قواعد فحص الملفات

يتم الفحص طبقا لمجموعتين وهما كالتالي:

أولا المستحضرات المقدمة الى:

1- شعبة التفتيش (لأي سبب باستثناء المورد ونقل التصنيع).

2- شعبة المراقبة.

ثانيا المستحضرات المقدمة الى:

1-شعبة التسجيل (تسجيل أول مرة- أعادة تسجيل بناء على الأخطار-متغيرات).

2-شعبة التفتيش (أضافة مورد- أضافة/تغيير مكان تصنيع).

المجموعة الأولى:

قواعد عامة:

1-يتم المراجعة والفحص طبقا للتقرير النهائي الصادر من شعبة التسجيل (او موافقة تحديث الملف) وفي حال عدم الاستدلال على التقرير النهائي يتم الالتزام بالألية التنسيقية المعتمدة من رئيس الإدارة المركزية للعمليات ورئيس الإدارة المركزية للرقابة الدوائية.

2-يتم التحليل طبقا للطرق المرفقة مع ملف التسجيل مع التزام الشركة برفع الطريقة على الرابط الخاص بالملف عند التقدم وفي حال رغبة الشركة بتغيير الطريقة عما تم التسجيل عليه يتم تطبيق الالية الحالية مع أرسال ما يفيد للشركة بالتحديث. (link method update)

3-يتم الالتزام بالفحص طبقا للتقرير النهائي مع مراعاة الاتي:

1) في حال عدم وجود حدود لاختبار أو أكثر من الاختبارات المذكورة بالتقرير النهائي تقوم الشركة صاحبة المستحضر بإضافة حدود هذا الاختبار الى مواصفات المستحضر طبقا للدستور او طبقا للمواصفات الخاصة للمستحضر المرفقة بموافقة قسم الثبات بالإدارة المركزية للمستحضرات الصيدلية دون تقديم التماس
   - لا يسري ما سبق على أضافة حدود اللون.
   - وبالنسبة لاختبارات ال microbial count & bacterial endotoxin limit يتم التحليل طبقا للحدود بالدستور (USP,BP or European pharmacopeia) في حال عدم ذكر الحدود بالتقرير النهائي.
2) في حال وجود أخطار محدث به مواصفة أو عبوة غير مشروط بأعاده التحليل او موافقة لجنة متغيرات غير مشروطة بأعاده التحليل يتم الالتزام بالفحص والتحليل طبقا لما جاء بهم دون طلب تعديل مواصفة المستحضر مع أضافة التحديثات الى الأرشيف الخاص بالملف بالإدارة المركزية للرقابة الدوائية.
3) في حال رغبة الشركة بتعديل (حذف – أضافة – تغيير حدود) أحد الاختبارات يتم توجيه الشركة الى قسم المتغيرات بالإدارة المركزية للمستحضرات الصيدلية لتطبيق القواعد.

4- الاختبارات التالية يستلزم تحديثها في مواصفات المستحضرات البشرية النهائية طبقا لقواعد فحص المستحضرات المجموعة الثانية دون تقديم التماس وذلك ***خلال 6 أشهر*** كحد أقصى من تاريخ أعلان القواعد للشركات مع الاخذ في الاعتبار الشكل الصيدلي للمستحضر (Dosage form):

1. Dissolution
2. Particulate matter
3. Uniformity of dosage unit
4. Bacterial endotoxin

5-المستحضرات الحاصلة على أي من موافقة FDA أو EMEA والمستحضرات المستوردة من أي من البلاد المرجعية قد يتم تطبيق Smart Analysis طبقا لتقييم المخاطر.

6-يعتبر المستحضر مستوفيا للفحص في الحالات الاتية:

- تقديمه خلال عام ميلادي من صدور التقرير النهائي بشعبة التسجيل.
- استيفاء المستحضر عن طريق الية الفحص المبكر مع الالتزام بالمهل الخاصة بالتسليم الموضحة بها.

المجموعة الثانية:

قواعد عامة:

1- الموافقات والقواعد الصادرة من أي من اللجان العلمية والفنية بهيئة الدواء المصرية ملزمة للإدارة المركزية للرقابة الدوائية.
2- الفحص والتحليل بالإدارة المركزية للرقابة الدوائية يتم طبقا لأحدث دستور دوائي.
3- المستحضرات الحاصلة على أي من موافقات الFDA او EMEA/ الواردة من أحد البلاد المرجعية/ المسجلة بنظام تسجيل الادوية المبتكرة يتم فحصها وتحليلها طبقا للمواصفات الخاصة بها.
4- المستحضر الدستوري هو المستحضر الذي يكون الدستور متضمن كجزء من الاسم التجاري للمستحضر.
5- التحليل يتم طبقا لل shelf life specifications .

Assessment of Finished Pharmaceutical Products

Physical analysis

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

Checklist guide

Dosage form	Checklist no.
Aerosols	1
Capsules	2
Creams	3
Emulsion	4
Films	5
Foams	6
Gels	3
Granules	7
Ointments	3
Powders	8
Solutions	9
Sprays	10
Suppositories	11
Suspensions	12
Tablets	13
Transdermal delivery systems	14

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

Test*	Applicability	Acceptance criteria
1. Description		
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 ○ Metered dose inhalation and nasal aerosols ○ 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**

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

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**

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*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.

** Equipment not available.

2. Checklist for tests performed on capsule:

Test*	applicability	Done?	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	
2- Mass uniformity (BP)** Procedure is according to BP (Ph. Eur. method 2.9.5).	Done on capsule content. ○ Not done 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 0016)*			•Not more than 2 of the individual masses deviate from the average mass (actual) by more than the percentage deviation. **Average mass (mg)** / **Deviation %** <300 mg / 10 ≥300 mg / 7.5 • none deviates by more than twice that percentage. (Ph. Eur. method 2.9.5))
3- Disintegration (USP, BP) **Procedure according to:** USP-NF ⟨**701**⟩ **DISINTEGRATION** ***(Ph. Eur. method 2.9.1)***	Done for all. **Where a dissolution test is prescribed, a disintegration test may not be required.** ***(Ph. Eur. monograph 0016)***			USP-NF ⟨**701**⟩ **DISINTEGRATION** ***(Ph. Eur. method 2.9.1)***

