Specific Tests / Criteria : New Drug products

- Additional tests and acceptance criteria generally should be included for particular new drug products.
- The ICH guidelines in Q6A presents a representative sample of both the drug products and the types of tests and acceptance criteria which may be appropriate.
- The specific dosage forms addressed include solid oral drug products, liquid oral drug products, and parenterals (small and large volume).
- Application of the concepts in this guideline to other dosage forms is encouraged.

Specific Tests / Criteria : New Drug products

Solid oral drug products:

a) Dissolution:

- The specification for solid oral dosage forms normally includes a test to measure release of drug substance from the drug product.
- immediate-release dosage forms → normally Single-point measurements
- extended-release dosage forms → multiple time point sampling should be performed
- delayed-release dosage forms → two-stage testing (using different media in succession or in parallel, as appropriate). E.g pH: 1.2, 6.8

Specific Tests / Criteria : New Drug products

Solid oral drug products:

a) Dissolution:

- For immediate-release drug products where changes in dissolution rate have been demonstrated to significantly affect bioavailability, it is desirable to develop test conditions which can distinguish batches with unacceptable bioavailability.
- If changes in formulation or process variables significantly affect dissolution and such changes are not controlled by another aspect of the specification, it may also be appropriate to adopt dissolution test conditions which can distinguish these changes.
- Where dissolution significantly affects bioavailability, the acceptance criteria should be set to reject batches with unacceptable bioavailability. Otherwise, test conditions and acceptance criteria should be established which pass clinically acceptable batches

Specific Tests / Criteria : New Drug products

Solid oral drug products:

a) Dissolution:

- For extended-release drug products, in vitro / in vivo correlation (IVIVC) may be used to establish acceptance criteria when human bioavailability data are available for formulations exhibiting different release rates.
- Where such data are not available, and drug release cannot be shown to be independent of in vitro test conditions, then acceptance criteria should be established on the basis of available batch data.
- Normally, the permitted variability in mean release rate at any given time point should not exceed a total numerical difference of +/-10% of the labeled content of drug substance (i.e., a total variability of 20%: a requirement of 50 +/- 10% thus means an acceptable range from 40% to 60%), unless a wider range is supported by a bioequivalency study.

date / /

" بسم الله الرحمن الرحيم "

اللهم فرج كرب أهل غزة

لو صار عندي Deviation معين تمرين خلال عملية الإنتاج حتأثر عندي على Dissolution.. وإذا إتأثر راح يأثر على الـ bioavailability ولازم لما أحط لـ Test لازم تكون قادرة عن كشف عن أي مشكلة في الـ formula .. أحيانًا مش تحتاج إلى Dissolution عادي .. تحتاج لشي اسمه Comparative Dissolut أو Conditions .. يعني إذا الـ Conditions الـ Standard كذا مثلًا .. بيصير الـ media عـ 75RpH بيصير الـ discriminatory conditions drug الـ you test .. على الـ formedia المحددين بالـ pp بتتنزل الـ RpH ماتخليها 75 ممكن 50 ليش؟ لأنه بالـ mixing مايكون كافي يصير لـ Test عندي more discriminatory

* Develop test conditions which can disinguish batch with unacceptable bioavailability

نعمل اختبارات بسيطة ذي الذوبان لحتى اتأكد أن الدواء عكن للجسم إمتصاصه

Specific Tests / Criteria : New Drug products

Solid oral drug products:

b) Disintegration:

- For rapidly dissolving (dissolution >80% in 15 minutes at pH 1.2, 4.0 and 6.8) products containing drugs which are highly soluble throughout the physiological range (dose/solubility volume < 250 mL from pH 1.2 to 6.8), disintegration may be substituted for dissolution.
- Disintegration testing is most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution.
- In such cases dissolution testing may not be necessary.
- It is expected that development information will be provided to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution vs. disintegration testing.

