○ Powders ○ Solution or suspension after reconstitution with certain viscosity or not	According to manufacturer specifications
2.Minimum fill (USP) Procedure according to USP- NF ⟨755⟩ Minimum Fill	○ Powders for oral suspension packaged in containers (where test of deliverable volume is applicable). ○ Other multiple dose powders. ○ Powder for inhalation (device metered)	○ No ○ Yes ○ Yes	Labeled amount	USP-NF ⟨755⟩ Minimum Fill
3.Deliverable volume (USP) Procedure according to USP-NF ⟨ 698⟩ Deliverable Volume	Only <u>oral</u> powders for reconstitution (after reconstitution) in: ○ Multiple dose container ○ Single dose container	○ Yes ○ Yes	Labeled volume	USP-NF ⟨698⟩ Deliverable Volume
4.Uniformity of Weight (Mass) of Delivered Doses from Multi-dose Containers (BP) Procedure according to: (Ph.Eur. method 2.9.27)	Oral powders which are supplied in multi-dose containers provided at manufacture with a measuring device. (Done for all doses)			• Not more than 2 of the individual masses deviate from the average mass by more than 10 per cent. • None deviates by more than 20 %. (Ph. Eur. method 2.9.27)

5. Mass uniformity* (BP) Procedure according to: (Ph. Eur. method 2.9.5).	○ Single dose powders ○ Powders for parenteral administration (single dose) ○ Powders for eye-drops and powders for eye lotions (single-dose) ○ If powder for parenteral administration average mass ≤40 mg If the test for uniformity of content is prescribed or justified and authorized for all the active substances, the test for uniformity of mass is not required**.** *(Ph. Eur. monograph 1165)*	○ Yes ○ Yes ○ Yes ○ No		• Not more than 2 of the individual masses deviate from the average mass (actual) by more than the percentage deviation • None deviates by more than twice that percentage. (Ph. Eur. method 2.9.5)
6. Disintegration Procedure according to: BP (Ph. Eur. Monograph 1165)	Effervescent powders			BP (Ph. Eur. monograph 1165)
7. Dissolution** Reference of method is chosen from one of the following: ○ USP or BP specific monograph. ○ FDA dissolution methods database (submit comparative dissolution profile in the most suitable media). ○ In-house method (submit comparative dissolution profile in the most suitable media)	o Powder reconstituted to form oral suspension unless otherwise justified). o Powder reconstituted to form sustained ophthalmic or parenteral suspension.	○ Yes ○ Yes	• <u>Dissolution Parameters:</u> ○ Filter type (common types Nylon, PVDF & PTFE) ○ Media composition & pH ○ Media volume ○ Apparatus type ○ RPM ○ Temp ○ Sampling time ○ Q (the amount dissolved)	USP-NF ⟨711⟩ Dissolution Ph. Eur. method 2.9.3

8. Water content (USP) Procedure according to: Specific monograph or manufacturer in house method.	If not stated by manufacturer: Need justification to skip test		According to manufacturer specifications
9. Reconstitution time (USP) Procedure according to USP-NF ⟨5⟩ Inhalation And Nasal Drug Products - General Information And Product Quality Tests	Powder for inhalation solution.		According to manufacturer specifications
10. pH (USP) Procedure according to Manufacturer's method.	For reconstituted powders (after reconstitution).		According to manufacturer specifications USP NF ⟨2⟩ Oral Drug Products—Product Quality Tests
11. Particulate matter Procedure is according to USP- NF ⟨788⟩ Particulate Matter In Injections. USP-NF ⟨789⟩ Particulate Matter In Ophthalmic Solutions	Powder and lyophilized powders for parenteral solutions and intra/extra ocular injections.		USP-NF ⟨788⟩ Particulate Matter in Injections for Extra-ocular solutions for injections and for parenteral solutions USP-NF ⟨789⟩ Particulate Matter in Ophthalmic Solutions for intra-ocular solutions for injections
12. Completeness of solution after reconstitution Procedure is according to -USP-NF ⟨5⟩ Inhalation And Nasal Drug Products— General Information And Product Quality Tests. -USP-NF ⟨1⟩ Injections And Implanted Drug Products (Parenteral)- Product Quality Tests.	Powder for parenteral solution		USP-NF ⟨5⟩ Inhalation And Nasal Drug Products— General Information And Product Quality Tests. USP-NF ⟨1⟩ Injections And Implanted Drug Products (Parenteral)- Product Quality Tests
13. Suspendability	For suspension after reconstitution		According to manufacturer specifications

14. Powder fineness (BP) Procedure is according to Sieve test BP 2.9.35	Topical powder	Done if prescribed (stated in the monograph or by manufacturer)		BP 2.9.35
15. Uniformity of dose of oral drops (BP) Procedure according to: Liquid Preparations for Oral Use, Ph. Eur. monograph 0672	For powders intended to give oral drops after reconstitution.			Liquid Preparations for Oral Use, Ph. Eur. monograph 0672
16- Specific gravity/Viscosity - Procedure of specific gravity according to USP-NF ⟨841⟩ - Procedure of viscosity according to manufacturer's method: Viscosity–Capillary Methods USP-NF⟨911⟩ Viscosity–Rationale Methods USP-NF⟨912⟩, and Viscosity–Rolling Ball Method USP-NF⟨913⟩	For reconstituted powder (after reconstitution) ○ Ophthalmic, ○ Nasal, ○ Inhalation ○ Topical, ○ Otic and Oral			According to manufacturer specifications
17-Acid-neutralizing capacity (USP) Procedure according to: USP-NF ⟨ 301 ⟩ Acid- Neutralizing Capacity	For antacids			According To Manufacturer Specifications.
18- Particle size distribution*** Procedure according to USP-NF ⟨601⟩ Inhalation and Nasal Drug Products_ Aerosols, Sprays, and Powders—Performance Quality Tests	Powder for reconstitution to give parenteral suspension			According To Manufacturer Specifications.
19. Aerodynamic size distribution (cascade impactor, Marple Miller Impactor) Procedure according to USP-NF ⟨601⟩ Inhalation and Nasal Drug Products_ Aerosols, Sprays, and Powders—Performance Quality Tests	Inhalation powder			According to manufacturer specifications

20. Plume Geometry Procedure according to USP-NF ⟨5⟩ Inhalation and Nasal Drug Products— General Information and Product Quality Tests	Nasal powder	If device is pump- dependent		According to manufacturer specifications

* Average weight could be considered if needed as IPC (USP-NF (1163) Quality assurance in pharmaceutical compounding).

** In case of locally acting API (not systemically absorbed), dissolution rate test may not be done.

*** Particle size distribution testing may be proposed in place of dissolution testing, when development studies demonstrate that particle size is the primary factor influencing dissolution; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and / or lower particle size limits should be well defined.

10. Tests performed on solutions:

Test	Applicability	Acceptance criteria
1.Description: ○ **Appearance** ○ **colour** ○ **Visual foreign matter** ○ **Viscous or not.**	All	According to manufacturer specifications
2.Minimum fill Procedure according to USP-NF ⟨755⟩ Minimum Fill	○ Nasal solution ○ Inhalation solution, ○ Vaginal solution, ○ Rectal solution, ○ Ophthalmic solution ○ Otic solution. ○ Topical solution.	USP-NF ⟨755⟩ Minimum Fill
3.Mass uniformity (BP) Procedure is according to Ph. Eur. Monograph 0671	Single-dose inhalation solutions	Ph. Eur. monograph 0671
4.pH	Aqueous solutions: it is formulation dependent, according to manufacturer specifications.	According to the manufacturer specifications
5. Specific gravity/Viscosity -Procedure of specific gravity according to: USP-NF ⟨841⟩ Specific Gravity -Procedure of viscosity according to manufacturer's method: Viscosity—Capillary Methods USP-NF ⟨911⟩, Viscosity-Rotational Methods USP-NF⟨912⟩, and Viscosity- Rolling Ball Method USP-NF⟨913⟩	○ Ophthalmic solution ○ Nasal solution ○ Inhalation solution ○ Topical solution ○ Otic solution ○ Oral solution	According to manufacturer specifications
6.Particulate and foreign matter Procedure is according to USP-NF ⟨788⟩ Particulate Matter In Injections. USP-NF ⟨789⟩ Particulate Matter In Ophthalmic Solutions.	○ Extra and intraocular solutions for injections ○ Parenteral solutions	USP-NF ⟨788⟩ Particulate Matter In Injections for Extra-ocular solutions for injections and for parenteral solutions USP-NF ⟨789⟩ Particulate Matter In Ophthalmic Solutions for intra-ocular solutions for injections