2. Checklist for tests performed on <u>capsule</u> (cont.):

4- Dissolution **(reference of method is one of the following:** ○ **(USP or BP specific monograph.** ○ **FDA dissolution method.** ○ **In-house method (with comparative dissolution study including the medium used in the in-house dissolution method).**	For all **Disintegration could substitute dissolution as a performance test*** if a justification submitted by the manufacturer that it obeys the ICH Q6A guidelines:** 1- Rapidly dissolving (dissolution >80% in 15 minutes at pH 1.2, 4.0 and 6.8) products 2- Containing drugs which are highly soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to 6.8). 3- Disintegration/dissolution correlation is done. Then disintegration may be substituted for dissolution. <u>In this case, the performed dissolution method should be supplied by the manufacturer.</u> N.B.: This guidance is not applicable for sublingual dosage forms (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.)		●<u>Dissolution Parameters:</u> ○ Media composition & pH ○ media volume (2&4 L are not available) ○ Apparatus type (Apparatus 1,2,5,6 only are available) ○ rpm ○ temp ○ sampling time ○ Q (the amount dissolved) ●<u>If HPLC detection after dissolution:</u> ○ HPLC validation method. ○ column specification ○ Mobile phase preparation & composition. ○ detector type ○ wavelength ○ Temperature of the column ○ std preparation ●<u>If UV detection after dissolution:</u> ○ std preparation ○ wavelength ○ blank used ●<u>If UV derivatization after dissolution:</u> ○ wavelength ○ blank used ○ order (1st, 2nd, ..) ○ Δλ ○ scaling factor/integration time. ●Check the availability of all chemicals used.	•The minimum accepted value of Q (amount dissolved) will be as stated in the latest Pharmacopeia (unless otherwise justified according to the comparative dissolution study). *(Ph. Eur. general texts 5.17.1)* (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. **<u>To skip water content test:</u>** The manufacturer should justify that there is no effect of hydration or water absorption on the drug product	○ Yes ○ Yes ○ No ○ Need justification to skip test		According to monograph or manufacturer's specifications

2. Checklist for tests performed on capsule (cont.):

6- Acid-neutralizing capacity (USP) Procedure according to USP-NF ⟨ 301 ⟩ ACID-NEUTRALIZING CAPACITY	○ Antacids only			According to manufacturer specifications USP-NF ⟨ 301 ⟩ ACID-NEUTRALIZING CAPACITY

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*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.

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

*** Dissolution test could be performed in the registration stage for check.

3. Checklist for tests performed for <u>creams, Gels & ointments:</u>

Test*	Applicability	Information should be available	Acceptance criteria
1. Description: ○ **Appearance** ○ **Colour** ○ **Homogeneity** ○ **Visible foreign matter**			
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 **<u>Generally:</u> 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.	<u>kind of product</u> ○ hydrophilic or ○ lipophilic <u>Preparation method to perform measurement:</u> ○ Solvent ○ Percent of dilution	According to the manufacturer specifications
4. **Apparent viscosity** Procedure is according to manufacturer's method except in case that the equipment is not available (In this case: this test will be performed using the available equipment and the resultant limits will be considered as the acceptance criteria in the registration batch and the subsequent batches.)	**For all** Acceptance criteria are product specific and defined to ensure that the apparent viscosity of each batch of semisolid drug product is within the range defined by the product design and is consistent between batches based on the product development specifications and statistical assessment of multiple product batches over the product's shelf life.	1. Type of device (model) 2. Device subtype 3. Spindle no. 4. Rpm 5. temperature	According to the manufacturer specifications except in case that the equipment is not available (In this case: this test will be performed using the available equipment and the resultant limits will be considered as the acceptance criteria in the registration batch and the subsequent batches.)

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

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 **To skip water content test:** ○ The manufacturer should justify that there is no effect of hydration or water absorption on the drug product.	○ Yes ○ Yes ○ Need justification to skip test.		According to the manufacturer specifications
6. Particle size**. **(BP)** Procedure is according to: (Ph. Eur. monograph 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. monograph 1163)

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*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.
** Equipment not available.

4. Checklist for tests performed on <u>emulsions:</u>

Test*	Applicability	Acceptance criteria
1. Description: ○ **Appearance** ○ **Colour** ○ **Viscous or not**	All	
2. **Minimum fill** Procedure according to USP-NF ⟨755⟩ MINIMUM FILL	○ vaginal emulsion, ○ rectal emulsion, ○ ophthalmic emulsion, ○ otic emulsion. ○ topical emulsion.	USP-NF ⟨755⟩ MINIMUM FILL
3. Deliverable volume Procedure according to: USP-NF ⟨698⟩ DELIVERABLE VOLUME	Oral emulsions (labelled volume should be known)	USP-NF ⟨**698**⟩ **DELIVERABLE VOLUME**
4. **pH** procedure of sample preparation to measure pH is according to manufacturer's method.	○ hydrophilic emulsions (o/w) It is formulation dependent, According to manufacturer specifications.	According to the manufacturer specifications
5. **Viscosity** Procedure is according to manufacturer's method except in case that the equipment is not available (In this case: this test will be performed using the available equipment and the resultant limits will be considered as the acceptance criteria in the registration batch and the subsequent batches.)	○ ophthalmic emulsion	According to manufacturer specifications except in case that the equipment is not available (In this case: this test will be performed using the available equipment and the resultant limits will be considered as the acceptance criteria in the registration batch and the subsequent batches.)
6. Specific gravity Procedure according to: USP-NF ⟨841⟩ SPECIFIC GRAVITY	Relatively viscous emulsions ○ Topical, ○ otic and ○ oral	According to manufacturer specifications
7. Uniformity of mass of delivered doses from multidose containers (BP) Procedure is according to: (Ph. Eur. method 2.9.27)	Oral emulsions which are supplied in multidose 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 per cent and none deviates by more than 20 %. *(Ph. Eur. method 2.9.27)*
8. 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)*
9. 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**
10. Globule size**	○ ophthalmic emulsion ○ parenteral emulsion	
11. Osmolality**	Only for products labelled with tonicity: ○ ophthalmic emulsions	According to manufacturer specifications
12. CONTAINER–CLOSURE INTEGRITY ****	Parenteral emulsions	USP-NF Package Integrity Leak Test Technologies ⟨1207.2⟩

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*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.

** Equipment not available.

5. Checklist for tests performed on Films:

Test*	applicability	Information should be available	Acceptance criteria
1. Description: ○ **Appearance** ○ **dimensions**			
2. **Dissolution** **(reference of method is one of the following:** ○ **USP or BP specific monograph.** ○ **FDA dissolution method.** ○ **In-house method with comparative dissolution study.**		●Dissolution Parameters: ○ Media composition & pH ○ media volume (2&4 L are not available) ○ Apparatus type (1,2,5,6 only are available) ○ rpm ○ temp ○ sampling time ○ std preparation ○ Q (the amount dissolved) ●If HPLC detection after dissolution: ○ HPLC validation method. ○ column specification ○ Mobile phase preparation & composition. ○ detector type ○ wavelength ○ Temperature of the column ●If UV detection after dissolution: ○ wavelength ○ blank used ●If UV derivatization after dissolution: ○ wavelength ○ blank used ○ order (1st, 2nd, ..) ○ Δλ ○ scaling factor/integration time. ○ ●Check the availability of all chemicals used.	•The minimum accepted value of Q (amount dissolved) will be as stated in the BP (unless otherwise justified according to the comparative dissolution study). *(Ph. Eur. general texts 5.17.1)* (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 ○ There is no specific monograph & Not stated by manufacturer. **To skip water content test:** The manufacturer should justify that there is no effect of hydration or water absorption on the drug product.	○ Yes ○ Yes ○ No ○ Need justification.	According to manufacturer specifications.

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*According to the 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.