الـ "robustness" قدرة الدواء أو عملية تصنيعه على الحفاظ على جودته وفعاليته رغم التغيرات في الظروف البيئية أو العوامل التصنيعية. ببساطة، هي قدرة الدواء على الصمود أمام التحديات دون التأثير على فعاليته.

date / /

* Disintegration :-

- تعمله عادةً أقل من 15 دقيقة .. والـ Coted خلال 30 دقيقة ..
بيحكيلك إنه في الـ high soluble ممكن إحنا نستجين بالـ Disintegration عن الـ Dissolutions .. يعني تكتفي بنتائج الـ Disintegration

لو حكت بالامتحان عن الـ Rapidly dissoluing product هو الـ product يلي 80٪ من الـ Drug يصيرله إطلاق خلال 15 دقيقة بـ Dissolutions مرّة انعمل بـ pH مرّة Test

بـ media = 1.2 ومرّة ٤ ومرّة 6.8 .. لازم انعمل ٣ مرّات بـ pH مختلفة كان الإطلاق أكثر من 80٪ .. هاد هو الـ rapidly dissoluing .. عند 15 دقيقة لازم يكون 80٪ منه صار له إطلاق .. أو أكثر

ومعنى الـ dose/solubility .. إنه معناها عندي Doses الـ Drug تاعته 500 لازم آخذ هدول الـ 500mg وأحطهم بكاسة فيها 250 ml أو أقل من هيك .. حتى اعتبر إنه الـ Drug عنده ذائبية عالية لما يذوب بـ pH ٣ يلي ذكرناهم بـ 250 ml أو أقل

الـ Dissolutions هو Kinatic يعني مرتبط بوقت / rate .. أما الـ Solubility هو parameter عبارة عن Dynamic مش مربوطة بزمن .. تتأثر فقط بحرارة / الظروف وهكذا

Specific Tests / Criteria : New Drug products

Solid oral drug products:

c) Hardness/friability:

- It is normally appropriate to perform hardness and/or friability testing as an in-process control → normally not necessary to include these attributes in the specification.
- If the characteristics of hardness and friability have a critical impact on drug product quality (e.g., chewable tablets), acceptance criteria should be included in the specification.

Specific Tests / Criteria : New Drug products

Solid oral drug products:

d) Uniformity of dosage units:

- This term includes
  - the mass of the dosage form
  - the content of the active substance in the dosage form
- A pharmacopoeial procedure should be used.
- In general, the specification should include one or the other but not both.
- If appropriate, these tests may be performed in-process; however, the acceptance criteria should be included in the specification.

Specific Tests / Criteria : New Drug products

Solid oral drug products:

d) Uniformity of dosage units:

<905> UNIFORMITY OF DOSAGE UNITS (USP monograph) →

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance	
			≥25 mg and ≥25%	<25 mg or <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Solutions in unit-dose containers and into soft capsules			WV	WV
Others			CU	CU

date / /

* Hardness
حكيناعنهم قبل مسؤول يجبرك إنك تحطهم أبدًا
والـ limit تاعهم in house إنت تحطهم على كيفك

* Uniformity of dosage form.
← في جدول كبير مهم حاطينه .. يحكيلك إنه يقسم لحدة Dosage عن تكون Capsules, Tablet ..... بلي يكون 25 < ما يكون مطلوب منك تعمل CU
وبلي 25 < يكون مطلوب منك تعمل CU .. كيف تعمل CU ؟ تروح على USP
↓
Content uniformity
على الشابتر الخاص بالـ CU وفي معايير تعمل 10 وحدات أو 10 جرعات إذا كان Tablet مثلًا أو إذا كان powder توزن شكوب .. وتقيس .. تحلل كل وحدة لحال .. وتحسب اشي اسمه L. value وبناءً عليها تحسب هل الـ content uniform ولا مش uniform .. هاد as general .. لكن عنا حالات إحنا بدنا نصير نفوت بتفاصيل .. مثلًا Filim Coated .. مثلًا Soft coted ..
ما بحتاج أعمل uniformity إلها .. مثلًا إذا كانت بتحتوي مش على sol تحتوي على gel مثلًا .. لأنه بدي أعمل uniformity للـ gel تصنع لحاله بجديد لنحط على الكبسولة أو جوانها .. أما sol صفاويها so no needed ..

لو عندي مثلًا sol .. شو راح يكون ؟ WV مش CU

← أبسط إلكم الفرق بين WV ← بستخدمه هاد الـ Test لما يكون العادة المخالة متوزعة بالتساوي .. أتأكد إنه الوزن متجانس مع الدواء .
(يركز على التجانس)

CU ← بستخدمه لقياس العادة المخالة جوا الدواء لحتى أتأكد إنه عنده نفس الكمية لكل قرص من المواد المخالة.
(يركز على توزيع المادة المخالة)

Specific Tests / Criteria : New Drug products

Solid oral drug products:

e) Water content:

- A test for water content should be included when appropriate.
- The acceptance criteria may be justified with data on the effects of hydration or water absorption on the drug product.
- A detection procedure which is specific for water (e.g., Karl Fischer titration) is preferred.