7.Uniformity of mass of delivered doses from multi-dose containers (BP) Procedure is according to Ph. Eur. method 2.9.27	Oral solutions which are supplied in multi-dose containers provided at manufacture with a measuring device. (Done for all doses)	• Not more than 2 of the individual masses deviate from the average mass by more than 10 per cent and none deviates by more than 20 %. *(Ph. Eur. method 2.9.27)*
8. Uniformity of dose of oral drops (BP) Procedure is according to Liquid Preparations for Oral Use, Ph. Eur. monograph 0672	Oral drops only	Liquid Preparations for Oral Use, Ph. Eur. monograph 0672
9. Deliverable volume Procedure is according to USP-NF ⟨698⟩ Deliverable Volume	Oral solutions	USP-NF ⟨698⟩ Deliverable Volume
10. Container content for injection (USP) Procedure is according to USP-NF ⟨697⟩ Container Content For Injections	Parenteral solution	USP-NF ⟨697⟩ Container Content For Injections
11. Osmolality Procedure according to USP-NF ⟨785⟩ Osmolality and Osmolarity	○ Inhalation solutions ○ Ophthalmic solutions ○ Parenteral solutions ○ Nasal solutions	According to manufacturer specifications
12. Container–closure integrity	Parenteral solutions	Package Integrity Leak Test Technologies ⟨1207.2⟩, Package Seal Quality Test Technologies ⟨1207.3⟩

11. Tests performed on sprays (non-pressurized liquid):

Test	Applicability	Acceptance criteria
1. Description	All	According to manufacturer specifications
2. Mass uniformity* (BP) Procedure is according to Ph. Eur. monograph 0676 Ph. Eur. monograph 1807) If the test for uniformity of content is prescribed or justified and authorized for all the active substances, the test for uniformity of mass is not required. *(Ph. Eur. monograph 1807)*	○ Metered-dose nasal sprays. ○ Metered dose oro-mucosal sprays and sublingual sprays that are solutions.	Ph. Eur. monograph 0676 Ph. Eur. monograph 1807 The preparation complies with the test if maximum 2 of the individual values deviate by more than 25% from the average value and none deviates by more than 35 per cent.
3. Net fill weight/ Minimum fill (USP) Procedure according to USP-NF ⟨755⟩ Minimum Fill	All	USP-NF ⟨755⟩ Minimum Fill
4. Pump delivery (shot wt test) (USP) Procedure according to USP-NF ⟨5⟩ Inhalation and Nasal Drug Products—General Information and Product Quality Tests	Nasal sprays (metered dose)	According to manufacturer specifications
5. pH Procedure is according to : Manufacturer's method.	Formulation dependent, according to manufacturer specifications	According to manufacturer specifications
6. Specific gravity / Viscosity -Procedure of specific gravity according to: USP-NF ⟨841⟩ Specific Gravity - Procedure of viscosity according to the manufacturer's method: Viscosity—Capillary Methods USP-NF ⟨911⟩, Viscosity— Rotational Methods USP- NF⟨912⟩, and Viscosity— Rolling Ball Method USP-NF⟨913⟩	For Nasal spray (Formulation dependent, according to manufacturer specifications)	According to manufacturer specifications
7. Droplet/Particle size distribution by laser diffraction. Procedure according to USP-NF ⟨601⟩ Inhalation and Nasal Drug Products_ Aerosols, Sprays, and Powders—Performance Quality Tests	○ Nasal spray suspension (particle size) ○ Nasal spray solution (droplet size)	According to manufacturer specifications

8. Aerodynamic particle size measurement (cascade impactor) (USP) Procedure according to USP-NF ⟨601⟩ Inhalation and Nasal Drug Products_ Aerosols, Sprays, and Powders-Performance Quality Tests	Inhalation spray only	According to manufacturer specifications
9.Osmolality Procedure according to USP-NF ⟨785⟩ Osmolality and Osmolarity	Nasal spray	According to manufacture specifications
10. Spray pattern (USP) Procedure according to USP-NF ⟨5⟩ Inhalation and Nasal Drug Products-General Information and Product Quality Tests (shape and size of evolving spray)	Nasal spray	According to manufacture specifications
11. Plume geometry (USP) Procedure according to USP-NF ⟨5⟩ Inhalation and Nasal Drug Products-General Information and Product Quality Tests	Inhalation spray	According to manufacture specifications

* Average weight could be considered if needed as IPC (USP-NF (1163) Quality assurance in pharmaceutical compounding).

12. Tests performed on suppositories:

Test	Applicability		Required Information	Acceptance criteria
	Type	Done/ Not Done		
1. Description: ○ **Appearance** ○ **Colour**	All			According to manufacturer specifications
2. Mass uniformity* (BP) Procedure is according to Ph. Eur. method 2.9.5	All suppositories and pessaries If the test for uniformity of content is prescribed or justified and authorized for all the active substances, the test for uniformity of mass is not required. *(Ph. Eur. monograph 1145)*			• Not more than 2 of the individual masses deviate from the average mass (actual) by more than the percentage deviation. • None deviates by more than twice that percentage. (Ph. Eur. method 2.9.5)
3. Disintegration (USP, BP)	Done for all unless intended for prolonged local action. Where a dissolution test is prescribed, a disintegration test may not be required *(Ph. Eur. monograph 1145)*.			USP-NF ⟨701⟩ Disintegration Ph. Eur. method 2.9.1
4. Dissolution ** Reference of method is one of the following: ○ USP or BP specific monograph. ○ FDA dissolution methods database (submit comparative dissolution profile in the most suitable media) ○ In-house method (submit comparative dissolution profile in the most suitable media)	All Suppositories and pessaries.		• <u>Dissolution Parameters:</u> ○ Filter type (common types Nylon, PVDF & PTFE) ○ Media composition. & pH ○ Media volume ○ Apparatus type ○ RPM ○ Temp ○ Sampling time ○ Q (the amount dissolve)	USP-NF ⟨711⟩ Dissolution Ph. Eur. method 2.9.3
5. Water content (USP) Procedure is according to manufacturer's method or specific monograph.	If not stated by manufacturer: Need justification to skip test			According to monograph or manufacturer specifications
6. Softening time (USP)	Lipophilic rectal suppositories			According to monograph or manufacturer specifications

* Average weight could be considered if needed as IPC USP-NF (1163) Quality assurance in pharmaceutical compounding.
** In case of locally acting API (not systemically absorbed), dissolution rate test may not be done and disintegration time is sufficient.

13. Tests performed on suspensions:

Test	Applicability	Acceptance criteria
1. Description: ○ **Appearance** ○ **Color/ with certain viscosity or not**	All	According to manufacturer specifications
2. Minimum fill (USP) Procedure according to USP-NF ⟨755⟩ Minimum Fill	○ Nasal suspension ○ Inhalation suspension, ○ Vaginal suspension, ○ Rectal suspension, ○ Ophthalmic suspension, ○ Otic suspension. ○ Topical suspension.	USP-NF ⟨755⟩ Minimum Fill
3. pH Procedure according to USP-NF ⟨791⟩ pH	Aqueous suspensions It is formulation dependent, According to manufacturer specifications.	According to manufacturer specifications
4. Specific gravity/Viscosity - Procedure of specific gravity according to**:** USP-NF ⟨841⟩ Specific Gravity - Procedure of viscosity according to: Manufacturer's method: Viscosity— Capillary Methods USP-NF ⟨911⟩, Viscosity— Rotational Methods USP- NF⟨912⟩, and Viscosity— Rolling Ball Method USP-NF⟨913⟩	Relatively viscous suspensions ○ Nasal suspension ○ Inhalation suspension ○ Ophthalmic suspension ○ Topical suspension ○ Otic suspension ○ Oral suspension	According to manufacturer specifications
5. Uniformity of mass of delivered doses from multi-dose containers (BP) Procedure is according to (Ph. Eur. method 2.9.27)	Oral suspensions which are supplied in multi-dose containers provided at manufacture with a measuring device. (Done for all doses)	• Not more than 2 of the individual masses deviate from the average mass by more than 10 per cent and none deviates by more than 20 %. (Ph. Eur. method 2.9.27)
6. Uniformity of dose of oral drops (BP) Procedure is according to (Liquid Preparations for Oral Use, Ph. Eur. monograph 0672)	Oral drops only	(Liquid Preparations for Oral Use, Ph. Eur. monograph 0672)
7. Deliverable volume (USP) Procedure is according to USP-NF⟨698⟩ Deliverable Volume	Oral suspensions	USP-NF ⟨698⟩ Deliverable Volume
8. Container content (USP)/ Extractable volume (BP) Procedure is according to USP-NF ⟨697⟩ Container Content For Injections	Parenteral suspension	USP-NF ⟨697⟩ Container Content For Injections