6. Checklist for tests performed on Foams:

Tests*	Applicability	Acceptance criteria
1. Description **Physical appearance (of the foam and of the collapsed foam) (USP)**		
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** **Its 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.** ○ **If There is no specific monograph & not stated by manufacturer, the manufacturer should justify that there is no effect of hydration or water absorption on the drug product to skip water content test.**	**According to manufacturer's specifications**

6. Checklist for tests performed on Foams (cont.):

10. Osmolarity and osmolality(USP)**	**If applicable and the product labelled with certain tonicity**	**According to manufacturer's specifications**
11. Pressure test(USP)**	**All**	**According to manufacturer's specifications**

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*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.

** Equipment not available.

7. Checklist for tests performed on Granules:

Test	applicability		Information should be available	Acceptance criteria
	Granules type	Done?		
1- Description: • **appearance** • **Colour** • **Visual Clarity (for solution of granules after reconstitution).**			• 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 oral granules for reconstitution (after reconstitution) in: ○ Multiple dose container ○ Single dose container **Not done for granules that are administered with food or beverages.**	 ○ Yes ○ Yes	Labeled volume	USP-NF ⟨ 698⟩ DELIVERABLE VOLUME
3- Minimum fill (USP) Procedure according to: USP-NF ⟨755⟩ MINIMUM FILL	○ granules for oral suspension packaged in containers (where test of deliverable volume is applicable). ○ other multiple dose granules.	○ No ○ Yes	Labeled amount	USP-NF ⟨**755**⟩ **MINIMUM FILL**
4- Uniformity of Weight (Mass) of Delivered Doses from Multidose Containers (BP) Procedure according to: (Ph. Eur. method 2.9.27)	oral granules which are supplied in multidose 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 % and 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)	○ Uncoated 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 authorised 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. **Dosage form** / **Average mass (mg)** / **Deviation %** -granules (uncoated, single-dose): <300 mg: 10; ≥300 mg: 7.5 • none deviates by more than twice that percentage. (Ph. Eur. method 2.9.5)

7. Checklist for tests performed on Granules (cont.):

6- Dissolution (reference of method is one of the following: ○ **USP or BP specific monograph.** ○ **FDA dissolution method.** ○ **In-house method ((with comparative dissolution study including the medium used in the in-house dissolution method).**	○ granules that result in a suspension.	●Dissolution Parameters: ○ Media composition & pH ○ media volume (2&4 L are not available) ○ Apparatus type (Apparatus 1,2,5,6 only are available) ○ rpm ○ temp ○ sampling time ○ Q (the amount dissolved) ●If HPLC detection after dissolution: ○ HPLC validation method. ○ test preparation ○ std preparation ○ column specification ○ Mobile phase preparation & composition. ○ detector type ○ wavelength ○ Temperature of the column ●If UV detection after dissolution: ○ test preparation ○ std preparation ○ wavelength ○ blank used ●If UV derivatization after dissolution: ○ wavelength ○ blank used ○ order (1st, 2nd, ..) ○ Δλ ○ scaling factor-integration ●Check the availability of all chemicals used.	•The minimum accepted value of Q (amount dissolved) will be as stated in the latest Pharmacopeia (unless otherwise justified according to the comparative dissolution study). *(Ph. Eur. general texts 5.17.1)* Ph. Eur. method 2.9.3) USP NF ⟨**1711**⟩ **ORAL DOSAGE FORMS—PERFORMANCE TESTS.** **USP NF ⟨711⟩ DISSOLUTION**
7- Disintegration (USP, BP) **Procedure according to:** **USP-NF ⟨701⟩ DISINTEGRATION** ***(Ph. Eur. method 2.9.1)***	○ effervescent granules		USP-NF ⟨**701**⟩ **DISINTEGRATION** ***(Ph. Eur. method 2.9.1)***

7. Checklist for tests performed on Granules (cont.):

8- Water content (USP) Procedure is according to manufacturer's method or specific monograph.	○ Effervescent granules ○ Granules for reconstitution **Other granules:** ○ Cited in monograph. ○ Stated by manufacturer. ○ Not cited in its specific monograph ○ There is no specific monograph & Not stated by manufacturer. **To skip water content test:** The manufacturer should justify that there is no effect of hydration or water absorption on the drug product.	○ Yes ○ Yes ○ Yes ○ Yes ○ No ○ Need justification to skip test		According to manufacturer specifications
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- Specific gravity/viscosity Procedure of specific gravity according to: USP-NF ⟨841⟩ SPECIFIC GRAVITY	For relatively viscous reconstituted suspensions (after reconstitution)			**According to manufacturer specifications**
12- Acid-neutralizing capacity (USP) Procedure is according to: USP-NF ⟨ 301 ⟩ ACID-NEUTRALIZING CAPACITY	For antacids			**According to manufacturer specifications**

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*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.

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

8. Checklist tests performed on Powders:

Test*	Applicability		Information should be available	Acceptance criteria
	Powder type	Done?		
1- Description: • **appearance** • **Colour** • **Visual Clarity (for solution of powder after reconstitution).**			Colour of o Powders o 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). o other multiple dose powders. o Powder for inhalation (device metered)	o No o Yes o 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: o Multiple dose container o Single dose container	o Yes o Yes	Labeled volume	⟨USP **698**⟩ **DELIVERABLE VOLUME**
4- Uniformity of Weight (Mass) of Delivered Doses from Multidose Containers (BP) Procedure according to: (Ph. Eur. method 2.9.27)	oral powders which are supplied in multidose 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)
5- Mass uniformity (BP)** Procedure according to: (Ph. Eur. method 2.9.5).	o single dose powders o Powders for parenteral administration (single dose) o Powders for eye-drops and powders for eye lotions (single-dose) o 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 1165)*	o Yes o Yes o Yes o No		•Not more than 2 of the individual masses deviate from the average mass (actual) by more than the percentage deviation. **Dosage form** / **Average mass (mg)** / **Deviation %** -Powders (single-dose) / <300 mg / 10 -Powders for eye-drops and powders for eye lotions (single-dose) / ≥300 mg / 7.5 Powders for parenteral administration (single dose) / >40 mg / 10 • none deviates by more than twice that percentage. ((Ph. Eur. method 2.9.5))

8. Checklist tests performed on Powders (cont.):

6- Dissolution (reference of method is one of the following: ○ **USP or BP specific monograph.** ○ **FDA dissolution method.** ○ **In-house method ((with comparative dissolution study).**	○ Powder reconstituted to form oral suspension (unless otherwise justified). ○ Powder reconstituted to form sustained ophthalmic or parenteral.	○ Yes ○ Yes	●Dissolution Parameters after comparative dissolution study: ○ Media composition & pH ○ media volume (2&4 L are not available) ○ Apparatus type (Apparatus 1,2,5,6 only are available) ○ rpm ○ temp ○ sampling time ○ Q (the amount dissolved) ●If HPLC detection after dissolution: ○ HPLC validation method. ○ St preparation ○ column specification ○ Mobile phase preparation & composition. ○ detector type ○ wavelength ○ Temperature of the column ●If UV detection after dissolution: ○ St preparation ○ wavelength ○ blank used ●If UV derivatization after dissolution: ○ wavelength ○ blank used ○ order (1st, 2nd, ..) ○ Δλ ○ scaling factor/integration time ●Check the availability of all chemicals used.	(Ph. Eur. method 2.9.3) USP NF ⟨1**711**⟩ **ORAL DOSAGE FORMS—PERFORMANCE TESTS.** **USP NF ⟨711⟩ DISSOLUTION**
7- Disintegration Procedure according to *BP (Ph. Eur. monograph 1165)*	Effervescent powders			*BP (Ph. Eur. monograph 1165)*

8. Checklist tests performed on Powders (cont.):

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 ○ Lyophilised powders ○ Cited in monograph. ○ Stated by manufacturer. ○ Not cited in its specific monograph ○ There is no specific monograph & Not stated by manufacturer. **To skip water content test:** ○ The manufacturer should justify that there is no effect of hydration or water absorption on the drug product.	○ Yes ○ Yes ○ Yes ○ Yes ○ Yes ○ Yes ○ Yes ○ Yes ○ No ○ 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.			
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 lyophilised powders for parenteral solutions and intra/extraocular 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.			

