Central Administration of Drug Control
General Administration For Technical Supprot

Guidelines for technical assessment of finished pharmaceutical products for human use files.

Year 2021

Code: EDREX:GL.CADC.002
Version No: 1/2021
Issue Date: 4/2021
Effective date: 4/2021

Table of Contents

1. 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.

2. 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 prior to marketing authorization, for MA renewal/ re-registration, and for post-approval changes.

3. Abbreviations

3.1 CADC: Central Administration of Drug control.

3.2 CAO: Central Administration of Operations.

3.3 CAPP: Central Administration of Pharmaceutical Products.

3.4 EDA: Egyptian Drug Authority.

3.5 EA: Administration of Evaluation and Approval

3.6 EMA: European Medicine Agency

3.7 FDA: Food & Drug Administration**.**

3.8 MAH : Marketing authorization holder

3.9 PAC: Administration of Post Approval Control**.**

3.10 TAE: Administration of Technical Assessment and Evaluation.

4. Definitions

4.1 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.

4.2 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.

4.3 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. Main topic

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

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

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

5.3.1 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.

5.3.2 Group II

Documents of products, which are either locally produced or imported, submitted to

5.3.2.1 The Administration of Evaluation and Approval, for MA, MA renewal/re-registration or post approval variations.

5.3.2.2 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.

5.4 Group I general rules:

5.4.1. Technical assessment shall be carried out with reference to the Final Report issued by the EA, or the updated specifications stipulated and approved by TAE for approval of MA renewal. In case the final report is not available, the guideline approved by the head of the CAO and the head of the CADC shall be adhered to.

5.4.1.1 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 pharmacopeia limits (USP, BP or EP), or according to product specifications approved by the General Administration for Stability of the CAPP, with no stipulation for the manufacturer to apply to CADC for modification of the previously issued Final Report. This does not apply to adding color limits, while for the microbial count & bacterial endotoxin limit tests, the analysis is performed according to pharmacopeia limits (USP, BP or EP in case the limits are not mentioned in the final report)

5.4.1.2 When a renewed MA is issued 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.

5.4.1.3 If the company wishes to amend (delete - add - change limits) for one of the tests, the company is directed to the Administration of Variation in CAPP and the relevant rules and regulations must be applied.

5.4.2. 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 or verification (if pharmacopeial) data and payment receipt via the link specified on the website for method update.

5.4.3. 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, prior to submission of the samples for analysis.

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

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

5.4.4.2. File assessment 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.

5.4.5. The following tests need to be updated regarding the type of the dosage form:

- Dissolution rate test
- Particulate matter
- Bacterial endotoxin

5.4.6. Local FPPs for human use may be submitted to the pre-assessment for obtaining the technical and the analysis requirements via the link for local pre-submission assessment, prior to submission of the samples for analysis.

5.5 Group II general rules:

5.5.1. Approvals and rules issued by any of the scientific and technical committees of EDA may be considered in the decision making process in CADC

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

5.5.3. 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:

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

5.5.3.2. 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, prior to submission of the samples for analysis

5.5.4. A pharmacopeial product is a product that has the name of a pharmacopeia included as part of the product trade name.

5.5.5. The product specifications that are evaluated to be included in the product's Final Report are shelf-life specifications.

5.6 Important Notes

5.6.1. Composition

5.6.1.1. The composition should be written as specified in the approval.

5.6.1.2. The function of inactive materials in product should be clarified according to Handbook of pharmaceutical excipients or any other reliable reference.

5.6.1.3. For Pharmacopeial API, it should comply with the latest version of the specified Pharmacopoeia.

5.6.2. Calculation sheet:

5.6.2.1. Separate calculation sheet to calculate equivalency of salt to the base.

5.6.2.2. For substances for which the potency is calculated as international unit, the amount of the substance will be mentioned in declaration composition in international unit and putting * below table with a footer that the amount used depend on potency of raw material.

5.6.3. Registration form

5.6.3.1. Full description of the package aligned with the attached samples.

5.6.3.2. Name of the manufacturer should be stated.

5.7 Finished Product specification and certificate of analysis of production should contain the active material as mentioned in registration approval and composition.

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

5.8.1. Full detailed method.

5.8.2. Complete validation or verification protocol and report.

5.8.3. Complete validation or verification charts.

5.8.4. Receipt of fees payment to change the method.

6. References:

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

6.2 ICH Q2(R1) Validation of Analytical Procedures.

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

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

6.5 Food and Drug Administration, "Methods, Method Verification and Validation", Laboratory Manual, ORA Laboratory Procedure, Volume II, ORA-LAB.5.4.5

6.6 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

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

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

6.9 British Pharmacopoeia Commission. British Pharmacopoeia 2022.

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

7. Annexes:

7.1 Annex I: Physical analysis

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

7.3 Annex III: Chemical analysis

7.4 Annex IV: Microbiological analysis

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

Annex I

Assessment of Finished Pharmaceutical Products (Physical analysis)

File assessment for any dosage form will be performed according to the following checklists:

Checklist guide

1. Checklist for tests performed on Aerosols (packaged under pressure):

Test	Applicability	Acceptance criteria
1. Description	All	
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	Perform this test only on topical 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) (performance Quality test) Procedure according to USP-NF ⟨601⟩ Inhalation and Nasal Drug Products_ Aerosols, Sprays, and Powders—Performance Quality Tests N.B. Appropriate and validated or calibrated emitted droplet/particle size analytical procedures should be described in sufficient detail to allow accurate and reproducible assessment.	Nasal aerosol Suspension (particle size) and solution (droplet size)	According to manufacturer specifications

10. 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 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. Checklist for tests performed on capsules:

Test	Applicability	Information should be available	Acceptance criteria
1-Description: • **Appearance** • **Colour**		○ 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) content	According to manufacturer specifications
2-Mass uniformity* (BP) Procedure is according to BP (Ph. Eur. method 2.9.5).	Done on capsule content. o Not done if 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 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)***	Done for 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.** ○ **In-house method** **Obey the dissolution method development criteria.** **Refer to (Annex 2)**	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. **In this case, the performed dissolution method should be supplied by the manufacturer**. N.B.: This guidance is not applicable for sublingual dosage forms (FDA Guidance for Industry. Dissolution tests and acceptance criteria for immediate-release solid oral dosage form drug products containing high solubility drug substances. Rockville, MD: Food and Drug Administration; August 2018.)	• Dissolution Parameters: ○ 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)	(Ph. Eur. method 2.9.3) USP-NF ⟨711⟩ DISSOLUTION
5- Water content (USP) Procedure is according to manufacturer's method or specific monograph.	○ Cited in monograph. ○ Stated by manufacturer. ○ Not cited in its specific monograph ○ There is no specific monograph & not stated by manufacturer.	○ Yes ○ Yes ○ No ○ Need justification to skip test	According to monograph or manufacturer's specifications
6-Acid-neutralizing capacity (USP) Procedure according to USP-NF ⟨ 301⟩ Acid neutralizing capacity	o 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.