Test	Applicability	Required Information	Acceptance criteria
9. Dissolution* Reference of method is chosen from one of the following: ○ USP or BP specific monograph. ○ FDA dissolution methods database (submit comparative dissolution profile in the most suitable media) ○ In-house method (submit comparative dissolution profile in the most suitable media)	○ Oral suspensions (unless otherwise justified). ○ Sustained ophthalmic suspensions ○ Sustained parenteral suspensions	• Dissolution Parameters: ○ Filter type (common types Nylon, PVDF & PTFE) ○ Media composition & pH ○ Media volume ○ Apparatus type ○ RPM ○ Temp ○ Sampling time ○ Q (the amount dissolved)	USP-NF ⟨711⟩ Dissolution Ph. Eur. method 2.9.3
10. Acid Neutralizing capacity Procedure is according to: USP-NF ⟨301⟩ Acid- Neutralizing Capacity	Antacids		According to manufacturer specifications
11. Re-Suspendability	All suspensions		According to manufacturer specifications
12. Particle size distribution ** Procedure according to: -USP-NF ⟨601⟩ Inhalation and Nasal Drug Products_ Aerosols, Sprays, and Powders- Performance Quality Tests - Ph. Eur. monograph 1163 **(**Ophthalmic suspension)	○ Nasal suspension ○ Ophthalmic suspension ○ Parenteral suspension ○ Inhalation suspension		According to manufacturer specifications
13. Aerodynamic particle size measurement (cascade impactor) (USP) (performance Quality test) Procedure according to: USP-NF ⟨601⟩ Inhalation and Nasal Drug Products_ Aerosols, Sprays, and Powders- Performance Quality Tests	Inhalation suspension		According to manufacturer specifications
14.Osmolality Procedure according to : USP-NF ⟨785⟩ Osmolality and Osmolarity	○ Nasal suspensions ○ Inhalation suspensions ○ Ophthalmic suspensions		According to manufacturer specifications
15. Container–closure integrity	Parenteral suspensions		Package Integrity Leak Test Technologies ⟨1207.2⟩, Package Seal Quality Test Technologies ⟨1207.3⟩

* In case of locally acting API (not systemically absorbed), dissolution rate test may not be done.

** Particle size distribution testing may be proposed in place of dissolution testing, when development studies demonstrate that particle size is the primary factor influencing dissolution; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and / or lower particle size limits should be well defined

14.Tests performed on tablets:

Test	Applicability		Required Information	Acceptance criteria
	Tablet Type	Done / Not done		
1.Description: ○ **Appearance** ○ **Colour of tablet**	All		○ Tablet shape ○ Colour ○ Colour of core & coat in case of coated tablets ○ Type of coating case of coated tablets ○ Scored or not. ○ Biconvex/flat.	According to manufacturer specifications
2. Mass uniformity* (BP) Procedure is according to: Ph. Eur. method 2.9.5	• <u>Type of coat:</u> ○ Uncoated ○ Film coat ○ Sugar coat ○ If the test for uniformity of content is prescribed or justified and authorised for all the active substances, the test for uniformity of mass is not required. *(Ph. Eur. Monograph 0478)*	○ Yes ○ Yes ○ No		• Not more than 2 of the individual masses deviate from the average mass (actual) by more than the percentage deviation. • None deviates by more than twice that percentage. (Ph. Eur. method 2.9.5)
3. Disintegration (USP, BP) Procedure according to: USP- NF ⟨701⟩ Disintegration (Ph. Eur. method 2.9.1)	○ Immediate release ○ Oral lyophilizates ○ Delayed release (enteric coated). ○ Extended release (sustained/modified/controlled). **N.B.** Where a dissolution test is prescribed, a disintegration test may not be required. *(Ph. Eur. monograph 0478)*	○ Yes ○ Yes ○ Yes ○ No		USP-NF ⟨**701**⟩ Disintegration Ph. Eur. method 2.9.1

4.Dissolution ** Reference of method is chosen from one of the following: ○ USP or BP specific monograph. ○ FDA dissolution methods database. (submit comparative dissolution profile in the most suitable media)*** ○ In-house method Obey the dissolution method development criteria. Refer to (Annex II)	○ Effervescent tablets that result in a solution ○ Others Where a dissolution test is prescribed, a disintegration test may not be required. *(Ph. Eur. monograph 0016)* Disintegration could substitute dissolution as a performance test if a justification submitted by the manufacturer that it obeys the ICH Q6A guidelines. In this case, the performed dissolution method should be supplied by the manufacturer.	○ No ○ Yes	• Dissolution Parameters: ○ Filter type (common types Nylon, PVDF & PTFE) ○ Media composition & pH ○ Media volume ○ Apparatus type ○ Sinkers needed (common type: coiled sinker) ○ RPM ○ Temp ○ Sampling time ○ Q (the amount dissolved)	(Ph. Eur. method 2.9.3) USP-NF ⟨711⟩ Dissolution
5.Friability (USP & BP)**** Procedure according to: USP-NF ⟨1216⟩ Tablet Friability BP (Ph. Eur. method 2.9.7)	○ Uncoated ○ Coated	○ Yes ○ No		USP-NF ⟨1216⟩ Tablet Friability BP (Ph. Eur. method 2.9.7)
6.Tablet breaking force (Hardness) (USP& BP)****	○ Uncoated ○ Coated	○ Yes ○ No		According to manufacturer's specifications
7. Subdivision (BP) Procedure according to: Ph. Eur. monograph 0478	○ Functional score. ○ Non-functional score. To skip subdivision test**:** the manufacturer should submit accepted justification. In this case, the word 'Indivisible' should be clearly written on the package. Exceptionally, the package without this word 'Indivisible' could be accepted with a written commitment only in case of pilot batches.	○ Yes ○ No		• NMT 1 individual mass is outside the limits of 85-115 % of the average mass. • The tablets fail to comply with the test if more than 1 individual mass is outside these limits, or if 1 individual mass is outside the limits of 75-125% of the average mass. (Ph. Eur. monograph 0478

8.Water content (USP) Procedure according to: Manufacturer's method or specific monograph.	If not stated by manufacturer: Need justification to skip test			According to manufacturer specifications
9.Fineness of dispersion (BP) Procedure according to: Ph. Eur. monograph 0478.	○ Dispersible tablets ○ Others	○ Yes ○ No		A smooth dispersion is produced, which passes through a sieve screen with a nominal mesh aperture of 710 µm.
10. Acid neutralizing capacity (USP) Procedure according to: USP-NF ⟨ 301 ⟩ Acid-Neutralizing Capacity	Antacids only			According to manufacturer specifications

* Average weight could be considered if needed as IPC USP-NF (1163) Quality assurance in pharmaceutical compounding.
** In case of locally acting API (not systemically absorbed), dissolution rate test may not be done and disintegration time is sufficient.
*** Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action EMA/CHMP/CVMP/QWP/336031/2017 may be referred to as guidance.
**** Not mandatory for uncoated tablets if done as in-process control.

15. Tests performed on Transdermal Delivery Systems (TDS)*

Test	Applicability		Required Information	Acceptance criteria
	TDS type	Done/ Not done		
1. Description	All			According to manufacturer's specifications
2. Dimensions	All			According to manufacturer's specifications
3. Water content (USP) Procedure is according to manufacturer's method or specific monograph.	If not stated by manufacturer: Need justification to skip test			According to manufacturer's specifications
4. Dissolution Reference of method is one of the following: ○ USP or BP specific monograph. ○ FDA dissolution methods database (submit comparative dissolution profile in the most suitable media) ○ In-house method (submit comparative dissolution profile in the most suitable media)	All		● <u>Dissolution Parameters:</u> ○ Media composition & pH ○ Media ○ Apparatus ○ RPM ○ Temp (32 ˚C) ○ Sampling time (at least three, expressed in hours) ○ Q (the amount dissolved)	USP-NF ⟨711⟩ Dissolution Ph. Eur. method 2.9.3
5. Particle size	○ Suspension in reservoir ○ Others	○ Yes ○ No		According to manufacturer's specifications
6.Specific Tests for TDS ○ Peel adhesion test ○ Release liner peel test ○ Tack test ○ Cold flow test ○ Shear test	All			According to manufacturer's specifications

*On the bases of nature of the article and scientific criteria additional tests may be applied according to the monograph or if stated by the manufacturer if the equipment is available.

(Annex II)

1. Development for in-house dissolution methods

The criteria of dissolution method development and setting dissolution specification of immediate release oral solid dosage forms

Based on the Bio-pharmaceutics classification system (BCS) of the drug substance

BCS class I or III	BCS class II or IV
Containing High Solubility Drug Substances (The dose/solubility volume of solution≤250 ml of aqueous media over the pH range of 1 to 6.8 at 37°C ± 1°C)[1]	Containing low Solubility Drug Substances
Guide I[2] Or **Guide II**[3]	**Guide II**

[1] Only for tablets and capsules to be swallowed intact. Not for narrow therapeutic index (NTI) drug products.
[2] FDA Guidance for industry: Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances. August 2018.
[3] FDA guidance for industry: Dissolution Testing of Immediate Release Solid Oral Dosage Forms. August 1997.