8. Checklist tests performed on Powders (cont.):

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- Specific gravity/viscosity Procedure of specific gravity according to: USP-NF ⟨841⟩ SPECIFIC GRAVITY	For reconstituted powder (after reconstitution)			According to manufacture specifications
16- Acid-neutralizing capacity (USP) Procedure according to USP-NF ⟨301⟩ ACID-NEUTRALIZING CAPACITY	For antacids			
17- 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	Nasal powders			According to manufacturer specifications. USP NF ⟨601⟩ INHALATION AND NASAL DRUG PRODUCTS: AEROSOLS, SPRAYS, AND POWDERS—PERFORMANCE QUALITY TESTS
18- 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
19- 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)			

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*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.

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

*** Equipment not available.

9. 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)*	○ Single-dose inhalation solutions	*(Ph. Eur. monograph 0671)*
4. **pH**	○ Aqueous solutions It is formulation dependent, According to manufacturer specifications.	According to the manufacturer specifications
5. **Viscosity** Procedure is according to manufacturer in-house method. *Viscosity—Capillary Methods USP-NF* ⟨911⟩, *Viscosity—Rotational Methods USP-NF*⟨912⟩, and *Viscosity—Rolling Ball Method USP-NF* ⟨913⟩	○ ophthalmic, ○ nasal, ○ inhalation	**According to manufacturer specifications**
6. Specific gravity Procedure of specific gravity according to: USP-NF ⟨841⟩ SPECIFIC GRAVITY	○ Topical, ○ otic and ○ oral	According to manufacturer specifications
7. 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**
8. Uniformity of mass of delivered doses from multidose containers (BP) Procedure is according to *(Ph. Eur. method 2.9.27)*	Oral solutions which are supplied in multidose 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)*

9. Checklist for tests performed on solutions (cont.):

10. 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)*
11. Deliverable volume Procedure is according to USP-NF ⟨698⟩ DELIVERABLE VOLUME	Oral solutions	USP-NF ⟨**698**⟩ **DELIVERABLE VOLUME**
12. 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**
13. Osmolality**	Only for products labelled with tonicity: ○ nasal solutions ○ inhalation solutions, ○ ophthalmic solutions	According to manufacturer specifications
14. CONTAINER–CLOSURE INTEGRITY **	Parenteral solutions	USP-NF Package Integrity Leak Test Technologies ⟨1207.2⟩

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*According to the 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.

** Equipment not available.

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

Test*	Applicability	Acceptance criteria
1. Description		
2. Mass uniformity (BP)** Procedure is according to (Ph. Eur. monograph 0676) (Ph. Eur. monograph 1807) If the test for uniformity of content is prescribed or justified and authorized for all the active substances, the test for uniformity of mass is not required. *(Ph. Eur. monograph 1807)*	○ Metered-dose nasal sprays. ○ Metered dose 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. Viscosity/ specific gravity	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

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

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

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*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.

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

*** Equipment is not available.

11. Checklist for tests performed on <u>suppositories:</u>

Test*	applicability	Done?	Information should be available	Acceptance criteria
1- Description: • **appearance** • **Colour**				
2- Mass uniformity (BP)** Procedure is according to (Ph. Eur. method 2.9.5)	Suppositories and pessaries **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 1145)*			•Not more than 2 of the individual masses deviate from the average mass (actual) by more than the percentage deviation. **Average mass (mg)** / **Deviation %** All masses / 5 • none deviates by more than twice that percentage. ((Ph. Eur. method 2.9.5))
3- Disintegration (USP, BP)	Done for all unless intended for prolonged local action. **Where a dissolution test is prescribed, a disintegration test may not be required *(Ph. Eur. monograph 1145)*.**			USP-NF ⟨**701**⟩ **DISINTEGRATION** ***(Ph. Eur. method 2.9.1)***
4- Dissolution (reference of method is one of the following: ○ **(USP or BP specific monograph.** ○ **FDA dissolution method.** ○ **In-house method (with comparative dissolution study including the medium used in the in-house dissolution method).)**	Suppositories and pessaries.		●<u>Dissolution Parameters:</u> ○ Media composition. & pH ○ media volume (2&4 L are not available) ○ Apparatus type ○ rpm ○ temp ○ sampling time ○ Q (the amount dissolved) ●<u>If HPLC detection after dissolution:</u> ○ HPLC validation method. ○ St preparation ○ column specification ○ Mobile phase preparation & composition. ○ detector type ○ wavelength ○ Temperature of the column ●<u>If UV detection after dissolution:</u> ○ St preparation ○ wavelength ○ blank used ●<u>If UV derivatization after dissolution:</u> ○ wavelength ○ blank used ○ order (1st, 2nd, ..) ○ Δλ ○ scaling factor/integration time ●Check the availability of all chemicals used.	(Ph. Eur. method 2.9.3) USP-NF ⟨711⟩ DISSOLUTION

11. Checklist for tests performed on <u>suppositories</u> (cont.):

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. **<u>To skip water content test:</u>** The manufacturer should justify that there is no effect of hydration or water absorption on the drug product.	○ Yes ○ Yes ○ No ○ Need justification to skip test		According to monograph or manufacturer's specifications
6- Softening time* (USP)**	**lipophilic suppositories**			

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.
*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.
** Average weight could be considered if needed as IPC USP-NF (1163) Quality assurance in pharmaceutical compounding.