3. Checklist for tests performed for creams, Gels & ointments:

Test	Applicability	Information should be available	Acceptance criteria
1.Description: ○ **Appearance** ○ **Colour** ○ **Homogeneity** ○ **Visible foreign matter**	All		
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—PRODUCTQUALITY TESTS)		USP-NF ⟨**755**⟩ **MINIMUM FILL**
3.**pH** **procedure of Sample preparation to measure pH is 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 the manufacturer specifications
4. **Apparent 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>**	ALL	○ Type of device (model) ○ Device subtype ○ Spindle no. ○ Rpm ○ temperature	According to manufacturer's specifications

5.Water content Procedure is according to manufacturer's method or specific monograph.	○ If cited in monograph. ○ If stated by manufacturer. ○ If There is no specific monograph & not stated by manufacturer	○ Yes ○ Yes ○ Need justification to skip test.	
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. Checklist for tests performed on emulsions:

Test	Applicability	Acceptance criteria
1. Description: ○ **Appearance** ○ **Colour** ○ **Viscous or not**	All	
2. **Minimum fill** Procedure according to USP-NF ⟨755⟩ MINIMUM FILL	o Vaginal emulsion, o Rectal emulsion, o Ophthalmic emulsion, o Otic emulsion. o 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 of sample preparation to measure pH is according to manufacturer's method.	o hydrophilic emulsions (o/w) 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⟩** - Procedure of viscosity according to ***Viscosity–Capillary Methods USP-NF*<911>, *Viscosity–Rationale Methods USP-NF*<912>, and *Viscosity–Rolling Ball Method USP-NF*<913>**	o Relatively viscous emulsions o Ophthalmic o Topical, o Otic and o Oral	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 and 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	
10. Osmolality Procedure according to USP-NF ⟨785⟩ Osmolality and Osmolarity	Only for products labeled with tonicity: o Ophthalmic emulsions	According to manufacturer specifications

6. Checklist for tests performed on Films:

Test	Applicability	Information should be available	Acceptance criteria
1. Description: ○ **Appearance** ○ **dimensions**	All		
2. Dissolution reference of method is one of the following: ○ **USP or BP specific monograph.** ○ **FDA dissolution methods database with dissolution profile in the most suitable media.** ○ **In-house method with comparative dissolution study.**		•Dissolution Parameters: ○ Media composition & pH ○ Media volume ○ Apparatus type ○ rpm ○ Temperature ○ Sampling time ○ Q (the amount dissolved)	(Ph.Eur. method 2.9.3) USP-NF ⟨711⟩ DISSOLUTION
3. Water content Procedure is according to manufacturer's method or specific monograph.	○ Cited in monograph. ○ Stated by manufacturer . ○ Not cited in its specific monograph o There is no specific monograph & not Stated by manufacturer.	○ Yes ○ Yes ○ No ○ Need justification.	According to manufacturer specifications.

6. Checklist for tests performed on Foams:

Tests	Applicability		Acceptance criteria
1. Description Physical appearance (of the foam and of the collapsed foam) (USP)	All		
2. Net fill weight/ Minimum fill (USP) procedure according to USP-NF ⟨755⟩ MINIMUM FILL	All		⟨USP 755⟩ MINIMUM FILL
3. Leak rate (USP) Procedure according to USP-NF ⟨604⟩ LEAK RATE	All		USP-NF ⟨604⟩ LEAK RATE
4. pH Procedure of sample preparation to measure pH is 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: ⟨607⟩ PHARMACEUTICAL FOAMS PRODUCT QUALITY TESTS.	Topical		According to manufacturer specifications
6. Time to Break (USP) Procedure is according to: ⟨607⟩ PHARMACEUTICAL FOAMS— PRODUCT QUALITY TESTS.	Topical		According to manufacturer's specifications
7. Delivery rate (USP) Procedure is according to: ⟨603⟩TOPICAL AEROSOLS	Topical		According to manufacturer's specifications
8. Delivered amount (USP) Procedure is according to: ⟨603⟩TOPICAL AEROSOLS.	Topical		According to manufacturer's specifications
9. Water content (USP) Procedure is according to manufacturer's method or specific monograph.	Mainly for non-aqueous foams ○ If cited in monograph. ○ If stated by manufacturer. ○ Not cited in its specific monograph ○ If there is no specific monograph & not stated by manufacturer	○ Yes ○ Yes ○ No ○ Need justification	According to manufacturer's specifications
10. Osmolarity and 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. Checklist for tests performed on Granules:

Test	Applicability		Information should be available	Acceptance criteria
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)	
2-Deliverable volume (USP) Procedure according to: USP-NF ⟨698⟩ DELIVERABLE VOLUME	Only <u>oral granules</u> 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 <u>provided at manufacture with a measuring device</u>.			○ 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 is according to: (Ph. Eur. method 2.9.5)	○ <u>Uncoated</u> single dose granules ○ Coated granules ○ Multiple dose granules -Not done if 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 ○ 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 with dissolution profile in the most suitable media.** ○ **In-house method with comparative dissolution study.**	o Granules that result in a 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)***	o 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.	○ Effervescent granules ○ Granules for reconstitution **<u>Other granules</u>:** ○ Cited in monograph. ○ Stated by manufacturer. ○ Not cited in its specific monograph ○ There is no specific monograph & not stated by manufacturer.	○ Yes ○ Yes ○ Yes ○ Yes ○ No ○ Need justification to skip test	

9-pH (USP) Procedure of sample preparation to measure pH 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	Suspendable or not
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 only 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)	**According to manufacturer specifications**
13- Acid neutralizing capacity (USP) Procedure is 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. Checklist for 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.	
2.Mass uniformity* (BP) Procedure is according to: Ph. Eur. method 2.9.5	○ Molded ○ Compressed	○ Yes ○ Yes		• 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- Water content (USP) **Procedure is according to Manufacturer's method or specific monograph.**	○ Not cited in its specific monograph ○ Cited in monograph or stated by manufacturer ○ There is no specific monograph & not stated by manufacturer	○ **No** ○ **Yes** ○ **Need justification to skip test**		According to monograph or manufacturer's specifications
5. Dissolution **Reference of method is chosen from one of the following:** ○ **USP or BP specific monograph.** ○ **FDA dissolution methods database with dissolution profile in the most suitable media.** ○ **In-house method with comparative dissolution study.**	• 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)	(Ph. Eur. method 2.9.3) USP-NF ⟨711⟩ DISSOLUTION

6.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)
7.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.