Guide I

Apparatus:	Commonly used: (1) Basket method (USP Apparatus 1) (2) Paddle method (USP Apparatus 2)
Dissolution Medium:	• **The volume of the dissolution medium** is generally 500 mL. (or 900 mL with appropriate justification) • **The composition of the dissolution medium:** ○ 0.1N HCl in aqueous medium ○ No surfactant in medium
Temperature	Should be conducted at 37±0.5°C.
Sinkers	In general, capsule dosage forms tend to float during dissolution testing with the paddle method. In such cases, it is acceptable to add a few turns of a wire helix (USP) around the capsule be used.
Agitation	(1) Basket method: 100 rpm. (2) Paddle method: 50 rpm (or 75 rpm with appropriate justification)
Dissolution criteria	Q=80% in 30 minutes.

Guide II

Apparatus:	Commonly used: (1) the basket method (Apparatus 1) (2) the paddle method (Apparatus 2) Described in the USP, and may be considered if needed: (3) reciprocating cylinder (Apparatus 3) and (4) a flow-through cell system (Apparatus 4)
Dissolution Medium:	• **The volume of the dissolution medium** is generally 500, 900, or 1000 mL. Sink conditions are desirable but not mandatory. (2, 4 L or low volume dissolution media in mini vessels need justification). • **The composition of the dissolution medium:** ○ An aqueous medium with pH range 1.2 to 6.8 (ionic strength of buffers the same as in USP) should be used. To simulate intestinal fluid (SIF), a dissolution medium of pH 6.8 should be employed. A higher pH should be justified on a case-by-case basis and, in general, should not exceed pH 8.0. ○ To simulate gastric fluid (SGF), a dissolution medium of pH 1.2 should be employed without enzymes. The need for enzymes in SGF and SIF should be evaluated on a case-by-case basis and should be justified. ○ Gelatin capsule products may need to add enzymes to the dissolution media (pepsin with SGF and pancreatin with SIF) to dissolve pellicles, if formed, to permit the dissolution of the drug. ○ Use of water as a dissolution medium is discouraged because test conditions such as pH and surface tension can vary depending on the source of water and may change during the dissolution test itself, due to the influence of the active and inactive ingredients. ○ The need for and the amount of the surfactant should be justified. Use of a hydro-alcoholic medium is discouraged.
Temperature	Should be conducted at 37±0.5°C.
Deaeration	Certain drug products and formulations are sensitive to dissolved air in the dissolution medium will need deaeration.
Sinkers	In general, capsule dosage forms tend to float during dissolution testing with the paddle method. In such cases, it is acceptable to add a few turns of a wire helix (USP) around the capsule be used.
Agitation	Basket method: 50-100 rpm. (higher than 100 rpm need justification) (Note: Should not exceed 150 rpm) Paddle method: 50-75 rpm (higher than 75 rpm need justification) (Note: Should not exceed 150 rpm) Reciprocating cylinder: 5-30 DPM. Flow through cell: flow rate 4, 8 and 16 mL/min.
Dissolution criteria	According to the comparative dissolution profile in the most suitable media.[4]

[4] Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action EMA/CHMP/CVMP/QWP/336031/2017.

2. Comparative dissolution study:

Recommendations should be considered in the submitted comparative dissolution studies:

1. The dissolution parameters should be submitted.
2. The dissolution measurements of the test and reference batches should be made under exactly the same conditions.
3. The dissolution time points for both the profiles should be the same (e.g., 15, 30, 45, 60 minutes).
4. Only one measurement should be considered after 85% dissolution of both the products.
5. To allow use of mean data, the percent coefficient of variation at the earlier time points (e.g., 10 minutes) should not be more than 20%, and at other time points should not be more than 10%.
6. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values up to 15 (0-15) and f_2 values greater than 50 (50-100) ensure sameness or equivalence of the two curves and, thus, of the performance of the test and reference products.

Annex III

Requirements for Chemical Analysis

1. Active pharmaceutical ingredients (API) used in the manufacture of finished pharmaceutical product (FPP):

1.1 Specifications:

1.1.1 In case the API reference according to the composition is one of the pharmacopeias; the specifications of the API in the certificate of analysis should follow that pharmacopeia.

1.1.2 In case of in-house API:

1.1.2.1 If the API has a monograph in any of the pharmacopeias, specifications of the API supplier are accepted only if they comply with the specifications listed in the pharmacopeia or tighter specifications.

1.1.2.2 If the API doesn't have any monographs in any of the pharmacopeias, specifications of supplier are accepted provided the following:

- Tests for impurities will be evaluated according to ICH Q3A guidelines for impurities.
- For API present as both a chiral single enantiomer and as racemate, identity testing(s) for verification of chirality is more appropriately addressed as part of the drug substance specification.

2. Finished pharmaceutical products (FPP): CADC laboratories

2.1 Specifications and Certificate of Analysis:

2.1.1 For products described as pharmacopeial, specifications of this product must follow the specifications in the whole monograph in the reference pharmacopeia.

2.1.2 For products that have pharmacopeial monograph(s), specifications listed in the pharmacopeial monograph are used as the main reference in the evaluation of the required tests and specifications.

2.1.3 Identification tests for API:

2.1.3.1 Identification test item must be included in the specification sheet and finished product certificate of analysis (CoA)

2.1.3.2 Titrimetry is not an identification test.

2.1.4 Assay of API, antimicrobial preservatives and antioxidants:

2.1.4.1 Limits for assay should be expressed in terms of active moiety (free acid or base, anhydrous basis) unless otherwise specified in the specific monograph

2.1.4.2 The general acceptance limits are as follows:

- General acceptance limit for the API is 90-110% of the Labeled claim.
- General acceptance limit for the preservative is 80-120% of the Labeled claim
- General acceptance limit for the antioxidant is according to manufacturer specification with scientific justification.

2.1.4.3 In case of approved stability overage where the limit of assay in such a case will be 90% of labeled claim to 110% of labeled claim +overage (approved in composition as stability overage).

2.1.4.4 Analysis of preservatives in solid dosage form in capsule shells is not mandatory unless it is listed in the manufacturer specifications.

2.1.4.5 Analysis of any other excipients is not mandatory unless it is listed in the manufacturer specifications.

In all cases deviation (wider) from general acceptance limit may be accepted only if justified by:
1- Specific monograph for the FPP.
2- Approved stability specifications.
Narrower limits are always accepted as manufacturer specifications.