*** Equipment not available.

12. Checklist for tests performed for suspensions:

Test*	Applicability	Information should be available	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	○ Aqueous suspensions It is formulation dependent, According to manufacturer specifications.		According to the manufacturer specifications
4. **Viscosity** Procedure is according to manufacturer in-house method. Viscosity—Capillary Methods USP-NF ⟨911⟩, Viscosity—Rotational Methods USP-NF⟨912⟩, and Viscosity—Rolling Ball Method USP-NF ⟨913⟩	○ ophthalmic, ○ nasal, ○ inhalation		According to manufacturer specifications
5. Specific gravity Procedure of specific gravity according to: USP-NF ⟨841⟩ SPECIFIC GRAVITY	relatively viscous suspensions ○ Topical, ○ otic and ○ oral		According to manufacturer specifications
6. Uniformity of mass of delivered doses from multidose containers (BP) Procedure is according to *(Ph. Eur. method 2.9.27)*	Oral suspensions which are supplied in multidose 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)*
7. 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)*
8. Deliverable volume (USP) Procedure is according to USP-NF ⟨698⟩ DELIVERABLE VOLUME	Oral suspensions		USP-NF ⟨**698**⟩ **DELIVERABLE VOLUME**
9. 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**

12. Checklist for tests performed for <u>suspensions</u> (cont.):

10. Dissolution **(reference of method is one of the following:** ○ **USP or BP specific monograph.** ○ **FDA dissolution method.** ○ **In-house method ((with comparative dissolution study including the medium used in the in-house dissolution method).**	○ **oral suspensions (unless otherwise justified).** ○ **sustained ophthalmic suspensions.** ○ **sustained parenteral suspensions.**	<u>Dissolution Parameters after comparative dissolution study:</u> ○ Media composition & pH ○ media volume (2&4 L are not available) ○ Apparatus type (1,2,5,6 only are available) ○ rpm ○ temp ○ sampling time ○ Q (the amount dissolved) ●<u>If HPLC detection after dissolution:</u> ○ HPLC validation method. ○ St preparation ○ column specification ○ Mobile phase preparation & composition. ○ detector type ○ wavelength ○ Temperature of the column ●<u>If UV detection after dissolution:</u> ○ St preparation ○ wavelength ○ blank used ●<u>If UV derivatization after dissolution:</u> ○ wavelength ○ blank used ○ order (1st, 2nd, ..) ○ Δλ ○ scaling factor/ integration time ●Check the availability of all chemicals used.	Ph. Eur. method 2.9.3) USP NF ⟨1711⟩ ORAL DOSAGE FORMS—PERFORMANCE TESTS. USP NF ⟨711⟩ DISSOLUTION
11. Acid Neutralizing capacity Procedure is according to: USP-NF ⟨301⟩ ACID-NEUTRALIZING CAPACITY	**Antacids**		According to manufacturer specifications.
12. Resuspendability	**All suspensions**		

12. Checklist for tests performed for suspensions (cont.):

13. Particle size distribution (performance test)	○ Nasal suspension (USP-NF ⟨601⟩ INHALATION AND NASAL DRUG PRODUCTS: AEROSOLS, SPRAYS, AND POWDERS-PERFORMANCE QUALITY TESTS). ○ ophthalmic suspension *(Ph. Eur. monograph 1163)* ○ parenteral suspension		According to manufacturer specifications
14. Aerodynamic particle size measurement (cascade impactor) ** (USP) (performance Quality test) Procedure according to USP-NF ⟨601⟩ Inhalation and Nasal Drug Products_ Aerosols, Sprays, and Powders—Performance Quality Tests	○ Inhalation suspension		According to manufacturer specifications
15. Osmolality**	Only for products labelled with tonicity: ○ nasal suspensions ○ inhalation suspensions, ○ ophthalmic suspensions		According to manufacturer specifications
16. CONTAINER–CLOSURE INTEGRITY **	Parenteral suspensions		USP-NF Package Integrity Leak Test Technologies ⟨1207.2⟩

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*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.

** Equipment not available.

13. Checklist for tests performed on Tablets:

Test*	applicability		Information should be available	Acceptance criteria
	Tablet Type	Done?		
1. Description: ○ **Appearance** ○ **Colour of tablet**			○ Tablet shape ○ Colour ○ Colour of core & coat in case of coated tablets ○ Type of coat in 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. Tablet weight (mg) / % deviation: 80 mg or less: 10% 80 -250 mg: 7.5% ≥250 mg: 5% • 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). ○ Chewable tablets (cited in monograph or stated by manufacture) ○ Extended release (sustained/modified/controlled). ○ Chewable tablets (not cited in monograph or not stated by manufacture) **N.B. Where a dissolution test is prescribed, a disintegration test may not be required.** ***(Ph. Eur. monograph 0478)***	○ Yes ○ Yes ○ Yes ○ Yes ○ No ○ No		USP-NF ⟨**701**⟩ **DISINTEGRATION** ***(Ph. Eur. method 2.9.1)***

13. Checklist for tests performed on Tablets (cont.):

4. **Dissolution** **(reference of method is one of the following:** ○ **USP or BP specific monograph.** ○ **FDA dissolution method.** ○ **In-house method with comparative dissolution study.**	○ Effervescent tablets that result in a solution ○ Others **Disintegration could substitute dissolution as a performance test***:** Need justification by the manufacturer that it **obeys the ICH Q6A guidelines:** 1- Rapidly dissolving (dissolution >80% in 15 minutes at pH 1.2, 4.0 and 6.8) products 2- Containing drugs which are highly soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to 6.8). 3- Disintegration/dissolution correlation is done. disintegration may be substituted for dissolution. In this case, the performed dissolution method should be supplied by the manufacturer. N.B. these guidelines are not applicable on orally disintegrating or sublingual tablets. (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.)	○ No ○ Yes	●Dissolution Parameters after comparative dissolution study: ○ Media composition & pH ○ media volume (2&4 L are not available) ○ Apparatus type (1,2,5,6 only are available) ○ rpm ○ temp ○ sampling time ○ Q (the amount dissolved) ●If HPLC detection after dissolution: ○ HPLC validation method. ○ St preparation ○ column specification ○ Mobile phase preparation & composition. ○ detector type ○ wavelength ○ Temperature of the column ●If UV detection after dissolution: ○ St preparation ○ wavelength ○ blank used ●If UV derivatization after dissolution: ○ wavelength ○ blank used ○ order (1st, 2nd, ..) ○ Δλ ○ scaling factor/ integration time ●Check the availability of all chemicals used.	•The minimum accepted value of Q (amount dissolved) will be as stated in the BP (unless otherwise justified according to the comparative dissolution study). (Ph. Eur. method 2.9.3) USP-NF ⟨**711**⟩ **DISSOLUTION**

13. Checklist for tests performed on Tablets (cont.):

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 **To skip water content test:** The manufacturer should justify that there is no effect of hydration or water absorption on the drug product.	○ Yes ○ Yes ○ Yes ○ Yes ○ No ○ Need justification to skip test		According to monograph or manufacturer's specifications

13. Checklist for tests performed on Tablets (cont.):

9. Fineness of dispersion (BP). Procedure is according to: *(Ph. Eur. monograph 0478)*)	○ dispersible tablets ○ others	○ Yes ○ No		A smooth dispersion is produced, which passes through a sieve screen with a nominal mesh aperture of 710 µm. *(Ph. Eur. monograph 0478)*)
10. Acid-neutralizing capacity (USP) Procedure according to USP-NF ⟨ 301 ⟩ ACID-NEUTRALIZING CAPACITY	○ Antacids only			According to manufacturer specifications

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*According to the 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.