9. Checklist tests performed on Powders:

Test	Applicability		Information should be available	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	
2-Minimum fill (USP) Procedure according to USP- NF ⟨755⟩ MINIMUM FILL	o Powders for oral suspension packaged in containers (where test of deliverable volume is applicable). ○ Other multiple dose powders. ○ Powder for inhalation (device metered)	o No ○ Yes ○ Yes	Labeled amount	⟨USP **755**⟩ **MINIMUM FILL**
3-Deliverable volume (USP) Procedure according to ⟨USP 698⟩ DELIVERABLE VOLUME	only **oral** powders for reconstitution (after reconstitution) in: ○ Multiple dose container ○ Single dose container	○ Yes ○ Yes	Labeled volume	⟨USP **698**⟩ **DELIVERABLE VOLUME**
4-Uniformity of Weight (Mass) of Delivered Doses from Multi-dose Containers (BP) Procedure according to: (Ph. ur. 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) ○ 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 with dissolution profile in the most suitable media.** **In-house method with comparative dissolution study.**	Powder reconstituted to form oral suspension otherwise justified). o Powder reconstituted to form sustained ophthalmic or parenteral.	○ Yes	○ 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 ⟨711⟩ DISSOLUTION

8- Water content (USP) Procedure is according to the specific monograph or manufacturer in house method.	**Obligatory without justification.** ○ Powder for parenteral solution and suspension. ○ Powder for inhalation solution ○ Inhalation powder ○ Powder for oral suspension or solution ○ Effervescent powders ○ Lyophilized powders ○ Cited in monograph. ○ Stated by manufacturer. ○ Not cited in its specific monograph ○ There is no specific monograph & not stated by manufacturer.	o Yes o Yes o Yes o Yes o Yes o Yes o Yes o Yes o No o Need justification to skip test		According to manufacturer specifications USP NF ⟨2⟩ **ORAL DRUG PRODUCTS —PRODUCT QUALITY TESTS**
9- Reconstitution time (USP) USP-NF ⟨5⟩ INHALATION AND NASAL DRUG PRODUCTS— GENERALINFORMATION AND PRODUCT QUALITY TESTS	Powder for inhalation solution.			According to manufacturer specifications
10- pH (USP) Procedure of sample preparation to measure pH is 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 USP-NF ⟨789⟩ PARTICULATE MATTER IN OPHTHALMIC SOLUTIONS
12- Completeness of solution after reconstitution USP-NF ⟨5⟩ INHALATION AND NASAL DRUG PRODUCTS—GENERALINFORMATION AND PRODUCT QUALITY TESTS. USP-NF ⟨1⟩ INJECTIONS AND IMPLANTED DRUG PRODUCTS(PARENTERALS) —PRODUCT QUALITY TESTS.	Powder for parenteral solution Powder for inhalation solution	
13- Suspendability	For suspension after reconstitution.	
14- Powder fineness (BP) Procedure is according to the sieve test BP (2.9.35)	Done if prescribed (stated in the monograph or by manufacturer) for Topical powder	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 only after reconstitution.	*(Liquid Preparations for Oral Use, Ph. Eur. monograph 0672)*

16- 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 reconstituted powder (after reconstitution)	According to manufacture specifications
17- Acid-neutralizing capacity (USP) Procedure according to USP-NF ⟨301⟩ ACID-NEUTRALIZING CAPACITY	For antacids	
18- Particle size distribution. *(performance test)** Procedure according to USP-NF ⟨601⟩ Inhalation and Nasal Drug Products_ Aerosols, Sprays, and Powders—Performance Quality Tests N.B. Appropriate and validated or calibrated emitted particle size analytical procedures should be described in sufficient detail to allow accurate and reproducible assessment. ICH Q6A	-Nasal powders -Powder for reconstitution give parenteral suspension	According to manufacturer specifications. USP NF ⟨601⟩ INHALATION AND NASAL DRUG PRODUCTS: AEROSOLS, SPRAYS, AND POWDERS— PERFORMANCE QUALITY TESTS
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 USP NF ⟨601⟩ INHALATION AND NASAL DRUG PRODUCTS: AEROSOLS, SPRAYS, AND POWDERS— PERFORMANCE QUALITY TESTS

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. Checklist for tests performed on solutions:

Test	Applicability	Acceptance criteria
1. Description: ○ **Appearance** ○ **colour** ○ **Visual foreign matter** ○ **Viscous or not.**	All	
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 Procedure is according to *(Ph. Eur. monograph 0671)*	o Single-dose inhalation solutions	*(Ph. Eur. monograph 0671)*
4. **pH**	o Aqueous solutions It is formulation dependent, According to manufacturer specifications.	According to the manufacturer specifications
7. 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⟩	○ Ophthalmic, ○ Nasal, ○ Inhalation ○ Topical, ○ Otic and ○ Oral	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** USP-NF ⟨**789**⟩ **PARTICULATE MATTER IN OPHTHALMIC SOLUTIONS**

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	Only for products labeled with tonicity: o nasal solutions o inhalation solutions, o ophthalmic solutions	According to manufacturer specifications

11. Checklist for the performed tests on Sprays (non-pressurized liquid):

Test	Applicability	Acceptance criteria
1. Description	All	
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 dos oromucosal 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 of sample preparation to measure pH 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. (performance test)*** Procedure according to USP-NF ⟨601⟩ Inhalation and Nasal Drug Products_ Aerosols, Sprays, and Powders—Performance Quality Tests N.B. Appropriate and validated or calibrated emitted droplet/particle size analytical procedures should be described in sufficient detail to allow accurate and reproducible assessment	nasal spray Suspension (particle size) and solution (droplet size)	According to manufacturer specifications

8. 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 spray only	According to manufacturer specifications
9. Osmolality Procedure according to USP-NF ⟨785⟩ Osmolality and Osmolarity	For nasal spray labeled with certain tonicity	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. Checklist for tests performed on suppositories:

Test	Applicability	Information should be available	Acceptance criteria
1-Description: • **Appearance** • **Colour**			
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 chosen from one of the following: ○ **USP or BP specific monograph.** ○ **FDA dissolution methods database with dissolution profile in the most suitable media.** ○ **In-house method with comparative dissolution study.**	All Suppositories and pessaries.		○Dissolution Parameters: ○ Filter type (common types Nylon, PVDF & PTFE) ○ Media composition. & pH ○ Media volume ○ Apparatus type ○ rpm ○ temp ○ sampling time ○ Q (the amount dissolve)	(Ph. Eur. method 2.9.3) USP-NF ⟨711⟩ DISSOLUTION
5- Water content (USP) Procedure is according to manufacturer's method or specific monograph.	○ Cited in monograph. ○ Stated by manufacturer. ○ Not cited in its specific monograph ○ There is no specific monograph & not stated by manufacturer	○ Yes ○ Yes ○ No ○ Need justification to skip test		According to monograph or manufacturer's specifications
6- Softening time(USP)	**Lipophilic suppositories**			

* 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 not to be done and disintegration time is sufficient.