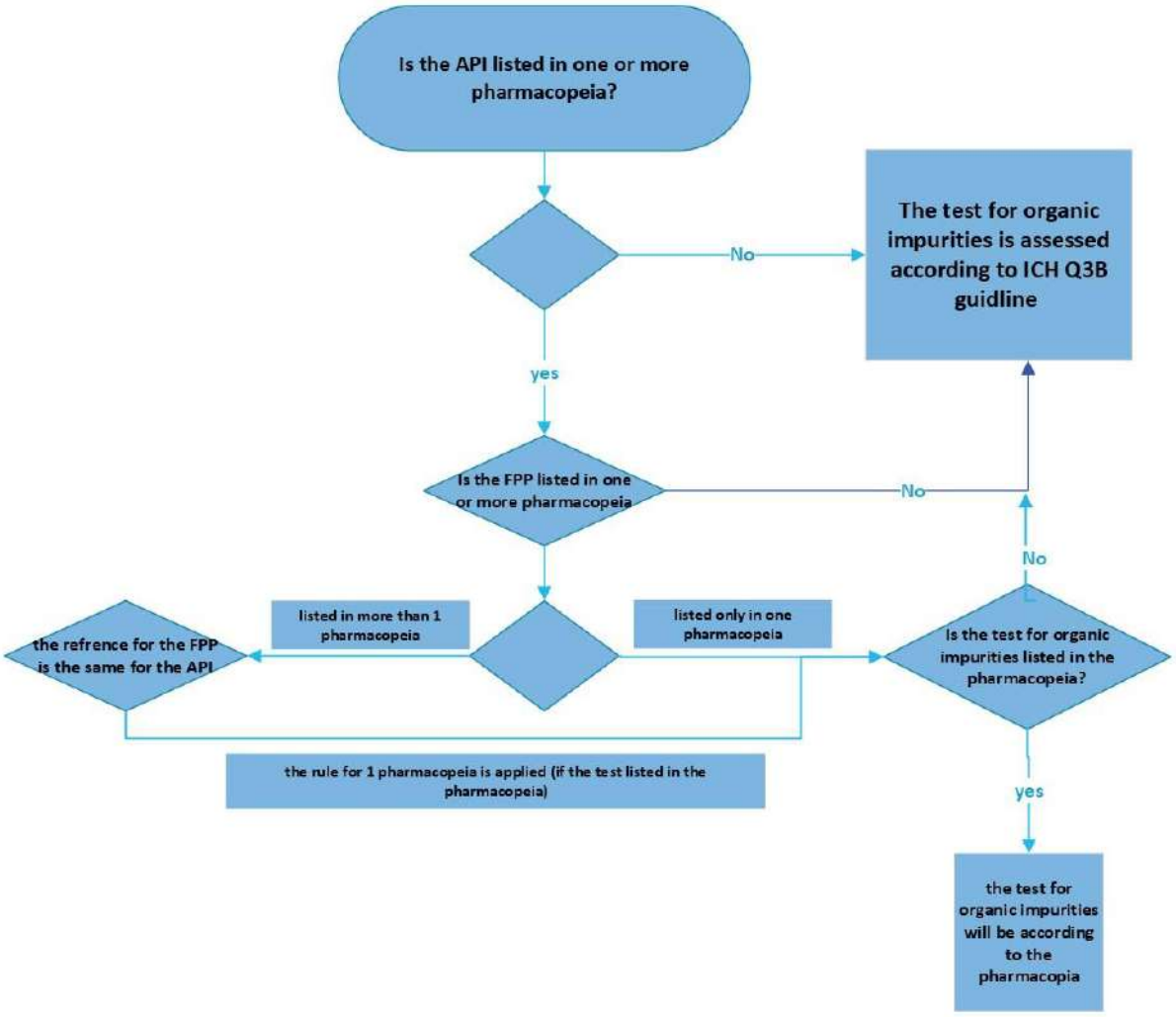
2.1.5 Test of impurities

2.1.5.1 Organic impurities/ related substances:

- In case the test for organic impurities is not indicated in the drug product monograph, the stability indicating power of the method will be used to evaluate the presence of unjustified peaks. Presence of unjustified peaks may require the performance of this test where applicable, which will be assessed according to ICH Q3B guideline.
- In USP monographs of capsules, the definition does not specify the type of capsule (gelatin, Hypromellose, starch derivative, hard, soft, etc.), or the type of filling in the capsule (powder, granules, pellets, liquid, semisolid, etc.). Accordingly, the test for organic impurities described under the monograph, if present, must be applied to any of the previously mentioned types.

- In USP monographs of tablets, unless otherwise stated, the tablets are considered immediate release regardless of the coat and shape of the tablets (film coated, sugar coated, caplets.) and test of organic impurities described under the USP monograph, if present must be applied.
- Same decision tree will be followed in case of presence of more than one API.

Decision tree for organic impurities:



* In case the applicant requests to change the pharmacopeial reference of the method of organic impurities for assessing FPP from that of the API, the test for organic impurities of the used API batch must then be tested in CADC laboratories following the pharmacopeial monograph of the API reference

2.1.5.2 Residual solvents:

- Assessment of residual solvents impurities will be according to ICH Q3C, unless otherwise specified in the specific monograph.
- Analytical procedures for the determination of solvent classes can be followed as described under USP < 467>.
- Alternative validated methodologies may also be used or modifications to the official methods may be done to demonstrate compliance with the defined limits where verification of USP procedures or validation of alternative methods for residual solvents is performed according to USP<1467>.
- If the residual solvent is controlled in an intermediate (like granules or pellets) by analysis in CADC raw material laboratories, reanalysis will not be necessary in the finished product but should be included in finished product specifications.

2.1.5 Uniformity of dosage unit:

To ensure the consistency of dosage units, each unit in a batch should have drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit. The uniformity of dosage unit's specification is not intended to apply to solutions, suspensions, emulsions, or gels in unit-dose containers intended for local action following external, cutaneous administration.

2.1.5.1 The test for content uniformity is not required for multivitamin and trace-element preparations Ph.Eur. 2.9.40.

2.1.5.2 CADC laboratories will use as in the interchangeable general chapter of the Uniformity of dosage units USP <905>, Ph.Eur. 2.9.40. and JP 6.02 where target Value (T) =100% otherwise stated in the product monograph.

2.1.5.3 (T) should be stated in the finished product monograph in case of asymmetric limits of assay (e.g.90-115%) and should not be considered as 100%.

2.1.5.4 Where different procedures are used for assay of the preparation and for the Content Uniformity test, it may be necessary to establish a correction factor to be applied to the results of the latter. USP <905>

2.1.5.5 CADC laboratories will apply; whenever applicable; the method of assay for the determination of API(s) in the evaluation of content uniformity test in case the method of content uniformity is not submitted.

2.1.6 Alcohol content.

For liquid formulation contains a quantity of alcohol this test will be evaluated according to USP <611>.

2.2 Method of analysis (MOA):

A specific, stability-indicating assay method to determine strength (content) should be included for all drug products.

In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where titration is adopted to assay the drug substance for release, the combination of the assay and a suitable test for impurities can be used.

2.3 Method Validation and Verification:

2.3.1 When a non-pharmacopeial method is used a full validation study must be submitted with the method of analysis. Validation will be assessed according to ICH Q2 (R1).

2.3.2 When official pharmacopeial analytical methods are applied out of their intended scope according to the description stated in the pharmacopeial monograph (e.g. method for API(s) to be applied on finished products, finished product of different dosage forms, or in presence of other API (s), full validation study will be essentially required to be submitted for the applied analytical method.

2.3.3 When a pharmacopeial method is used, verification of is performed according to USP <1226> and OMCL guideline.

2.4 Analysis requirements:

2.4.1 Standards:

2.4.1.1 A certified reference material (CRM), pharmacopeial or otherwise, is preferable.

2.4.1.2 In case a working standard is submitted, EDA template for COA of a working standard is mandatory, and the lot number for the primary standard used in its qualification, as evidence of traceability, must be stated in the submitted COA.

2.4.2 Analytical Columns:

The use of equivalent columns is accepted if within permissible limits according to USP < 621>

2.4.3 Placebo:

Placebo should be provided in case of organic impurities testing. If the placebo is unavailable the company should send a declaration of acceptance to start the analysis of impurities without placebo and will be committed to provide it with other analysis requirements and reference standards in case the analysis gives unsatisfactory results.

2.5 Special considerations:

2.5.1 Sodium edetate (EDTA) analysis:

Submission of a method of control for sodium edetate as a synergist antioxidant agent is not mandatory & it will be done only if it is stated in the FPP shelf-life specifications.

2.5.2 Benzalkonium chloride:

The presence of at least Benzalkonium chloride homologs c12 and c14 is mandatory for confirmation of identification of Benzalkonium chloride and the submitted method of analysis must be able to discriminate Benzalkonium chloride homologs.

2.5.3 Hazardous methods of assay e.g. Amikacin injection:

In case that organic impurities test is required, the international pharmacopeia will be used instead of the BP.

2.5.4 For products used as sources of elements &/or minerals:

2.5.4.1 Identification:

The identification testing is needed for either the salt itself or the individual ions composing it according to the latest pharmacopeia and in case of complexes such as iron dextran, iron polymaltose, iron sucrose ……etc.,

detailed identification method for both the cation (e.g. iron) & organic moiety should be attached.

2.5.4.2 Assay:

It is accepted for the salt itself or the cations (Na^{+}, K^{+}, Ca^{++}, Mg^{++}, Cu^{++}, Mn^{++}, Se^{3+}, Cr^{3+}, Mo^{+}, Zn^{++}, Fe^{++}, B^{++}, $Bi^{3+,}$ P^{4+}) and/or the anions (Citrate, acetate, chloride, oxalate, lactate, carbonate, bicarbonate, fluoride and iodide)

2.5.4.3 For limits of assay, pharmacopeial acceptance criteria are generally applied whenever available.

Annex IV

Requirements for Microbiological Analysis

1. **Microbiological Examination of non-sterile products.**
2. **Sterility testing.**
3. **Antibiotic potency testing.**
4. **Disinfectant challenge testing.**
5. **Bacterial endotoxin test.**
6. **Rabbit test.**

1- MICROBIOLOGICAL EXAMINATION OF NON-STERILE PRODUCTS

1. **Definition**: are tests designed primarily to determine whether non-sterile pharmaceutical products comply with an established specification for microbiological quality.
2. **Requirements:**

2.1 Sample size for testing

The following table shows the required quantities of the samples for different sample types sufficient to carry out the test and ensure accurate and reliable results:

Sample Type	Required quantities for one test
Solid or liquid	10 g or 10 ml
Fluids or solids in aerosol form	10 containers
Transdermal patches	10 patches
If the amount per dosage unit (tablets or capsules) is less than 1 mg	The amount present in 10 dosage units is required
If the batch size is less than 1000 ml or 1000 g	1% of the batch is required

Note: Sample size can be reduced on a basis of the ratio 1:10 (sample: medium), at least 1gm or ml for testing **once** and this reduction is acceptable only in special cases judged by CADC.