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

*** Dissolution test could be performed in the registration stage for check.

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

Test	Applicability		Information should be available	Acceptance criteria
	TDS type	Done?		
1- Description	○ All types	○ Yes		According to manufacturer's specifications
2- Dimensions	○ All types	○ 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. **To skip water content test:** The manufacturer should justify that there is no effect of hydration or water absorption on the drug product.	○ Yes ○ Yes ○ No ○ Need justification		According to manufacturer's specifications

14. Checklist for tests performed on Transdermal Delivery Systems (TDS) (cont.):

4- Dissolution **(reference of method is one of the following:** ○ USP or BP specific monograph. ○ FDA dissolution method. ○ In-house method ((with comparative dissolution study including the medium used in the in-house dissolution method).	All types		• **Dissolution Parameters:** ○ Media composition & pH ○ Media volume (2&4 L are not available) ○ Apparatus type (Apparatus 1,2,5,6 only are available) ○ RPM ○ Temp (32 ˚C) ○ Sampling time (at least three, expressed in hours) ○ Q (the amount dissolved) ●**If HPLC detection after dissolution:** ○ HPLC validation method. ○ Standard preparation. ○ Column specification ○ Mobile phase preparation & composition. ○ Detector type ○ Wavelength ○ Temperature of the column. ●**If UV detection after dissolution:** ○ Standard preparation ○ Wavelength ○ Blank used ●**If UV derivatization after dissolution:** ○ Wavelength ○ Blank used ○ Order (1st, 2nd, ..) ○ Δλ ○ Scaling factor/integration time. ●Check the availability of all chemicals used.	(Ph. Eur. method 2.9.3) USP-NF ⟨**711**⟩ **DISSOLUTION**

14. Checklist for tests performed on Transdermal Delivery Systems (TDS) (cont.):

5- particle size	○ suspension in reservoir	○ Yes		• According to manufacturer's specifications
	○ Others	○ No		
6- • **Peel adhesion**,** • **Release liner peel**,** • **Tack**,** • **Cold flow**,** • **Shear****	○ All types	○ Yes		• According to manufacturer's specifications

*All tests' procedures are performed according to the latest pharmacopeia except if sated in the checklist that the test procedure is according to manufacturer's method.

*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.

** Equipment not available.

Indicative form

(optional)

A- Aerosols:

1- Route of administration:
   - Inhalation
   - Nasal
   - Topical

2- Valve type:
   - Continuous valve
   - Metered valve

B-

- **Cream,**
- **gel**
- **ointment:**

1- Type:
   - hydrophilic
   - lipophilic

2- route of administration:
   - Topical
   - Ophthalmic

C- Foams:

Route of administration:
   - Topical
   - Rectal
   - Vaginal

D- Granules:

1- Granules for reconstitution giving:
   - suspension
   - solution

2- container contains:
   - multiple dose
   - single dose

3- Provided with a measuring device:
   - Yes
   - No

4- Non-conventional granules:
   - Effervescent granules

5- Coat:
   - Coated o Uncoated

E- powders:

1- Powders for reconstitution giving:
- suspension
- solution

2- container contains:
- multiple dose
- single dose

3- route of administration:
- Powder for inhalation
- oral
- Parenteral
- Ophthalmic
- Nasal
- topical

4- Provided with a measuring device:
- Yes
- No

5- Non-conventional powders:
- Effervescent powders
- Lyophilized powders.

F- Solutions:

1- Route of administration:
- nasal solution
- inhalation solution,
- vaginal solution,
- rectal solution,
- ophthalmic solution,
- otic solution.
- topical solution
- Parenteral

2- solution type:
- Aqueous.
- Non aqueous.

3- provided with a measuring device:
- Yes
- No

G- Sprays:

1- Route of administration:
- o Inhalation
- o Nasal
- o Topical

2- Valve type:
- o Continuous valve
- o Metered valve

I- Suppositories:

1- Have a prolonged local action:
- o Yes
- o No

2- Lipophilic:
- o Yes
- o No

J- Suspension:

1- Route of administration:
- o nasal
- o inhalation,
- o vaginal,
- o rectal,
- o ophthalmic,
- o otic.
- o topical
- o Parenteral

2- Suspension type:
- o Aqueous.
- o Non aqueous.

3- provided with a measuring device:
- o Yes
- o No

4- In the form of drops:
- o Yes
- o No

H- Tablets:

1- Type of tablet:
   - Uncoated
   - Coated

2- type of coat if coated:
   - Sugar coat.
   - Film coat.
   - Enteric coat.

3- Type of release:
   - Immediate release.
   - Extended (sustained/modified/controlled) release.
   - Delayed release (gastric resistant).

4- Scored
   - No.
   - Yes.

5- Type of score
   - Functional.
   - Non-functional.

6- Non-conventional tablets:
   - Orodispersible.
   - Buccal.
   - Sublingual.
   - Lyophilized oral product.
   - Effervescent tablet giving:
   - Solution
   - suspension
   - Dispersible tablets forming:
   - Solution.
   - Suspension.

K- Transdermal delivery system:

Form-fill-seal-type (reservoir or pouched) TDS.:
   - Yes
   - No

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 to 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 Q3 A 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):

General

CADC labs 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. Tighter 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 follow the general chapter of the uniformity of dosage units USP <905> 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 required for multivitamin and trace-element preparations (<100 ppm) and in other justified and authorized circumstances. (EP 2.9.6.)

