Specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances

ICH Guidelines Q6A (www.ich.org)

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Definitions and general concepts

Specifications and acceptance criteria

Specification: A list of tests, references to analytical procedures, and appropriate acceptance criteria.

It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use.

Acceptance criteria: Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

- Example:
- Assay acceptance criteria 90-110%
- 110.5%--→ pass or fail??

OURSTORYBEGINS

30/Oct

« بسم الله الرحمن الرحيم »

« Specification »

شرحت الدكتورة الفرق بين الـ specification والـ Certificate of analysis اختصاره (COA) وهما عبارة عن مستند نستخدمهم لحتى نقيّم جودة المنتجات .. في إختلاف بينهم من ناحية الهدف والمحتوى :-

Spcification ← مجموعة من المتطلبات المحددة يلي لازم المنتج عندي يكون مستوفيها .. وهي دليل مرجعي لحتى أحدد ما إن كان المنتج عندي بيتوافق مع المعايير يلي طالبينها.

COA ← عبارة عن شهادة تحليل تظهر عندي تأكيد تام إنه المنتج الفلاني تم فحصه ويظهر جواته الاختبارات يلي أجريت.
وتحتوي أيضًا على الـ Limit المقبولة لهاد الـ Test.

← حكينا عن الـ Spcification وإنه يكون عندي جداول بعض فيها المواد، سواء كانت مواد فعّالة أو مواد عاديّة (Drug product)
عكن نستبدل كلمة spcification بـ Acceptable Criteria، مثلًا
عندي جدول حاكيلي فيه إنه نسبة الشوائب بالمنتج عندي مالازم تتعدى 1% .. هاي هي acceptable Criteria.

عندي بالسلايد مثال تاع Assay acceptance criteria
90-110%
لو كانت 5.110 ؟ طبعًا fail.

Specifications and acceptance criteria

Example: Drug product specifications

Attribute	Acceptance Criteria (typical values)	Analytical Procedure (for example)
Identity	Matches Standard	IR or HPLC/UV
Appearance	Color, Imprint	Visual
Assay	90-110%	HPLC
Dose Uniformity	Statistical Criterion (USP)	HPLC or Weight
Release from Dosage Form	80% in 15 or 30 minutes	Stirred Aqueous Vessel
Impurities (Related Substances)	<1% to few %	HPLC
Microbial Limits Or Sterility	# of total aerobes and fungi per gram Pathogen (-)	Growth in special media
Water Content	Few %	Chemical or wgt. loss
Preservative Content	NLT 75% of Initial	HPLC

Specifications and acceptance criteria

Example: Drug product specifications

Table 2: Example of solid oral drug product specifications for early development.

Test Name	Test Method	Acceptance Criteria
Description Shape Colour	Visual	Product specific shape and colour
Identity by HPLC	HPLC	Consistent with reference*
Identity by UV	HPLC–PDA	Consistent with reference*
Assay by HPLC (% label claim)	HPLC	90.0–110.0%*
Degradation products by HPLC Individual unspecified Total	HPLC	 ≤1.0%* ≤5.0%*
Dissolution	HPLC or UV	Report*
Disintegration	USP<701>	≤15 min
Uniformity of dosage units	HPLC or weight variation	Corresponds to USP<905>*

عشان جداول توضحلي الفرق بين Drug substance وما بين
الـ Drug product .. حيث إنه الـ Drug S معناها المواصفات
والمعايير للمادة الفعالة ذي تركيبها الكيميائي و قوتها والشوائب تاعتها..
أما بالنسبة Drug product هو المنتج النهائي يلي راح يصل للمريض
بكل المواد يلي فيه مع المادة الفعالة.

⇐ بحاول قدر الإمكان أضع حكي الدكتورة تحت سلايداتها مباشرة لأنها
بتشرح عشوائي .. إذا فيتوا حاولوا إقرأوا التفريغ و بعدين السلايدات.

⇐ حكينا برضه عن الـ Universal والـ Specific وكيف أميزتهم تيفريغ
المحاضرة السادسة .. إذا فش واضح إحكولي.
مثلًا الـ Assay ، الـ Discribtion ، الـ impurite كلهم صفات المنتج
بتميزهم universal بينما مثلًا الـ pH تعتبر specific .. أي شي عين
يلي ذكرتهم عن الـ universal بتميزهم specific بيعتمد على الـ ROA
أو على Dosge form .. طبعًا هاي الـ specific ممكن تكون
in house زي الـ partical size ..

Specifications and acceptance criteria

- "Conformance to specifications" means that the drug substance and / or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.
- Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.

Specifications and acceptance criteria

- Specifications should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.

- The quality of drug substances and drug products is determined by :

1. their design,
2. development,
3. in-process controls,
4. GMP controls,
5. process validation, and
6. by specifications applied to them throughout development and manufacture.