Specific Tests / Criteria : New Drug products

Solid oral drug products:

البكتريا حفظ

f) Microbial limits:

- Acceptance criteria should be set for:
  - the total count of aerobic microorganisms,
  - the total count of yeasts and molds,
  - the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas aeruginosa*).
- These should be determined using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture which is justified by data and experience.

➢ The type of microbial test(s) and acceptance criteria should be based on the

1. nature of the drug substance,
2. method of manufacture,
3. the intended use of the drug product:

Specific Tests / Criteria : New Drug products

Solid oral drug products:

f) Microbial limits:

- In general, it is advisable to test the drug product unless:
  1. its components are tested before manufacture and
  2. the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination or proliferation.

➢ With acceptable scientific justification, it should be possible to propose no microbial limit testing for solid oral dosage forms. Why???

Specific Tests / Criteria : New Drug products

USP 2012

Table 1. Acceptance Criteria for Microbiological Quality of Nonsterile Dosage Forms

Route of Administration	Total Aerobic Microbial Count (cfu/g or cfu/mL)	Total Combined Yeasts/Molds Count (cfu/g or cfu/mL)	Specified Microorganism(s)
Nonaqueous preparations for oral use	10^3	10^2	Absence of *Escherichia coli* (1 g or 1 mL)
Aqueous preparations for oral use	10^2	10^1	Absence of *Escherichia coli* (1 g or 1 mL)
Rectal use	10^3	10^2	—
Oromucosal use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Gingival use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Cutaneous use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Nasal use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Auricular use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL)
Vaginal use	10^2	10^1	Absence of *Pseudomonas aeruginosa* (1 g or 1 mL) Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Candida albicans* (1 g or 1 mL)
Transdermal patches (limits for one patch including adhesive layer and backing)	10^2	10^1	Absence of *Staphylococcus aureus* (1 patch) Absence of *Pseudomonas aeruginosa* (1 patch)
Inhalation use (special requirements apply to liquid preparations for nebulization)	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL) Absence of bile-tolerant Gram-negative bacteria (1 g or 1 mL)

Specific Tests / Criteria : New Drug products

Oral liquids:

One or more of the following specific tests will normally be applicable to oral liquids and to powders intended for reconstitution as oral liquids.

a) pH: Acceptance criteria for pH should be provided where applicable and the proposed range justified.

Specific Tests / Criteria : New Drug products

Oral liquids:

b) Uniformity of dosage units

In general, the specification should include weight variation or content uniformity test but not both.

If dispensing equipment (such as medicine droppers or dropper tips for bottles) is an integral part of the packaging, this equipment should be used to measure the dose. Otherwise, a standard volume measure should be used.

If appropriate, tests may be performed in-process; however, the acceptance criteria should be included in the specification.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

Specific Tests / Criteria : New Drug products

Oral liquids:

c) Microbial limits

- Skip testing may be an appropriate approach where permissible.
- With acceptable scientific justification, it may be possible to propose no microbial limit testing for powders intended for reconstitution as oral liquids.
- Acceptance criteria should be set for:
  1. the total count of aerobic microorganisms,
  2. the total count of yeasts and molds,
  3. the absence of specific objectionable bacteria (e.g., Staphylococcus aureus, Escherichia coli, Salmonella, Pseudomonas aeruginosa).

Specific Tests / Criteria : New Drug products

Oral liquids:

d) Antimicrobial preservative content:

Acceptance criteria for preservative content should be established for oral liquids needing an antimicrobial preservative.

The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Specific Tests / Criteria : New Drug products

Oral liquids:

d) Antimicrobial preservative content:

- normally performed at release → Under certain circumstances, in-process instead of release testing → however, the acceptance criteria should remain part of the specification.
- Antimicrobial preservative effectiveness should be demonstrated:
  - during development,
  - during scale up, and
  - throughout the shelf-life.