13. Checklist for tests performed for suspensions:

Test	Applicability	Acceptance criteria
1. Description: ○ **Appearance** ○ **Color/ with certain viscosity or not**	All	
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	o Aqueous suspensions It is formulation dependent, According to manufacturer specifications.	According to the manufacturer specifications
4. 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⟩	relatively viscous suspensions ○ Ophthalmic, ○ nasal, ○ Inhalation ○ Topical, ○ Otic and ○ Oral	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**

9. Dissolution* **Reference of method is chosen from one of the following:** o **USP or BP specific monograph.** o **FDA dissolution methods database with dissolution profile in the most suitable media.** o **In-house method with comparative dissolution study.**	o **Oral suspensions (unless otherwise justified).** **o Sustained Ophthalmic suspensions** o **Sustained parenteral suspensions**	Dissolution Parameters: o Filter type (common types Nylon, PVDF & PTFE) o Media composition & pH o Media volume o Apparatus type o rpm o temp o sampling time o Q (the amount dissolved)	(Ph. Eur. method 2.9.3) USP-NF ⟨711⟩ DISSOLUTION
10. Acid Neutralizing capacity Procedure is according to: USP-NF ⟨301⟩ ACID- NEUTRALIZING CAPACITY	**Antacids**		According to manufacturer specifications
11. Re-Suspendability	**All suspensions**		
12. Particle size distribution ** (performance test)	o Nasal suspension (USP-NF ⟨601⟩ INHALATION AND NASAL DRUG PRODUCTS: AEROSOLS, SPRAYS, AND POWDERS- PERFORMANCE QUALITY TESTS). o ophthalmic suspension *(Ph. Eur. monograph 1163)* o parenteral 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	o Inhalation suspension		According to manufacturer specifications
14. Osmolality Procedure according to USP-NF ⟨785⟩ Osmolality and Osmolarity	Only for products labeled with tonicity: o nasal suspensions o inhalation suspensions, o ophthalmic suspensions		According to manufacturer specifications

* 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. Checklist for tests performed on Tablets:

Test	applicability		Information should be available	Acceptance criteria
	Tablet Type	Done/ Not done		
1.Description: ○ **Appearance** ○ **Colour of tablet**			○ Tablet shape ○ Colour ○ Colour of core & coat in case of coated tablets ○ Type of coating case of coated tablets ○ Scored or not. ○ Biconvex/flat.	
2.Mass uniformity* (BP) Procedure is according to: Ph. Eur. method 2.9.5))	• Type of coat: ○ Uncoated ○ Film coat ○ Sugar coat ○ If average mass ≤40 mg **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 ○ 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 is 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.** ○ **In-house method Obey the dissolution method development criteria. Refer to (Annex 2)**	○ 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. Refer to (Annex 2: Development for in-house dissolution methods)** In this case, the performed dissolution method should be supplied by the manufacturer. N.B.: This guidance is not applicable for sublingual dosage forms (FDA Guidance for Industry. Dissolution is testing and acceptance criteria for immediate-release solid oral dosage form drug products containing high solubility drug substances. Rockville, MD: Food and Drug Administration; August 2018.)	○ No ○ Yes	Dissolution Parameters: ○ Filter type (common types Nylon, PVDF & PTFE) o Media composition & pH o Media volume o Apparatus type o Sinkers needed (common type: :coiled sinker) o rpm o temp o sampling time o Q (the amount dissolved)	(Ph. Eur. method 2.9.3) USP-NF ⟨711⟩ DISSOLUTION
5. Friability (USP & BP) Procedure is 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 is 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 is according to manufacturer's method or specific monograph.	○ Effervescent tablets ○ Oral lyophilizates ○ Cited in monograph ○ Stated by manufacturer. ○ Not cited in its specific monograph ○ There is no specific monograph & Not stated by manufacturer	○ Yes ○ Yes ○ Yes ○ Yes ○ No ○ Need justification to skip test	According to monograph or manufacturer's specifications
9. Acid neutralizing capacity (USP) **Procedure according to USP-NF ⟨ 301 ⟩ ACID-NEUTRALIZING CAPACITY**	Antacids only		-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)*)

* 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

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15. Checklist for tests performed on Transdermal Delivery Systems (TDS)

Test	Applicability		Information should be available	Acceptance criteria
	TDS type	Done/ Not done		
1- Description	o All types	o Yes		According to manufacturer's specifications
2- Dimensions	o All types	o Yes		According to manufacturer's specifications
3- Water content Procedure is according to manufacturer's method or specific monograph.	○ Cited in monograph ○ Stated by manufacturer. ○ Not cited in its specific monograph ○ There is no specific monograph & not stated by manufacturer.	o Yes o Yes o No o Need justification	○ Cited in monograph or stated by manufacturer . ○ Not cited in its specific monograph ○ There is no specific monograph & not stated by manufacturer	According to manufacturer's specifications

4- Dissolution **Reference of method is chosen from one of the following:** ○ **USP or BP specific monograph.** ○ **FDA dissolution methods database with dissolution profile in the most suitable media.** ○ **In-house method with comparative dissolution study.**	All types		• **<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)	(Ph. Eur. method 2.9.3) USP-NF ⟨**711**⟩ **DISSOLUTION**
5- particle size	• Suspension in reservoir • Others	o Yes o No		• According to manufacturer's specifications
6- • **Peel adhesion test,** • **Release liner peel test,** • **Tack test,** • **Cold flow test,** • **Shear test**	o All types	o Yes		• 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)

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
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)

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

Or

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

BCS class II or IV
Containing low Solubility Drug Substances

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

BCS class I or III

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)

Method

A. Basket Method (USP apparatus 1)
- **Stirring rate = 100 RPM**
- **500 mL of 0.1N HCl in aqueous medium**
- **No surfactant in**

Or

B. Paddle Method (USP apparatus 2)
- **Stirring rate = 50 RPM (or 75 rpm with appropriate justification**
- **500 mL of 0.1N HCl in aqueous medium**
- **No surfactant in medium**

FDA guidance for industry:

Dissolution Testing of Immediate Release Solid Oral Dosage Forms. August 1997

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.
Deareation	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 recommended that 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.

Comparative dissolution study:

A. When to submit comparative dissolution study?

Dissolution method reference	The need to submit comparative dissolution study
○ USP or BP specific monograph.	No need to submit comparative dissolution study
○ FDA dissolution methods database.	Submit dissolution profile with the reference in the most suitable medium only
○ In case of highly soluble drugs (BCS I or III) obeying one of the two methods mentioned in the FDA Guidance for Industry: "Dissolution testing and acceptance criteria for immediate-release solid oral dosage form drug products containing high solubility drug substances. Rockville, MD: Food and Drug Administration; August 2018." And the acceptance criteria is Q=80% in 30 minutes. (Annex 2)	No need to submit comparative dissolution study
○ In-house method: Obeying the dissolution method development criteria mentioned in (Annex 2): 1- USP –NF ⟨1092⟩ THE DISSOLUTION PROCEDURE: DEVELOPMENT AND VALIDATION and 2- FDA Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms Rockville, MD: Food and Drug Administration; August 1997). And the acceptance criteria is Q=75% in 45 minutes or less	Submit dissolution profile with the reference in the most suitable medium only.
○ In-house method: Obeying the dissolution method development criteria mentioned in (Annex 2): 1- USP –NF ⟨1092⟩ THE DISSOLUTION PROCEDURE: DEVELOPMENT AND VALIDATION and 2- FDA Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms Rockville, MD: Food and Drug Administration; August 1997). And the acceptance criteria is Q < 75% in 45 minutes or more than 45 minutes.	Submit the complete comparative dissolution study in the 3 buffers dissolution media (pH 1.2, 4.5 & 6.8) in addition to the most suitable dissolution medium.