2.2 Test specifications

The following should be provided:

Tested parameter	e.g. Total aerobic microbial count (TAMC), Total combined yeasts/molds count (TYMC), Tests for specified microorganisms
Method used	e.g. Plate-count method, Membrane filtration, Most-Probable-number method, Test method for specified microorganisms
Neutralizer (If used)	Please mention the name of neutralizer used and percentage %
Acceptance criteria	Expressed in cfu/g or cfu/ml
Reference	e.g. *USP, BP, Ph. Eur.*

Table 1: Acceptance criteria for microbiological quality of non-sterile dosage forms (according to *USP* except **a** is according to *Ph. Eur*)

Route of administration	**TAMC (cfu/g or cfu/ml)**	**TYMC (cfu/g or cfu/ml)**	**Specified microorganism(s)****
No aqueous preparations for oral use	10^3	10^2	Absence of *Escherichia coli* (1g or 1 ml)
Aqueous preparation for oral use	10^2	10^1	Absence of *Escherichia coli* (1g or 1 ml)
Rectal use	10^3	10^2	---
Oromucosal, Gingival, Nasal, Cutaneous, Auricular use Transdermal patches (limits for one patch including adhesive layer and backing)	10^2	10^1	Absence of *Staphylococcus aureus* (1g, 1 ml or patch) *Pseudomonas aeruginosa* (1g, 1 ml or patch)
Vaginal use	10^2	10^1	Absence of *Staphylococcus aureus* (1g or 1 ml) *Pseudomonas aeruginosa* (1g or 1 ml) *Candida albicans* (1g or 1ml)
Inhalation use	10^2	10^1	Absence of *Staphylococcus aureus* (1g or 1 ml) *Pseudomonas aeruginosa* (1g or 1 ml) Bile tolerant gram-negative bacteria (1g or 1 ml)
Oral dosage forms containing raw materials of natural origin (TAMC of raw material > 10^3 cfu/g or ml)[a] (*Ph. Eur.*)	10^4	10^2	Absence of *Staphylococcus aureus, E. coli* (1g or 1ml) *Salmonella spp.* (10 g or 10 ml) *Bile tolerant gram-negative bacteria* (NMT 10^2 cfu /g or ml)

****** An update of the test for specified/objectionable microorganisms (at USP 43) includes test for absence of "*Burkholderia cepacia"* as an established specification for inhalation use or aqueous oral, oromucosal, cutaneous, or nasal use.

Table 2: Acceptance criteria for microbiological quality of non-sterile substances for pharmaceutical use

	TAMC (cfu/g or cfu/ml)	TYMC (cfu/g or cfu/ml)	Specified microorganism(s)
Substances for pharmaceutical use	10^3	10^2	The assessment takes account of the processing to which substance is subjected

Table 3: Recommended microbial limits for botanical ingredients and products (according to *USP* except **b** is according to *Ph. Eur*)

Material	TAMC (cfu/g or cfu/ml)	TYMC (cfu/g or cfu/ml)	Specified microorganism(s)
Dried or powdered botanicals	10^5	10^3	Absence of *Salmonella spp. and E. coli in* 10 g *Bile tolerant gram-negative bacteria* (NMT 10^3 cfu/g or ml)
Powdered botanical extracts, Nutritional supplements with botanicals	10^4	10^3	Absence of *Salmonella spp. and E. coli in* 10 g
Tinctures, Fluid extracts	10^4	10^3	---
Infusions/decoctions	10^2	10	---
Botanicals to be treated with boiling water before use	10^6	10^4	Absence of *Salmonella spp. and E. coli in* 10 g *Bile tolerant gram-negative bacteria* (NMT 10^2 cfu /g or ml)
Premixes for medicated feeding stuff for vet use using excipients of plant origin[b] (*Ph. Eur*.)	10^5	10^4	Absence of *E. coli* (1g or ml) and Salmonella spp. (25 g or ml) *Bile-tolerant gram-negative bacteria* (NMT 10^4 cfu/g or ml)

Table 4: Recommended microbial limits for Dietary supplement ingredients and products

Material	TAMC (cfu/g or cfu/ml)	TYMC (cfu/g or cfu/ml)	Specified microorganism(s)
Other raw materials and Dietary supplement ingredients	10^3	10^2	Absence of *E. coli in* 10 g
Nutritional supplements with synthetic or highly refined ingredients	10^3	10^2	Absence of *E. coli in* 10 g

Note (1): Applicant can set the limit for TAMC and TYMC for a given product lower than indicated acceptance criteria in Tables 1, 2, 3 and 4.

Note (2): In addition to microorganisms listed in Tables 1, 3, and 4; the applicant can add more objectionable microorganisms to be tested depending on the nature of the starting material and manufacturing process.

Note (3): When the acceptance criterion for microbiological quality is prescribed, it is interpreted as follow:
10^1 cfu: maximum acceptable count =20,
10^2 cfu: maximum acceptable count =200,
10^3 cfu: maximum acceptable count =2000; and so forth.

2.3 Method suitability certificate: especially for products with proved antimicrobial activity or if insufficient information about the product exists to judge its probable growth inhibiting activity.

2.4 Reduced frequency of microbial testing

Pharmaceutical drug products with water activities well below **0.75** (e.g., direct compression tablets, powder and liquid-filled capsules, non-aqueous liquid products, ointments, and rectal suppositories) would be excellent candidates for reduced microbial limit testing.

In order to obtain approval for reduced frequency of microbial testing or skipped lot testing or eliminate routine testing; the applicant should introduce the following (USP 44 chapter 1112):

○ Formulation of the drug product has antimicrobial properties (as antibiotics) or it does not support microbial growth or viability (i.e: with low water activity).
○ Proof that the product has been manufactured from ingredients of good microbial quality.
○ Demonstrated effectiveness of microbial contamination control of the raw material, ingredient water, manufacturing process, formulation, and packaging system that prevent moisture.
○ Proof that manufacturing sites have an established testing history of low bioburden associated with their products.
○ Historic testing database of the product; the testing history would include microbial monitoring during product development and routine testing of sufficient marketed product lots (e.g up to 20 lots) to ensure that the product has little or no potential for microbial contamination.

2. STERILITY TESTING

1. **Definition**: is a test applied to substances, preparations, or articles which, according to the Pharmacopeia, are required to be sterile. However, a satisfactory result only indicates that no contaminating microorganism has been found in the sample examined under the conditions of the test.
2. **Requirements:**

2.1 Sample size for testing

The following table shows the required quantities of the samples for different sample types:

Quantity per Container	Minimum Quantity to be Used (unless otherwise justified and authorized) *
Liquids	
Less than 1 mL	The whole contents of each container
1-40 mL	Half the contents of each container, but not less than 1 mL
Greater than 40 mL, and not greater than 100 mL	20 mL
Greater than 100 mL	10% of the contents of the container, but not less than 20 mL
Antibiotic liquids	1 mL
Insoluble preparations, creams, and ointments to be suspended or emulsified	Use the contents of each container to provide not less than 200 mg
Solids	
Less than 50 mg	The whole contents of each container
50 mg or more, but less than 300 mg	Half the contents of each container, but not less than 50 mg
300 mg-5 g	150 mg
Greater than 5 g	500 mg
Catgut and other surgical sutures for veterinary use	3 sections of a strand (each 30-cm long)
‘Surgical dressing/cotton/gauze (in packages)	100 mg per package
Sutures and other individually packaged single-use material	The whole device
Other medical devices	The whole device, cut into pieces or disassembled

* Sample size for each medium can be reduced on a basis of that the volume of the product is not more than 10% of the volume of the medium and this reduction is acceptable only in special cases judged by CADC.

2.2 Test specifications

The following should be provided;

Tested parameter	Sterility of the product
Technique used	Direct inoculation or membrane filtration method
Neutralizer (If used)	Please mention the name of neutralizer used and percentage %
Sterilization method of the product	By filtration, steam, dry heat, irradiation or ethylene oxide gas
Acceptance criteria	Pass sterility testing (comply)
Reference	*Ph. Eur., BP, USP.*

2.3 Method suitability certificate: especially for products with proved antimicrobial activity or if insufficient information about the product exists to judge its probable growth inhibiting activity.

3. ANTIBIOTICS POTENCY TESTING

1. **Definition**: are tests that can demonstrate the activity (potency) of antibiotics by their inhibitory effect on microorganisms under suitable conditions. A reduction in antimicrobial activity may not be adequately demonstrated by chemical methods.