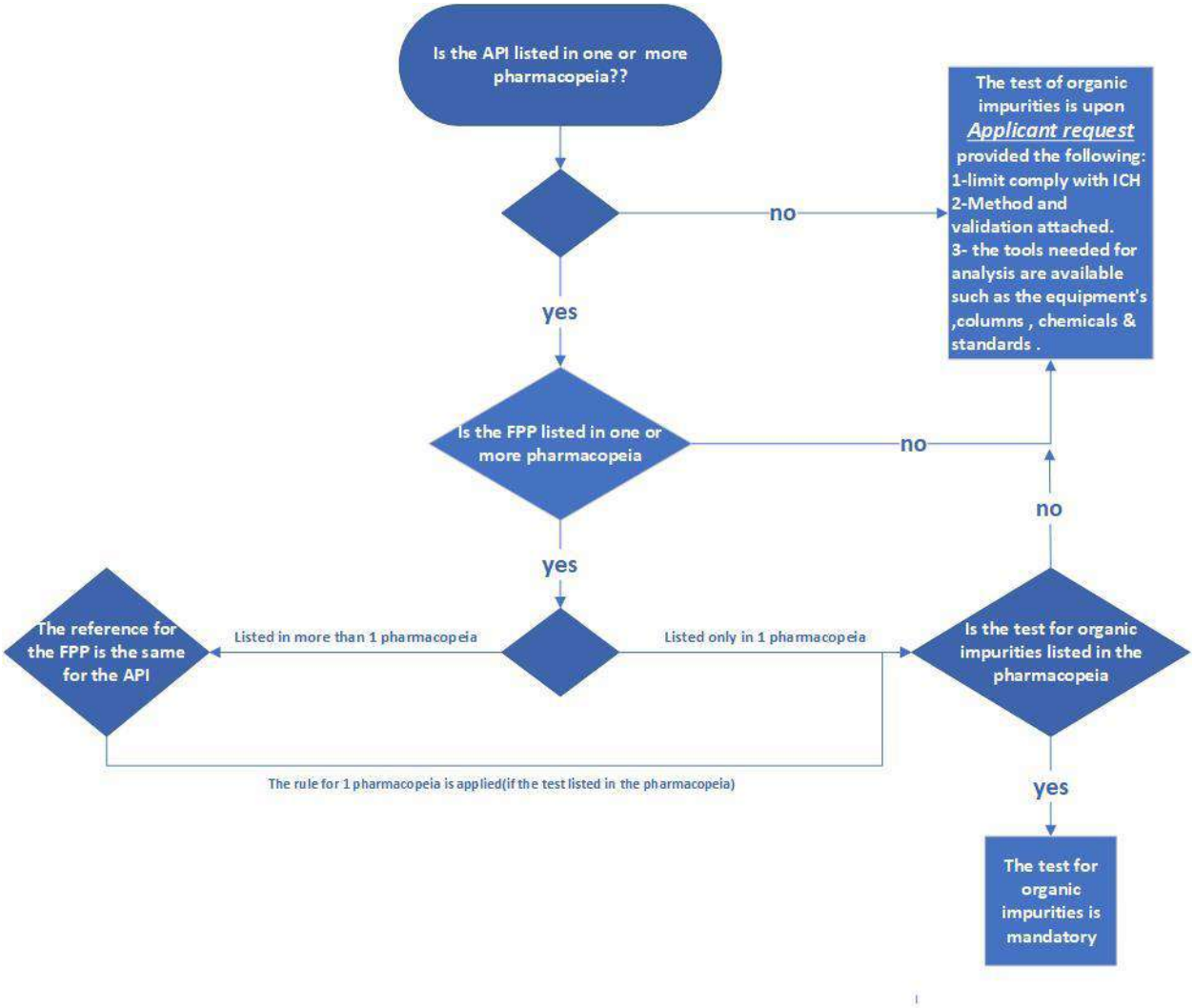
4-Test of impurities

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 is performed according to USP<1467>.

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 requested pharmacopeia regarding the method of analysis and limits.
- 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- <u>Method of analysis (MoA):</u>

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- <u>Method Validation (MV):</u>

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>

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 follows:

Type of analytical procedure / characteristics	IDENTIFICATION	TESTING FOR IMPURITIES quantitat.	TESTING FOR IMPURITIES 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

Acceptance criteria for validation parameters of Drug Product quality characteristics:

Quality characteristic	Item to be validated	Acceptance Criteria
Identity HPLC	**Selectivity/specificity**	All known peaks are separated. Major (API) peak is “pure” [Peak purity Angle ≤ peak threshold angle].
Assay	**Linearity** **Correlation coefficient** • y-intercept • Residual standard deviation	n ≥ 5 r > 0.99 ≤ 2% ≤ 2%
	Range	At least 80–120% of declared content

		(100% = concentration X of final sample stock solution)
	Accuracy (Mean): ▪ Recovery % ▪ RSD	 98-102% ≤ 2.0%, n ≥ 9 (at least three concentrations)
	Precision (using the recovery % of determinations of test solution at 100% concentration) ▪ Repeatability ▪ Intermediate precision	 RSD ≤ 2.0%, n ≥ 6. RSD ≤ 3.0%, [when combined from two analysts]
	Specificity • **HPLC**	▪ Chromatographic peaks are separated. ▪ No indication of interference (≤ 1%) from placebo solution at the retention time of API. ▪ No indication of another peak under the API peak (R ≥ 2) in degradated solution of API under various stress conditions (hydrolytic, oxidative, thermal ,photolysis). ▪ Major (API) peak is “pure” [Peak purity Angle ≥ peak threshold angle].”in case of using DAD “
	Robustness	≤ 2.0% difference for each intentionally altered sensitive parameter e.g. pH of mobile phase, column, temperature, flow rate, wavelength, etc…
	System suitability	

	▪ **Standard solution (100%)**	RSD ≤ 2 %, n = 5
	▪ **Resolution**	≥ 2 otherwise specified.
	▪ **Tailing factor**	≤ 2 otherwise specified.
	▪ **Theoretical plates**	≥ 2000
	▪ **Capacity factor (k)**	≥ 2
Content uniformity	**Linearity** **Correlation coefficient** • y-intercept • Residual standard deviation	n ≥ 5 r > 0.99 ≤ 5% ≤ 2%
	Range	At least 70–130% of declared content (100% = concentration X of final sample stock solution)
	Accuracy (Mean): ▪ Recovery % ▪ RSD	 98-102% ≤ 2.0%, n ≥ 9 (at least three concentrations)
	Precision (using the recovery % of determinations of test solution at 100% concentration) ▪ Repeatability ▪ Intermediate precision	 RSD ≤ 2.0%, n ≥ 6. RSD ≤ 3.0%, [when combined from two analysts]
	Specificity	▪ Chromatographic peaks are separated.

	• **HPLC**	▪ No indication of interference (≤ 1%) from placebo solution at the retention time of API.
	Robustness	≤ 2.0% difference for a each intentionally altered sensitive parameter e.g. pH of mobile phase, column, temperature, flow rate, wavelength, etc…
Drug product related substance and degradation products	**System suitability** ▪ **Standard solution (100%)** ▪ **Resolution** ▪ **Tailing factor** ▪ **Theoretical plates** ▪ **Capacity factor (k)**	 RSD ≤ 2 %, n = 5 ≥ 2 otherwise specified. ≤ 2 otherwise specified. ≥ 2000 ≥ 2
	Linearity **Correlation coefficient** • y-intercept Residual standard deviation	n ≥ 5 r ≥ 0.990, Level< 0.5%: ≤ 25% Level 0.5– < 1%: ≤ 10% Level ≥ 1% : ≤ 5.0% Level < 0.2%: ≤ 20% Level 0.2–< 0.5%: ≤10% Level 0.5–< 5%: ≤ 5.0% Level ≥ 5%: ≤ 2.5%
	Range	LOQ to 120% of specification limit of largest impurity or related substance.
	Accuracy (Mean):	

	▪ Recovery % ▪ RSD	Level < 0.2%: 70–130% 0.2– < 0.5%: 80–120% Level 0.5– < 5%: 90–110% Level ≥ 5%: 95–105% Level < 0.5%: ≤ 10%, Level 0.5 – < 5%: ≤ 5% Level ≥ 5%: ≤ 2.5% For all, n = 9 (at least three concentrations).
	Precision ▪ Repeatability ▪ Intermediate precision	 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 Level ≥ 5%, RSD ≤ 2.5%, n≥ 6 The % RSD of the assay/recovery values generated by single analyst should not be greater than 2.0% The % RSD of the combined assay/recovery values generated by both analyst over both days should not be greater than 3.0%
	Specificity **HPLC**	▪ Chromatographic peaks are separated. ▪ No indication of interference (≤ 1%) from placebo solution at the retention time of API. ▪ No indication of another peak under the API peak (R ≥ 2) in degradated solution of API under various stress conditions (hydrolytic, oxidative, thermal ,photolysis).