B- 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.

Validation of the analytical methods employed in quantitative analysis of dissolution samples

Validation Items	Required Procedure	Acceptance Criteria
1- Linearity	✔ A minimum of 5 concentrations is recommended	✔ The Y-intercept should not be significantly different from zero. ✔ R^2 should be ≥ 0.98.
2- Range	✔ +/-20 % over the specified range, e.g., if the specifications for a controlled released product cover a region from 20%, after 1 hour, up to 90%, after 24 hours, the validated range would be 0-110% of the label claim.	
3- 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%
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 (Ruggedness)*	✔ 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.
✔ **Reproducibility**	✔ Reproducibility is assessed by means of an inter-laboratory trial	
5- 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%

* In cases where reproducibility has been performed, intermediate precision is not needed.

Annex III

Chemical analysis

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

I. Specifications:

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

2- In case of in-house API:

a) If it has a monograph in any of the pharmacopeias, specifications of supplier are accepted if it only complies with the specifications listed in the pharmacopeia or tighter specifications.

b) If it doesn't have any monographs in any of the pharmacopeias, specifications of supplier are accepted providing 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.

B. Finished pharmaceutical products (FPP): generally CADC laboratories use latest editions of pharmacopeias in assessment of submitted dossiers for:

- Products described as Pharmacopeial where specifications of this product must follow the specifications in the whole monograph in the reference pharmacopeia.
- Products that have pharmacopeial monograph(s) where specifications listed in the pharmacopeial monograph are used as the main reference in the evaluation of the required tests and specifications.

1) Specifications and Certificate of Analysis:

1-Identification tests for API:

- Identification test item must be included in the specification sheet and finished product certificate of analysis (CoA)
- Titrimetry is not an identification test.

2-Assay of API, Antimicrobial preservatives and antioxidants:

a. General acceptance limit for the API is 90-110% of the Labeled claim.
b. General acceptance limit for the preservative is 80-120% of the Labeled claim.
c. General acceptance limit for the antioxidant is 50-120% of the Labeled claim.

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

d. Analysis of preservatives in solid dosage form in capsule shells is not mandatory unless it is listed in the manufacturer specifications.
e. Analysis of any other excipients is not mandatory unless it is listed in the manufacturer specifications.
f. 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).
g. Limits for assay should be expressed in terms of active moiety (free acid or base, anhydrous basis) unless otherwise specified in the specific monograph.

3-Uniformity of dosage unit:

a) 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.

b) (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%.

-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>

-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.

- The test is not intended to apply to suspensions emulsions, or gels in unit-dose containers intended for external, cutaneous administration.

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

4-Test of impurities

a) Residual solvents:

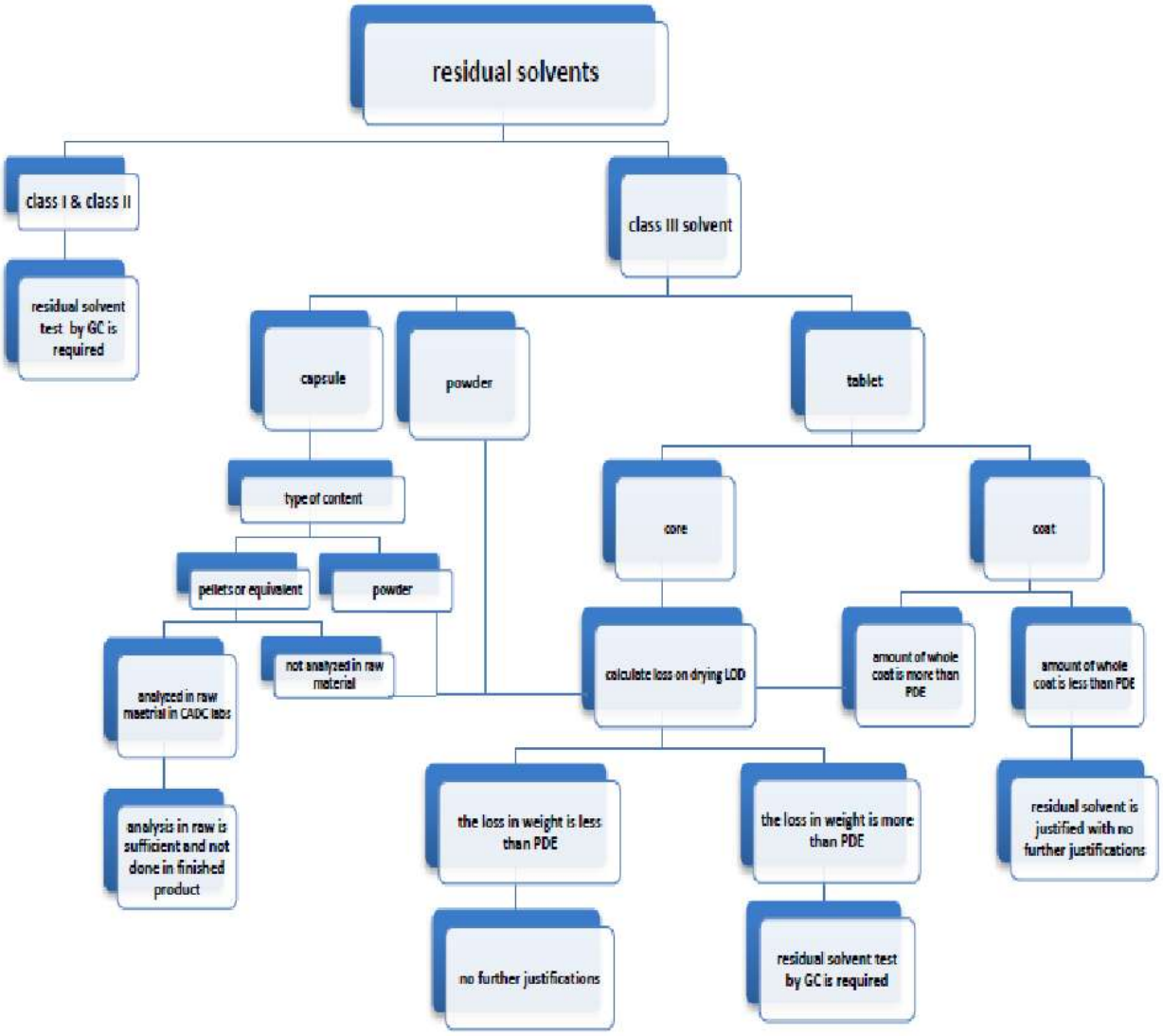
-Assessment of residual solvents impurities will be according to ICH Q3C otherwise specified in the specific monograph.