2. Requirements

2.1 Sample Size:

Sample Type	Required quantities for test and retest
For samples of 50 gm - 1000 gm	1 package
For samples 10gm- 40 gm	2 packages
For samples less than 10 gm	4 packages
For liquid samples	Not less than 50 ml

2.2 Test specifications:

The following should be provided;

Tested parameter	Potency of Antibiotics
Technique used	Cylinder-plate assay or Turbidimetric assay
Test organisms (ATCC number) with procedure for inoculum preparation and standardization	As indicated in used reference
Details of method of assay as indicated in used reference	○ Procedure for preparations of initial, final and median concentrations for both reference standard and tested antibiotic ○ Initial solvents, further and final diluents ○ Buffers used with their preparation procedure ○ Incubation conditions, Culture media used, Specific temperature requirements, incubation time
Calculations for determining antibiotic potency	○ Detailed equation shall be submitted with the definition of each parameter (USP, BP, IP or three point assay equation according to the used reference) ○ Excel sheet copy (on demand)
Acceptance criteria	According to reference
Reference	○ Ph. Eur., BP, USP, in-house and version ○ Copies of the non-Compendial analytical procedures used to generate testing results should be provided. ○ Unless modified, it is not necessary to provide copies of the Compendial analytical procedures.

3. General Notes

3.1 Non Pharmacopeial raw materials and finished products will be analyzed according to in-house methods attached with their validation protocols.

3.2 For non-Pharmacopeial combinations, the in-house methods should include separation technique between antibiotics and validation protocols

4. DISINFECTANTS CHALLEMGE TESTING

1. Definitions:

Disinfectant: a chemical or physical agent that destroys or removes vegetative forms of harmful microorganisms when applied to a surface.

Antiseptic: an agent that inhibits or destroys microorganisms on living tissues including skin, oral cavity, and open wounds.

2. Requirements:

2.1 Test specifications: the following information should be provided

Unless other Compendial method suggested by the applicant, the microbiology section will apply the following test parameters;

Tested parameter	Disinfectant efficacy test.
Test method	Dilution test method.
Neutralizing agents	Will be chosen based on chemical composition of the disinfectant.
Challenge organisms	**Bactericide**: *Escherichia coli*, ATCC 11229; *S. aureus*, ATCC 6538; *P. aeruginosa*, ATCC 15442. **Fungicide**: *C. albicans*, ATCC 10231 or 2091; *Penicillium chrysogenum*, ATCC 11709; *Aspergillus niger*, ATCC 16404. **Sporicide**: *B. subtilis*, ATCC 19659.
Acceptance criteria	≥ 5 Log reduction. (for vegetative bacteria) and ≥ 4 Log reduction. (for bacterial spores)
Reference	E.g. *CEN,USP, AOAC.*

2.2 Required information

Chemical composition of disinfectant	i.e. aldehydes, alcohols, phenolic, quaternary ammonium compounds, *etc.*
Classification or intended use	General purpose disinfectant, bactericidal, fungicidal, or sporicidal agent.
Directions for Use	Should be addressed in the labeling including suggested concentrations and suggested contact time.

5. BACTERIAL ENDOTOXINS TEST

1. Requirements:

1.1 Sample size for testing

Three to five samples are required,
Sample size can be reduced to at least one sample but not less than 2 ml and this reduction is acceptable only in special cases judged by CADC (**Must be compatible with the MVD**)

** Max. Valid Dilution (M.V.D) = Endotoxin limit X product conc.*
Lysate sensitivity (λ)

1.2 Test Specifications

1)Tested parameter	Bacterial endotoxin limit (B.E.L)
2)Detailed method of analysis	Inhibition/Enhancement test is highly recommended with any special precautions.
3) Reference used in addition to the edition	*(USP-Ph. Eur.-BP)* e.g.: *USP 44*
4) Calculation of B.E.L (K/M)	In case of non-pharmacopeial products.

Table 4. Acceptance criteria for bacterial endotoxins according to route of administration

Route of administration	**Bacterial Endotoxin Limit (B.E.L)**		
	Pharmacopeial products According to *(USP-Ph. Eur.-BP)*	**Non-Pharmacopeial products** (Calculate *BEL= K/M*)	
		K (the max. pyrogenic dose/Kg), (Constant depends on RoA)	**M** (the max. recommended dose /Kg)
Intravenous (IV) for parenteral products	Depending on specific monograph of each product	5 EU/kg of body weight	Maximum dose per kilogram administered in 1 h
IV for radiopharmaceuticals		175 EU	Volume of the maximum recommended dose
Intrathecal (IT) for parenteral products		0.2 EU/kg of body weight	Maximum dose per kilogram administered in 1 h
IT for radiopharmaceuticals		14 EU	Volume of the maximum recommended dose
Parenterals administered per square meter of body surface ***(USP)***		100 EU/m^2	Maximum dose per square meter per hour

Injections other than IV (intramuscular, subcutaneous, etc.)		5 EU/kg of body weight	Maximum dose per kilogram administered in 1 h
Intraocular fluids ***(USP)***	----------	0.2 EU/mL	----------
Anterior segment solid devices ***(USP)***	----------	0.2 EU/device	----------
Ophthalmic irrigation products ***(USP)***	----------	0.5 EU/mL	----------
Injected or implanted ophthalmic drug product ***(USP)***	----------	2 EU/dose	----------

Notes:

- The chosen dose should be the greatest recommended dose for the lowest body weight in targeted patient population (**take into consideration the recommended doses for pediatrics**).
- For veterinary products administrated to variety of different species, you should select the smallest animal
that receiving the greatest dose per Kg.

6. RABBIT TEST

Rabbit test is only accepted in case of products incompatible with LAL techniques due to interference. Complete justification that proves the incompatibility must be submitted with its supportive results

1. Requirements

1.1 Test Specifications

1)Tested parameter	Testing for pyrogens
2)Detailed method of analysis	Detailed SOP of each product must be submitted containing at least the following: ○ Diluent used in case of powder products/materials which will be reconstituted. ○ Dose to be administrated per Kg. ○ Dose preparation.
3) Reference	e.g.*: Ph. Eur.-General chapter (2.6.8)*

2. Acceptance criteria

No rabbit shows an individual rise in temperature of 0.5 C° or more above its respective control temperature to meet the requirements for the absence of pyrogen, or:

Any other mentioned criteria according to the used reference.

3. Exemptions:

-Preparations for veterinary use **(**following European and British Pharmacopeia specifications) when the volume to be injected in a single dose is less than 15ml and is less than 0.2ml/Kg of body mass.

(Unless the label states that the preparation is apyrogenic or free of bacterial endotoxin).

-Topical intraocular preparations (Eye drops, ointments, etc.)

Annex V

Method Validation and Verification

1. As per ICH Q2 (R2) guideline, the submitted validation study should provide sufficient evidence to demonstrate that the analytical procedure is suitable for its intended purpose, through validation of the relevant performance characteristics of the procedure, using appropriate validation tests, to ensure the quality of the measured result.

ICH Q2(R2) Guideline

Table 1: Typical performance characteristics and related validation tests for measured quality attributes

Measured Quality Attribute / Analytical Procedure Performance Characteristics to be Demonstrated (2)	IDENTITY	IMPURITY (PURITY) Other quantitative measurements (1)		ASSAY Content or potency / Other quantitative measurements (1)
		Quantitative Test	Limit Test	
Specificity (3) Specificity Test	+	+	+	+
Range Response (*Calibration Model*)	-	+	-	+
Lower Range Limit	-	QL†	DL	-
Accuracy (4) Accuracy Test	-	+	-	+
Precision (4) Repeatability Test	-	+	-	+
Intermediate Precision Test	-	+ (5)	-	+ (5)

- signifies that this test is not normally conducted

+ signifies that this test is normally conducted

† in some complex cases DL may also be evaluated

QL, DL: quantitation limit, detection limit

(1) other quantitative measurements can follow the scheme for impurity, if the range limit is close to the DL/QL.; other quantitative measurements can follow the scheme for assay (content or potency), if the range limit is not close to the DL/QL

(2) some performance characteristics can be substituted with technology-inherent justification in the case of certain analytical procedures for physicochemical properties

(3) lack of specificity of one analytical procedure should be compensated by one or more other supporting analytical procedures, unless appropriately justified

(4) alternatively, a combined approach can be used to evaluate accuracy and precision

(5) where reproducibility has been performed and intermediate precision can be derived from the reproducibility data set, an independent study for intermediate precision is not required

Figure 1. Typical performance characteristics and related validation tests for measured quality attributes -ICH Q2(R2)

Table 1 Acceptance criteria for validation parameters of analytical methods employed in quantitative analysis of drug product quality characteristics