Specific Tests / Criteria : New Drug products

Oral liquids:

e) Antioxidant preservative content:

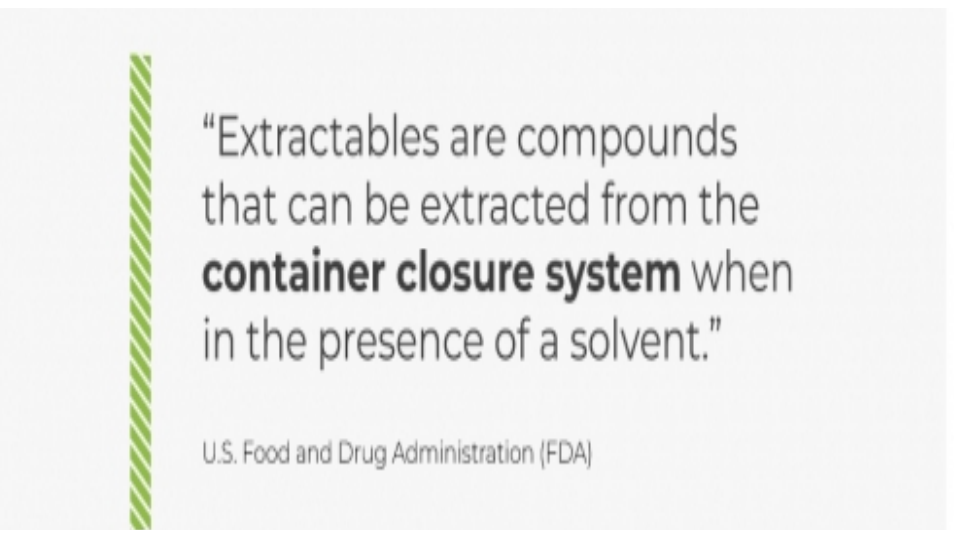
- Release testing for antioxidant content should normally be performed.
- Under certain circumstances, where justified by developmental and stability data,
  - shelf-life testing may be unnecessary,
  - in-process testing instead of release testing → the acceptance criteria should remain part of the specification.

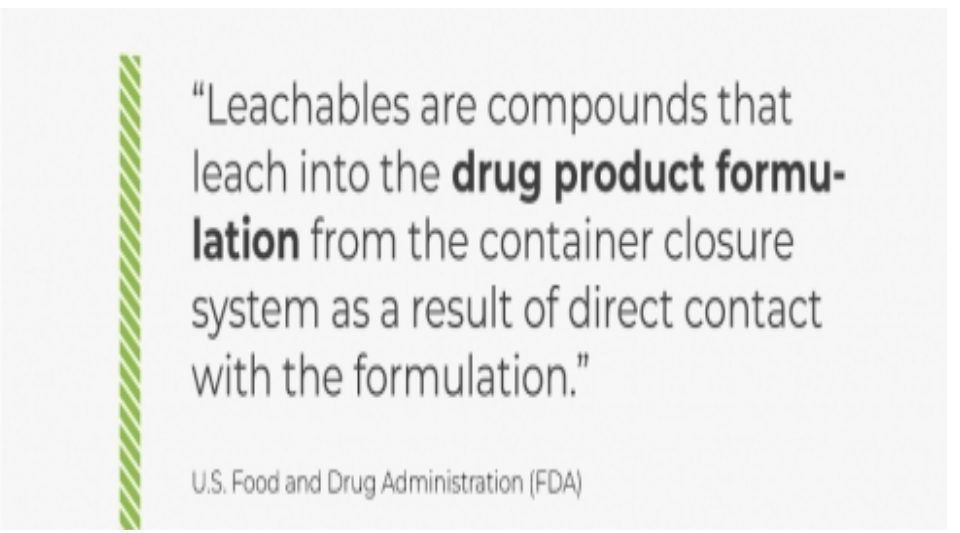
Specific Tests / Criteria : New Drug products

Oral liquids:

f) Extractables:

- Tests and acceptance criteria for extractables from the container/closure system components (e.g., rubber stopper, cap liner, plastic bottle, etc.) are considered appropriate for oral solutions packaged in:
  - non-glass systems
  - glass containers with non-glass closures.





Specific Tests / Criteria : New Drug products

Oral liquids:

f) Extractables:

- Generally, where development and stability data show evidence that extractables are consistently below acceptable and safe levels, elimination of this test can normally be accepted.
- This should be reinvestigated if the container/closure system or formulation changes.

date / /

* Uniformity of dosage unite.