- 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

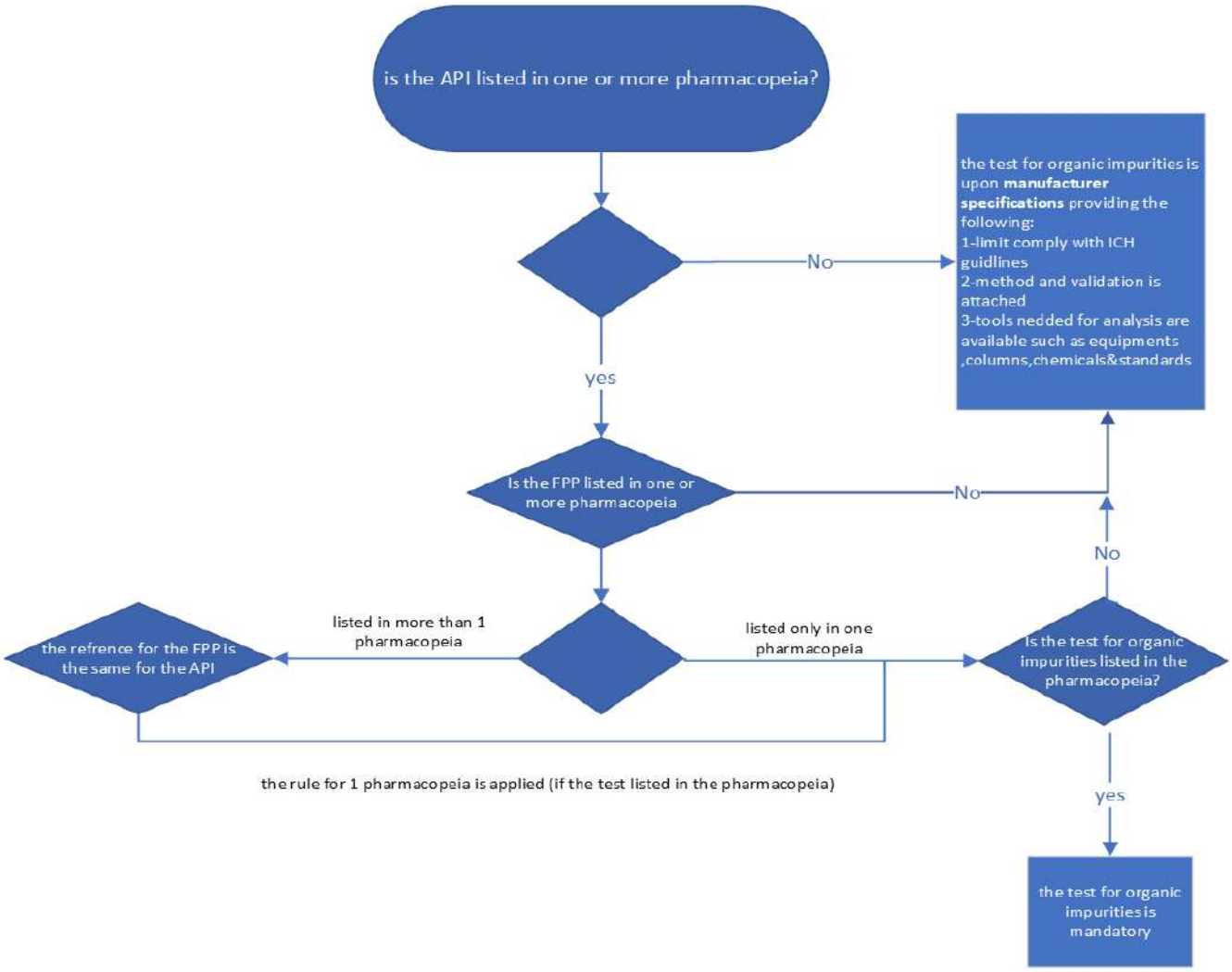
where verification of USP procedures or validation of alternative methods for residual solvents are performed according to USP<1467>.

Assessment of class III solvents



b) Organic impurities/ related substances:

Decision tree for organic impurities test:



• 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

• 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.

• 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 filing in the capsule (powder, granules, pellets, liquid, semisolid, etc.) and accordingly test for organic impurities described under the monograph if present must be applied to any of the previous.

- In USP monographs of tablets, unless otherwise stated the tablets are considered immediate release regardless 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.

5- Alcohol content.

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

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.

3) Method Validation (MV):

a) When a non-pharmacopeial method is used a full validation study must be submitted with the method of analysis.

b) Verification of Pharmacopeial methods is performed according to USP <1226> and OMCL guideline.

c) 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.

d) Validation will be assessed according to ICH Q2 (R1) as table 1:

Type of analytical procedure characteristics	IDENTIFICATION	TESTING FOR IMPURITIES quantitat.	 limit	ASSAY - dissolution (measurement only) - content/potency
Accuracy	-	+	-	+
Precision				
Repeatability	-	+	-	+
Interm.Precision	-	+ (1)	-	+ (1)
Specificity (2)	+	+	+	+
Detection Limit	-	- (3)	+	-
Quantitation Limit	-	+	-	-
Linearity	-	+	-	+
Range	-	+	-	+

\- signifies that this characteristic is not normally evaluated

\+ signifies that this characteristic is normally evaluated

(1) in cases where reproducibility (see glossary) has been performed, intermediate precision is not needed

(2) lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s)

(3) may be needed in some cases

e) Minimum Acceptance criteria for validation parameters of Drug Product quality characteristics table 2:

Specificity	Blank measurement	Resolution: NLT 1.5/ Blank interference NMT 1%
	Placebo measurement	Resolution: NLT 1.5/ Placebo interference NMT 2%
	Peak purity	Demonstration of lack of interference according to 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).
Linearity and range	Minimum five standard solutions covering: ● 80-120% **(assay)** ● 70-130% **(content uniformity)** ● +/-20 % over the specified range **(dissolution)** ● reporting level - 120% of specifications **(impurities)**	R2 ≥ 0.995 (For drug Products) R2 ≥ 0.99 (For impurities)
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%
LOD	The lowest amount of analyte in a sample which can be detected but not necessarily quantitated	Signal to noise ratio (S/N) ≥ 3.
LOQ	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.
Robustness	Defined based on an experimental design and data (sensitive parameters and a range for each parameter in the final test method).	