Validation Items	Requirement	Acceptance Criteria
Specificity	Blank measurement	Resolution: NLT 1.5/ Blank interference NMT 1%
	Placebo measurement	Resolution: NLT 1.5/ Placebo interference NMT 2%
	Peak purity	of lack of interference according to Demonstration software used
	Spiking with potential impurities	Resolution between the target analyte and adjacent peaks NLT 1.5
	Degradation under stress condition	No indication of another peak under the API peak (Resolution ≥ 2) in degraded solution of API under various stress conditions (Hydrolytic, oxidative, thermal, photolysis).
Range **Response**	Minimum five standard solutions covering: o 80-120% **(assay)** o 70-130% **(content uniformity)** o Reporting level - 120% of specifications **(impurities)**	R2 ≥ 0.995 (For drug Products) R2 ≥ 0.99 (For impurities)
Lower range limit **LOD** **(limit of detection)**	The lowest amount of analyte in a sample which can be detected but not necessarily quantitated	Signal to noise ratio (S/N) ≥ 3.
LOQ **(limit of quantification)**	The lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy.	Signal to noise ratio (S/N) ≥ 10.
Precision **Repeatability**	Minimum of nine determinations covering the specified range for the procedure (i.e., three concentrations and three replicates of each concentration) or using a minimum of six determinations at 100% of the test concentration	For drug Products RSD ≤ 3% For impurities: Level < 0.1%, RSD ≤ 30%, n ≥ 6 Level 0.1% - 0.2%, RSD≤ 20%, n ≥ 6 Level 0.2 - 0.5%, RSD ≤10%, n ≥ 6 Level 0.5 - 5%, RSD ≤ 5%, n ≥ 6
Intermediate Precision	Expresses within laboratories variations: different days, different analysts, and different equipment.	RSD ≤ 2% drug substance RSD ≤ 3% drug Product

Accuracy	Matrix spiked at 3 levels covering linearity range (nine determinations) (i.e., three concentrations and three replicates of each concentration) (n=9)	95-105.0% drug product for impurities: Level ≤ 0.2%: 70–130% 0.2–0.5%: 80–120% Level 0.5–5%: 90–110%
System suitability	100% concentration of standard solution	Otherwise specified in specific monograph: System repeatability n=5; RSD NMT 2% Resolution R ≥ 2 Tailing factor ≤ 2 Theoretical plates ≥ 2000 Capacity factor K ≥ 2

Robustness testing should show the reliability of an analytical procedure in response to deliberate variations in *analytical procedure parameters*, as well as the stability of the sample preparations and reagents for the duration of the procedure, if appropriate. The robustness evaluation can be submitted as part of development data for an analytical procedure on a case-by-case basis or should be made available upon request.[5]

Table 2 Acceptance criteria for validation parameters of analytical methods employed in quantitative analysis of dissolution

Validation Items	Requirement		Acceptance Criteria
1- Specificity	Demonstrate the absence of interferences of the following: ○ Placebo.		○ Should not exceed 2%
	○ Dissolution media.		○ Should not exceed 1%
	○ Other active drug substances & Degradants		○ Should not exceed 2%
2- Range **Response**	A minimum of 5 concentrations is recommended		○ The Y-intercept should not be significantly different from zero. ○ R^2 should be ≥ 0.98.
	Immediate release • One point specification Q – 45% of the lowest strength • Multiple point specification Lower limit of reportable range (as justified by the specification) or QL, as appropriate Modified release Lower limit of reportable range (as justified by the specification) or QL, as appropriate	to 130% of declared content of the highest strength	

[5] ICH Q2(R2)

4- Precision **Repeatability**	○ A minimum of 9 determinations covering the specified range for the procedure (e.g. 3 concentrations/ 3 replicates each) or ○ A minimum of 6 determinations at 100% of the test concentration.	○ %RSD < 2%
Intermediate Precision[6]	○ Typical variations to be studied include days, analysts, equipment, etc. "At least 2 different analysts on 2 days"	○ The difference in the mean value for dissolution results between any two conditions does not exceed an absolute 10% at time points with <85% dissolved and does not exceed 5% for time points NLT 85%. ○ Acceptance criteria may be product specific, and other statistical tests and limits may be used
7- Accuracy & Recovery	○ Accuracy should be assessed using a minimum of 9 determinations over a minimum of 3 concentration levels covering the specified range (e.g. 3 concentrations/ 3 replicates each of the total analytical procedure). ○ Accuracy should be reported as percent recovery.	○ Recovery percentage should be between 95% - 105%

Reproducibility is assessed by means of an inter-laboratory trial. Investigation of reproducibility is usually not required for regulatory submission but should be considered in cases of standardisation of an analytical procedure, for instance, for inclusion of procedures in pharmacopoeias and in cases where analytical procedures are conducted at multiple sites.

2. The verification process for compendial test procedures is the assessment of whether the procedure can be used for its intended purpose, under the actual conditions of use and drug product matrix.

Type of Analytical Procedure	Required Parameters
Identification:	– No requirement
Testing for Impurities:	– Specificity: no interference from excipients; – Reporting threshold (at least the LOQ)
Assay:	- Specificity, - Accuracy: mainly recovery, minimum 1 determination. - Precision (repeatability): around the target test concentration (minimum 2 independent determinations) - Response: Linearity at three measuring points in the range around the target value.

[6] In cases where reproducibility has been performed, intermediate precision is not needed

Annex VI

Required documents for file submission to CADC

Group 1	Documents of products, which are either locally produced or imported, that have previously received MA, submitted to the Administration of Post Approval Control, for laboratory testing for purposes other than post approval changes/ variations.
Group 2	Documents of products, which are either locally produced or imported, submitted to o The Administration of Evaluation and Approval, for MA, MA renewal/re-registration or post approval variations. o The Administration of Post Approval Control, for specific post approval variations: Addition or change of API supplier, addition or change of manufacturing site, scale-up of production.

Group 1 Files

The file consists of the following:

- **Regulatory folder**
- **Technical quality folder**

Regulatory folder contains the following:

1. Sample analysis request and sample collection report, and renewed report if present.
2. Registration license and other relevant approvals (eg. variation approvals)
3. Copy of the Final Report of analysis, issued by CADC for registration of the product, and in case it is not available, Group I general rules, subclause 6.4.1, shall be followed.
4. Copy of the stability studies approval, if available.
5. Quantitative composition according to which product has been manufactured

Technical quality folder file consists of the following:

1. Certificate of analysis of batches, sub batches.
2. Method of analysis and validation in case of changing from registration file and receipt for this change
3. Certificate of analysis and supplier's specifications for reference standard

Group 2 Files

The file consists of the following:

- **Regulatory Folder**
- **Technical Folder**

Regulatory folder contains the following:

1. Registration license and other relevant approvals (eg. variation approvals)
2. Registration Form
3. Quantitative composition
4. Sample analysis request and sample collection report, and renewed report if present.
5. COA of APIs
6. Finished product specifications
7. Finished product COA.
8. Box approval
9. Payment receipt
10. Material safety data sheet for all API and anti-oxidant and preservative
11. A declaration, by the applicant, of the category of sample collection and the number of batches sampled
12. Declaration that the information in the file submitted for assessment is correct

Technical quality folder file consists of the following sections of the CTD:

Table 1. Information required for each section

Section	Information required
3.2.p.4.1 Specification of excipients	• Specification of in-house excipients or monograph of compendial excipients
3.2.p.5.1 Specification of finished pharmaceutical products	• A list of tests, references to analytical procedures and acceptance criteria (which are numerical limits, ranges or other criteria) in a tabulated form. • FPP should conform to the specifications to be considered acceptable for its intended use. • Two separate sets of specifications may be set out: after packaging of the FPP (release) and at the end of shelf-life. • The specifications should be summarized according to the tables including the tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods): **Type**: type of analytical procedure used (e.g. visual, IR, UV, HPLC) Source: reference to the analytical procedure used (e.g. BP, Ph. Eur., Ph.Int., JP, USP, in-house) **Version:** (e.g. code number, version and date)

3.2.p.5.2. Analytical procedures	• Copies of the in-house analytical procedures used should be provided • It isn't necessary to provide copies of officially-recognized Compendial analytical procedures.
3.2.P.5.3 Validation of analytical procedures	• The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. • Copies of the validation reports for the in-house analytical procedures used should be provided including: specificity, linearity, accuracy, repeatability, intermediate precision and, for purity: LOD/LOQ. • For officially-recognized Compendial analytical procedures, verification is done. • Verification: is the assessment of whether the Compendial test procedure can be used for its intended purpose, under the actual conditions of use for a specified drug substance and/or drug product matrix. • Revalidation may be necessary if there is a change in the synthesis of the drug substance &/or changes in the composition of the finished product &/or changes in the analytical procedure.
3.2.p.5.4 Batch analysis	• Certificate of analysis of batch should be provided • A description of batch (include strength, batch number, date, site of production and results of batch analyses should be provided.
3.2. p.5.6 Justification of specs	• A discussion should be provided on the omission or inclusion of particular tests, evolution of tests, analytical procedures and acceptance criteria
3.2.p.6 Reference standard	• Information of reference standard used in analysis should be provided