		▪ Major (API) peak is "pure" [Peak purity Angle ≥ peak threshold angle]."in case of using DAD "
	Robustness	Defined based on an experimental design and data (sensitive parameters and a range for each parameter in the final test method).
	LOD	Peak signal/noise ratio ≥ 3 : 1
	LOQ (≤ reporting threshold)	Peak signal/noise ratio ≥ 10 : 1 and RSD ≤ 10%, n ≥ 5
	System suitability ▪ **Sensitivity solution** ▪ **Resolution** ▪ **Tailing factor** ▪ **Theoretical plates** ▪ **Capacity factor (k)**	 Peak signal/noise ratio ≥ 10 : 1 and RSD ≤ 10%, n ≥ 5 ≥ 2 otherwise specified ≤ 2 otherwise specified ≥ 2000 ≥ 2

4-Analysis requirements:

a) Standards:

For the API Standard:

- The submission of Reference standards is preferred whenever possible
- In case a working standard is submitted lot number for primary standard used in its qualification should be mentioned as evidence of traceability in the COA submitted.

For standards used in organic impurities:

- For quantitative applications: primary reference (pharmacopeial is preferred) standards are only accepted for the evaluation of these types of tests.

- For qualitative applications: e.g. system suitability evaluation purposes, IR identification; other sources of reference standards other than the pharmacopeial source are accepted, if it has a well traceable certificate.

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> in case of isocratic elution mode.
- No modifications are allowed in column dimensions in case of using gradient elution mode.

c) placebo:

Placebo should be provided in case of organic impurities testing. If the placebo is unavailable the company should send a declaration of accepting 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 gave unsatisfactory results.

For the methods of analysis that require unavailable equipment in the laboratories of CADC or inability of analysis with the available equipment, an appeal should be presented to the head of the central administration of drug control to request: 1- The analysis at one of the governmental associations. 2- The analysis at one of the labs approved by the central administration for drug control. 3- Exemption of analysis in case that option 1 & 2 are not applicable.

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.

& 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.

Microbiological analysis

1. MICROBIAL ENUMERATION TESTS

*__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) Method suitability test procedure (this test assesses the ability of the chosen enumeration method to detect microorganisms in the presence of product to be tested) especially for products with proved antimicrobial activity or if insufficient information about the product exists to judge its probable growth inhibiting activity.

2) Sufficient sample size for testing,

The following table shows the required quantities of the samples for different sample types sufficient for carrying out the test for **Once**:

Sample Type	Required quantities for testing
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 but, at least 1gm or ml for testing **Once** and this reduction is acceptable only in special cases judged by CADC.

3) Alternative microbiological procedures used for testing the products containing viable microorganisms as active ingredients. These procedures should include identification and microbial concentration of the active ingredient, microbial enumeration of the product and test for specified/objectionable microorganisms, providing their equivalence to the pharmacopeial method.

Note: The ordinary microbial enumeration test procedure is not applicable for these products.

4) 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
Acceptance criteria	Expressed in CFU/g or CFU/ml
Reference	e.g. *USP, BP, Ph. Eur.*

Example: Paracetamol 500 mg tablets

Tested parameter	Total aerobic microbial count (TAMC), Total combined yeasts/molds count (TYMC), Tests for specified microorganisms
Method used	Plate-count method Testing method of product for E. coli
Acceptance criteria	Total aerobic microbial count (TAMC) 10^3 cfu/g, Total combined yeasts\molds count (TYMC) 10^2 cfu/g Absence of *E. coli* in 1g
Reference	e.g *USP 40*

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)**
Nonaqueous 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)

**** Update at USP 43 of the test for specified microorganisms, test for "*Burkholderia cepacia*" is 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.

5) Water activity of the product should be provided,

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 eliminating routine testing; the applicant should introduce the following:

• Formulation of the drug product has antimicrobial properties (as disinfectants and antiseptics) 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) Method suitability test procedure (this test assesses the ability of the chosen sterility testing method to detect microorganisms in the presence of product to be tested) especially for products with proved antimicrobial activity or if insufficient information about the product exists to judge its probable growth inhibiting activity.

2) 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.**

3) Test specifications: the following should be provided;

Tested parameter	Sterility of the product
Technique used	Direct inoculation or membrane filtration method
Sterilization method of the product	By filtration, steam, dry heat or ethylene oxide gas
Acceptance criteria	Pass sterility testing (comply)
Reference	*Ph. Eur., BP, USP.*

3. ANTIBIOTICS – MICROBIAL ASSAYS

*__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.

- **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
Reference standard with Potency expressed in µg/mg or IU/mg	▪ The applicant should provide working standards with its storage condition specifications and certificate of analysis that proofs the potency of the standard. ▪ The source of reference standards or reference materials
Calculations for determining antibiotic potency	Using software copy (if available)
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.

Notes

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

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

c- For non-pharmacopeial combinations, the in-house methods should include separation technique between antibiotics and validation protocols.

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

4. DISINFECTANTS AND ANTISEPTICS-EFFECTIVENESS 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, phenolics, 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	>3 Log reduction (for vegetative bacteria) and >2 Log reduction (for bacterial spore)
Reference	*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 42*
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	Five to Three 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)* = $\frac{\textit{Endotoxin limit X product conc.}}{\textit{Lysate sensitivity } (\lambda)}$
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	Depending on specific monograph of each product	5 EU/kg of body weight	Maximum dose per kilogram administered in 1 h
IV for radiopharmaceuticals		175 EU	Volume of the maximum recommended dose
Intrathecal (IT) for parenteral products		0.2 EU/kg of body weight	Maximum dose per kilogram administered in 1 h

IT for radiopharmaceuticals		14 EU	Volume of the maximum recommended dose
Parenterals administered per square meter of body surface ***(USP)***		100 EU/m^2	Maximum dose per square meter per hour
Injections other than IV (intramuscular, subcutaneous, etc.)		5 EU/kg of body weight	Maximum dose per kilogram administered in 1 h
Intraocular fluids ***(USP)***	----------	0.2 EU/mL	----------
Anterior segment solid devices ***(USP)***	----------	0.2 EU/device	----------
Ophthalmic irrigation products ***(USP)***	----------	0.5 EU/mL	----------
Injected or implanted ophthalmic drug product ***(USP)***	----------	2 EU/dose	----------

Notes:

- The Chosen dose should be the greatest recommended dose for the lowest body weight in targeted patient population (**take into consideration the recommended doses for pediatrics**).

- For Vet products administrated to variety of different species, you should select the smallest animal
that receiving the greatest dose per Kg.

	Acceptance criteria	**Requirements**
Rabbit test	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	Rabbit acceptance Cover letter contains manufacturer's approval for carrying out endotoxin rabbit test outside CADC laboratories on expense of the manufacturer. (موافقة الشركة على اجراء اختبار البروجيين باستخدام الأرانب خارج معامل الهيئة مع تحمل الشركة كافة التكاليف المطلوبة) In addition to "Product name & Batch number"

Exemptions: (الاعفاءات)

1- 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 from bacterial endotoxin).

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