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

f) 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.

Identification:	– no formal validation required
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) – Linearity at three measuring points in the range around the target value.

4) Analysis requirements:

a) Standards:

- Primary Reference standard is preferable
- EDA schedule for CRM is applied
- In case a working standard is submitted EDA template for working standard is mandatory illustrating lot number for primary standard used in its qualification as evidence of traceability in the COA submitted.

In case of non-Pharmacopeial standard: commitment is given that if those sent standards gave unsatisfactory results, the company is obliged to send the official Pharmacopeial reference standards.

b) Analytical Columns:

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

c) 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.

Special considerations:

a. 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.

b. 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.

c. 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.

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

- 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.

- 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)

- For limits of assay, Pharmacopeial acceptance criteria are generally applied whenever available.

Annex IV

File Assessment 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.**
1. **Rabbit test.**

1- Microbiological Examination of non-sterile products

*__Definition__: are tests designed primarily to determine whether **Non-sterile pharmaceutical products** comply with an established specification for microbiological quality.

 # The following data are required:

1) Sufficient 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) 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 ml) and *Salmonella spp.* (10 g or 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- 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- 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 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

*__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.

 # The following data are required:

1) Sufficient sample size for testing,

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

Table 5: Minimum Quantity to be used for Each Medium;

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) 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*.

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

*__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.

1- General Notes

a- Raw materials and finished products mentioned in pharmacopeia will be tested according to recent version of pharmacopeia.

b- Sample size for test and retest

For samples of 50 gm - 1000 gm: one package

For samples 10gm- 40 gm: 2 packages

For samples less than 10 gm: 4 packages

For liquid samples: not less than 50 ml

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

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

e- CADC has rights to ask for analysis tools (e.g. Reference strains and/or reference standards) as needed.

2- Test specifications: the following information should be provided;

Tested parameter	● Potency of Antibiotics
Antibiotic composition	● Mentioned
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.

I-Notes:

a. Raw material mentioned in pharmacopeia will be tested according to recent version of pharmacopeia.
b. Products of formula identical to that mentioned in the monographs of the pharmacopeia will be tested according to recent version of pharmacopeia.
c. If Products of formula identical to that mentioned in the monographs of the pharmacopeia were assayed by chemical assays, microbiological assays will not be allowed. (Follow the pharmacopeia).
d. The only case for accepting the in-house method is when the raw material or the product has formula not mentioned in the pharmacopeia. (e.g. non-Pharmacopeial combinations)
e. For non-Pharmacopeial combinations, the in-house methods should include separation technique between antibiotics and validation protocols.

4. DISINFECTANTS CHALLEMGE TESTING

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.

- **Test specifications:** the following information should be provided;

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.

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.*

5. BACTERIAL ENDOTOXINS TEST

 # The following data are required:

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.
5) Pamphlet of the product	If unavailable then the pamphlet of reference product is recommended.
6) Sufficient 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)*
7) Specifications of the product	----------

8) Acceptance criteria:

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		5 EU/kg of body weight	Maximum dose per kilogram administered in 1 h

IV for radiopharmaceuticals	Depending on specific monograph of each product	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 Vet products administrated to variety of different species, you should select the smallest animal
that receiving the greatest dose per Kg.

6. Rabbit test

1. Rabbit test is only accepted in case of products incompatible with LAL techniques due to interference.
2. Complete justification that proves the incompatibility must be delivered with its supportive results.
3. Detailed SOP of each product must be delivered containing at least the followings:
   3.1. Diluent used in case of powder products/materials which will be reconstituted.
   3.2. Dose to be administrated per Kg.
   3.3. Dose preparation.
   3.4. Reference.
4. Acceptance criteria

	Acceptance criteria
Rabbit test	e.g. 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.

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.

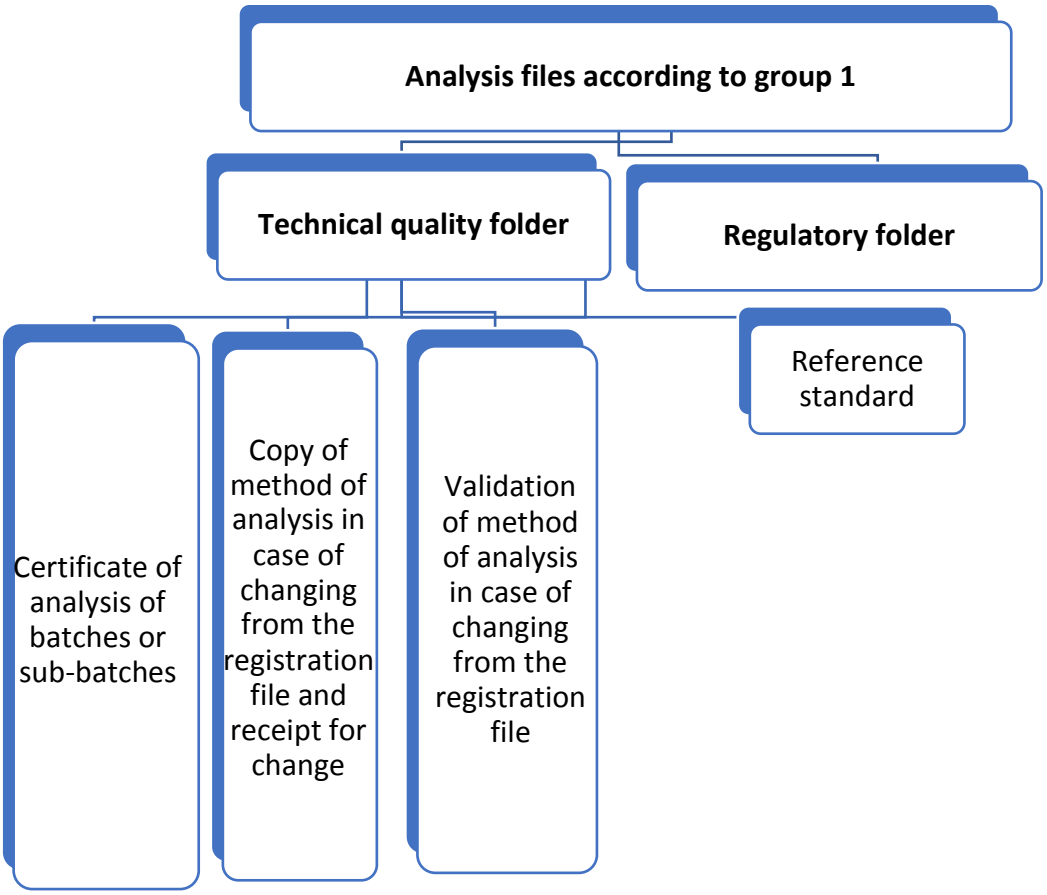
(Unless otherwise the label states that the preparation is apyrogenic or free of bacterial endotoxin).