← الشركة عالقبي الـ suspin هل تفحص الـ MO إله ؟ ما في water .. أكيد لأ.
راح تجيبه powder .. بجد 14 يوم ينكب معروف .. بالتالي شو نوع الـ Test تاعه هون ؟ الـ skip

* Microbial limits

إذا هو بيباع as liquid أكيد حفحص الـ MO .. إذا لأ .. ما بفحص

* preservative

← برجعه إلها limit معيّن ومحدد.

* Extractables.

← الطبيعي إنه يفحصوا ويختبروا المواد إذا كانت مناسبة للتحبئة أو لأ.
كلما غيرنا البكج .. لازم نعمل Test الـ extractable

Specific Tests / Criteria : New Drug products

Oral liquids:

g) Alcohol content:

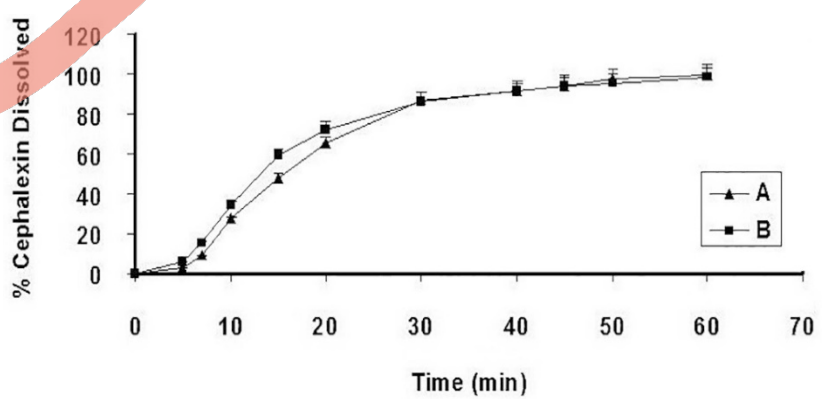
- Where it is declared quantitatively on the label in accordance with pertinent regulations, the alcohol content should be specified.
- It may be assayed or calculated.

Specific Tests / Criteria : New Drug products

Oral liquids:

h) Dissolution:

- In addition to the attributes recommended immediately above, it may be appropriate (e.g., insoluble drug substance) to include dissolution testing and acceptance criteria for:
  - oral suspensions
  - dry powder products for resuspension.
- The testing apparatus, media, and conditions should be pharmacopoeial, if possible, or otherwise justified.

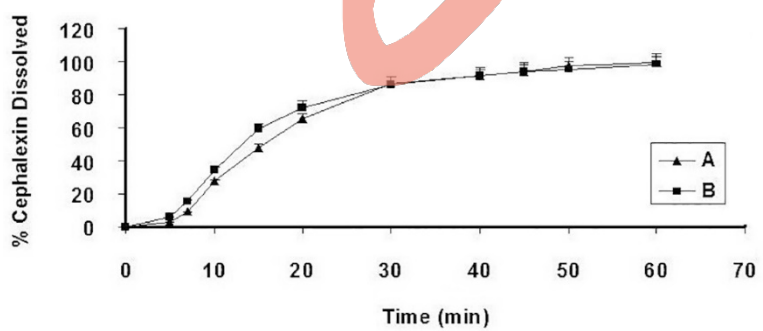


Specific Tests / Criteria : New Drug products

Oral liquids:

h) Dissolution:

- Single-point measurements are normally considered suitable for immediate-release dosage forms.
- Multiple-point sampling, at appropriate intervals, should be performed for modified-release dosage forms.
- Acceptance criteria should take into account the dissolution profiles of the batches that showed acceptable performance in vivo.