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

Annex V

Group 1	(الملفات المقدمه الى ادراه الرقابه بعد الاعتماد(فى ما عدا تغيير مورد او نقل مكان تصنيع
Group 2	(الملفات المقدمه الى اداره التقييم والاعتماد واداره الرقابه بعد الاعتماد (تغيير مورد ونقل مكان تصنيع

Analysis file submitted to CADC group 1



The file consists of the following folder:

- **Regulatory folder**
- **Technical quality folder**
- **Regulatory folder contains the following:**

١- اورنيك السحب ومحضر المفتش ومحضر التجديد ان وجد

٢- اخطار التسجيل وأى موافقات اخرى مثال ....(تغيير عبوة/ بيان تركيب /.....)

٣- صوره احدث تقرير نهائى للمستحضر ان وجد وفى حاله عدم الاستدلال يتم الالتزام بالاليه التنسيقيه بين الاداره المركزيه للرقابه الدوائيه والاداره المركزيه للعمليات.

٤- صوره من موافقه الثبات ان وجد.

5- بيان التركيب الذى تم التصنيع عليه.

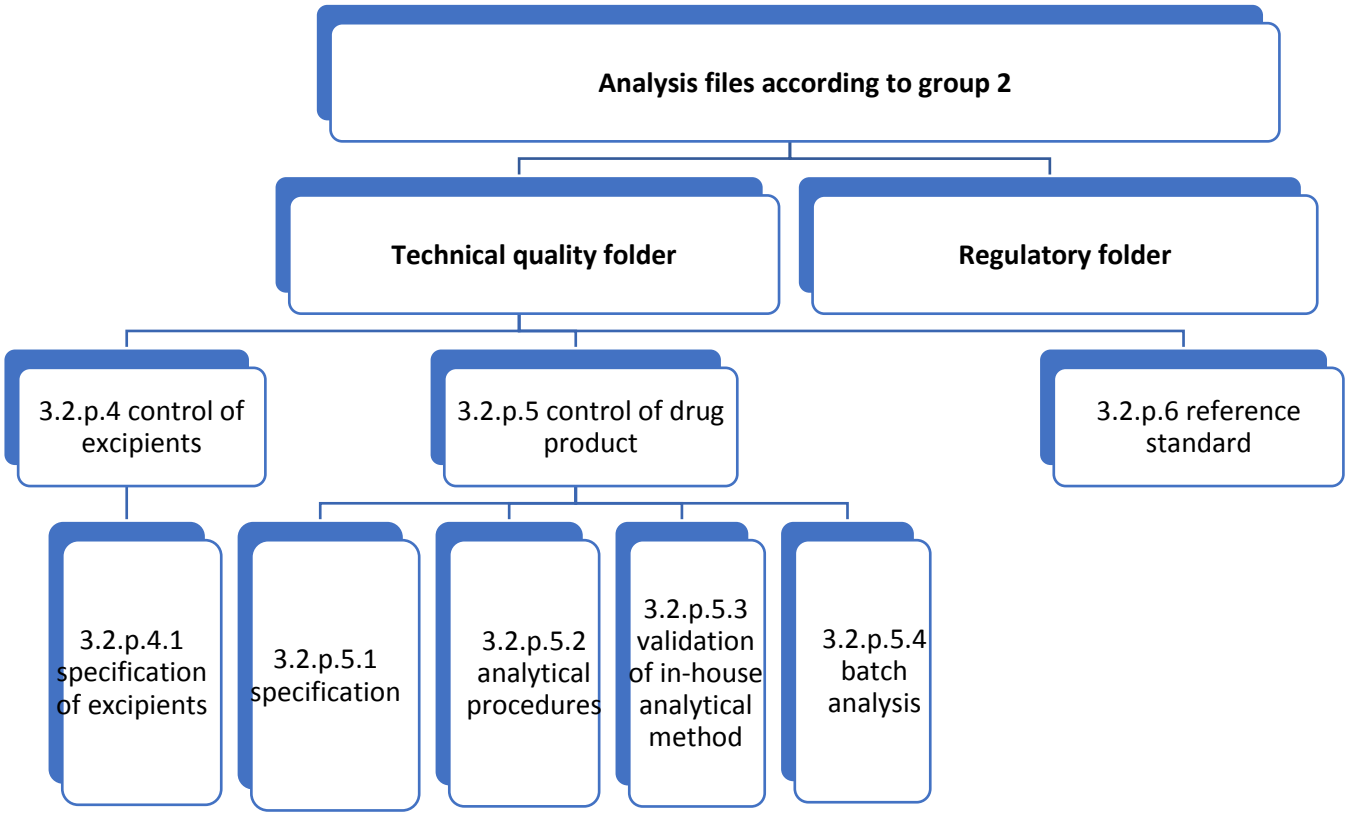
- **Technical quality folder file consists of the following:**

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- **Reference standard**

Analysis file submitted to CADC group 2

The file consists of the following folder:

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



Regulatory folder contains the following:

1. إخطار الإدارة وأى موافقات للإدارة من تغيير عبوة/ بيان تركيب / مصنع / نقل ملكية (Variation) .
2. نموذج تسجيل مستحضر صيدلى خاص (صحه 17 سابقا) موضح بها وصف العبوة كاملا و وفي حالة R & D موضح أسم طالب التسجيل والشركة المصنعه.
3. بيان التركيب المعتمد أو المختوم بختم المفتش للمستحضرات المسجلة طبقا للقرار الوزاري .
4. محضر السحب موضح به رقم تشغيلة المستحضر وصلاحيته ورقم تشغيلة المادة الخام .
5. أورنيك الحرز (علي أن يكون محضر السحب وأورنيك الحرز بنفس التاريخ).
6. شهادة تحليل المادة الخام مطابقة لما هو مذكور فى محضرالسحب من حيث المصدر ورقم التشغيلة .
7. مواصفات المستحضر النهائى.
8. شهادة تحليل المستحضر النهائى.
9. موافقه صنوق المثائل.
10. إيصـــال الدفـــع (الشيك) مكتوبا عليه اسم المستحضر.
11. Material safety data sheet for all API and anti-oxidant and preservative
12. تعهد بصحه البيانات المقدمه مع الملف الذي تم فحصه.
13. تعهد بسلامة العينات المقدمة للتحليل.
14. تعهد باسترداد عمود الفصل (في حال تسليمه) في خلال شهر من صدور التقرير النهائي.

Technical quality folder file consists of the following:

3.2. P.4 control of excipients

- **2.3.p.4.1 specification of excipients**

3.2. P.5 control of drug product

- **3.2. p.5.1 specification of drug product**
- **3.2. p.5.2 analytical method procedures**
- **3.2. p.5.3 validation of analytical procedure**
- **3.2. p.5.4 batch analysis**

3.2. P.6 reference standard

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.

section	Information required
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, plus 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.6 Reference standard	• Information of reference standard used in analysis should be provided