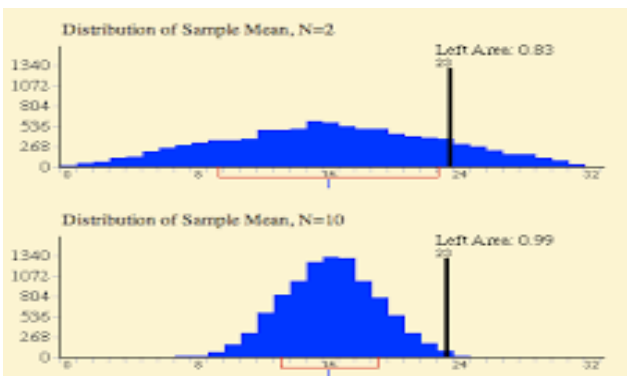


Specific Tests / Criteria : New Drug products

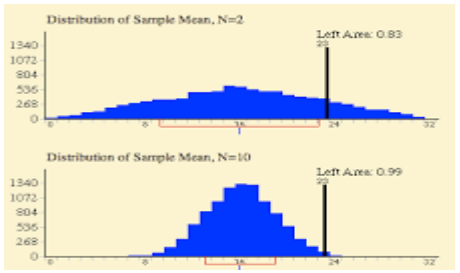
Oral liquids:

i) Particle size distribution:

- Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for oral suspensions.
- performed at release → in-process test when justified by product development data.



Specific Tests / Criteria : New Drug products

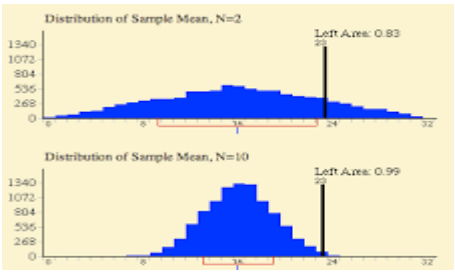


Oral liquids:

i) Particle size distribution:

- If these products have been demonstrated during development to have consistently rapid drug release characteristics, exclusion of a particle size distribution test from the specification may be proposed.
- Particle size distribution testing may also be proposed in place of dissolution testing; justification should be provided.
- Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

Specific Tests / Criteria : New Drug products



Oral liquids:

i) Particle size distribution:

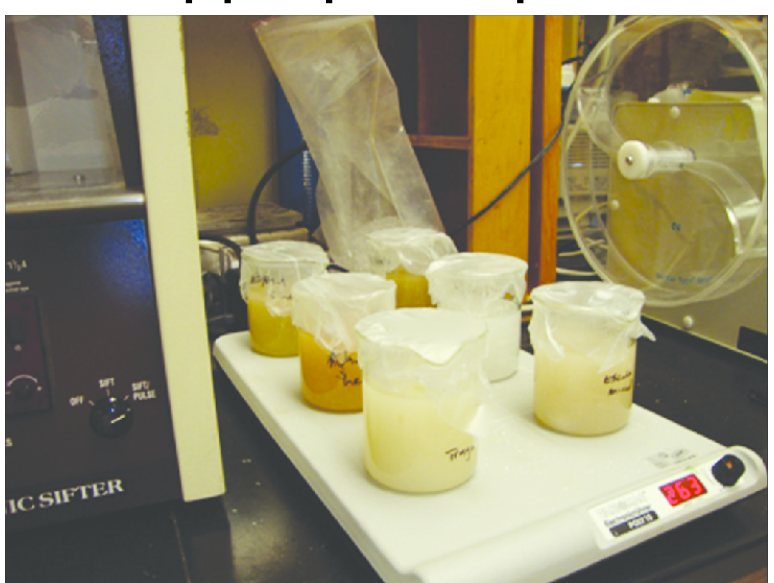
- The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and / or lower particle size limits should be well defined.
- The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

Specific Tests / Criteria : New Drug products

Oral liquids:

j) Redispersibility:

- For oral suspensions which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate.
- The procedure (mechanical or manual) should be indicated. Shaking may be an appropriate procedure.



Specific Tests / Criteria : New Drug products

Oral liquids:

k) Rheological properties:

- For relatively viscous solutions or suspensions, it may be appropriate to include rheological properties (viscosity/specific gravity) in the specification.

l) Reconstitution time:

- Acceptance criteria for reconstitution time should be provided for dry powder products which require reconstitution.

m) Water content:

- For oral products requiring reconstitution, a test and acceptance criterion for water content should be proposed when appropriate.

Specific Tests / Criteria : New Drug products

Parenteral Drug Products :

a) Uniformity of dosage units

b) pH: Acceptance criteria for pH should be provided where applicable and the proposed range justified.

c) Sterility: All parenteral products should have a test procedure and acceptance criterion for evaluation of sterility. Where data generated during development and validation justify parametric release, this approach may be proposed for terminally sterilized drug products.

d) Endotoxins/Pyrogens: A test procedure and acceptance criterion for endotoxins, using a procedure such as the limulus amoebocyte lysate test, should be included in the specification.

Pyrogenicity testing may be proposed as an alternative to endotoxin testing where justified.

Specific Tests / Criteria : New Drug products

Parenteral Drug Products :

***e) Particulate matter*:** Parenteral products should have appropriate acceptance criteria for particulate matter.

This will normally include acceptance criteria for:

1. visible particulates and / or clarity of solution,
2. for sub-visible particulates as appropriate.

***f) Water content*:**

For non-aqueous parenterals, and for parenteral products for reconstitution, a test procedure and acceptance criterion for water content should be proposed when appropriate.

Loss on drying (LOD) is generally considered sufficient for parenteral products, if the effect of absorbed moisture vs. water of hydration has been adequately characterized during development.

In certain cases a more specific procedure (e.g., Karl Fischer titration) may be preferred.

Specific Tests / Criteria : New Drug products

Parenteral Drug Products :

g) Antimicrobial preservative content:

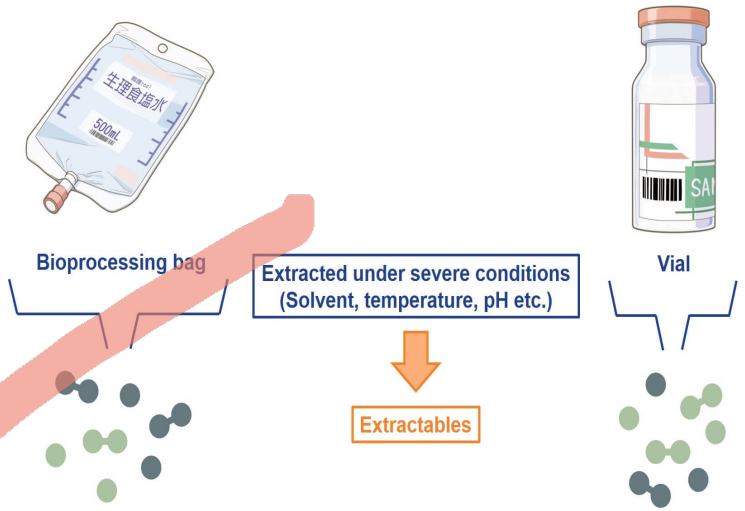
- For parenteral products needing an antimicrobial preservative (e.g. multidose vials).
- The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Specific Tests / Criteria : New Drug products

Parenteral Drug Products :

i) Extractables:

- Control of extractables from container/closure systems is considered significantly more important for parenteral products than for oral liquids.
- However, where development and stability data show evidence that extractables are consistently below the levels that are demonstrated to be acceptable and safe, elimination of this test can normally be accepted.
- This should be reinvestigated if the container/closure system or formulation changes.



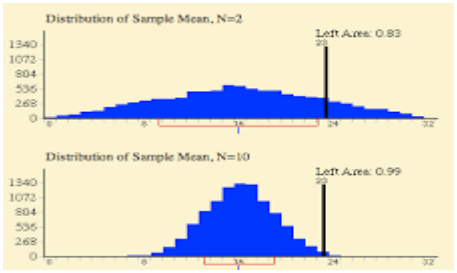
Specific Tests / Criteria : New Drug products

Parenteral Drug Products :

j) Functionality testing of delivery systems:

- Parenteral formulations packaged in pre-filled syringes, autoinjector cartridges, or the equivalent should have test procedures and acceptance criteria related to the functionality of the delivery system (e.g.inj. volume).
- Under certain circumstances these tests may be performed in-process.
- Data generated during product development may be sufficient to justify skip lot testing or elimination of some or all attributes from the specification.

Specific Tests / Criteria :
New Drug products



Parenteral Drug Products :

k) Osmolarity: When the tonicity of a product is declared in its labeling, appropriate control of its osmolarity should be performed.

l) Particle size distribution:

Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for injectable suspensions.

Particle size distribution testing may also be proposed in place of dissolution testing, when development studies demonstrate that particle size is the primary factor influencing dissolution; justification should be provided.

m) Redispersibility: similarly to oral liquids

n) Reconstitution time: similarly to oral liquids

Hawazen Abdallah

Don't forget to pray for

♥ GAZA