OURSTORYBEGINS

تماشي
عندي مصطلح اسمه ال specif to Conformance ومعناه إنه ال
product تاعي لما إجيت أعمله سواء الحالة الفعالة تاعته أو شو ماكان
لازم يكون متوافق مع ال Specification

وتحت عندي تعريف واضح إله .. إنه لازم هاي المعايير تكون
موافق عليها من قبل الجهات التنظيمية.
و ضرورة الإلتزام بالمعايير لحتى أضمن الأمان والفعالية للدواء ..
حيث تُحدد هاي المعايير ومدى الإلتزام فيها من خلال النقاط
المذكورة وأهمها c GMP .. ال Design .. الDevelopment

Definitions

Specific test: A test which is considered to be applicable to particular new drug substances or particular new drug products depending on their specific properties and/or intended use.

Universal test: A test which is considered to be potentially applicable to all new drug substances, or all new drug products; e.g., appearance, identification, assay, and impurity tests.

Definitions

New drug substance: The designated therapeutic moiety, which has not previously been registered in a region or Member State (also referred to as a new molecular entity or new chemical entity).

- It may be a complex, simple ester, or salt of a previously approved drug substance.

New drug product: A pharmaceutical product type, for example, tablet, capsule, solution, cream, etc., which has not previously been registered in a region or Member State, and which contains a drug ingredient generally, but not necessarily, in association with excipients.

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GENERAL CONCEPTS

Periodic or Skip Testing

- Periodic or skip testing is the performance of specified tests at release on pre-selected batches and / or at predetermined intervals, rather than on a batch-to-batch basis with the understanding that those batches not being tested still must meet all acceptance criteria established for that product.
- This represents a less than full schedule of testing and should therefore be justified and presented to and approved by the regulatory authority prior to implementation.
- This concept may be applicable to, for example, residual solvents and microbiological testing for solid oral dosage forms.

GENERAL CONCEPTS

Periodic or Skip Testing

- This concept should generally be implemented post-approval.
- When tested, any failure to meet acceptance criteria established for the periodic test should be handled by proper notification of the appropriate regulatory authority(ies).
- If these data demonstrate a need to restore routine testing, then batch by batch release testing should be reinstated.

* Periodic or skip testing

← ال periodic عبارة عن Test نعملوه كل فترة معيّنة من السنة على المنتج تاعي لحتى أتأكد إنه أموره تمام

← Skip عبارة عن إختبار برضه بس ما يكون محدد إله وقت معيّن لإجراءه نعمل بشكل عشوائي، لأنه الثقة بالمنتج كثير عالية وما في داعي لـ Test دوري إله

← من الأمثلة على هاي الـ Tests هو "residual solv" مثلًا جبت Active ingredrant وفحصت فيها الـ Organic solv طلعت كميتها كذا، وروحت صنعت Tablet، هل من الضروري أرجع افحص الـ solv كمان مرّة؟ لا .. هاي هي Skip والـ periodic

وكمان عندي الـ microbioligical للـ Test هاي..

مثلًا الـ Solid dos، كل منتج عندي فيه أو كل مادة فيه فحصت الميكروبات فيه .. في داعي ارجع افحصها لتبدأ [illegible] ؟

Final prodact. ✓

ولاحظوا ماكين لما Solid dosage oral، يعني لو ظل MO راح تطحنهم المعدة.

لو تطلب مني أرجع أعمل Test حيكون periodic يعني كل ٦ أشهر مرة مثلًا وهكذا.

GENERAL CONCEPTS

Release Acceptance Criteria vs. Shelf-life Acceptance Criteria

- The concept of different acceptance criteria for release vs. shelf-life specifications applies to drug products only.
- It pertains to the establishment of more restrictive criteria for the release of a drug product than are applied to the shelf-life.
- Examples where this may be applicable include assay and impurity (degradation product) levels.
-

GENERAL CONCEPTS

Release Acceptance Criteria vs. Shelf-life Acceptance Criteria

- In Japan and the United States, this concept may only be applicable to in-house criteria, and not to the regulatory release criteria.
- However, an applicant may choose to have tighter in-house limits at the time of release to provide increased assurance to the applicant that the product will remain within the regulatory acceptance criterion throughout its shelf-life.

Acceptance Criteria

- بس يكتبوا الـ Tablet يوخذوا منهم عينات ويروحوا يحللوها، ويصدوا إذا هي pass ولا فشلت عندي.. شو هي الـ Accept .. هي يلي تسجلها بالـ JFDA
- يلي هي الـ Specifications نفسها.. يعني تيجي الـ JFDA تسحب عينة من السوق فجأة ونشوف هل تتوافق مع المحابس أو لأ يلي عندهم بالملف.

أما الـ Release Acceptance هي لما تبلش تصنع بالمواد يعني لما المواد يكون عمره zero، بدهم يطلعوه.. عشان يكون Release (مقبول) أو مرفوض.. إذا Release خلص يطلعوا إلها packaging ويودها على JFDA لحتى تنزل على السوق.

- خلينا نوضحها أكثر.. الـ Shelf-life يرجع لـ ICHL (limit).. يعني إنت مجموع تطلع عن هاد الـ range.. إذا إنت مهتم بالـ Quality ومهتم هادير مشكلة وتظهر تسحب المنتج تبحث.. خلال عملية التطوير والتصنيع للدواء.. يكون عندك Friability ما تتجاوز 1% مثلاً.. ما تخلي Friability خلال عملية التصنيع للمنتج تاعك 1% بالتمام.. أي خطأ يصير راح تتجاوز الـ 1%.. حتى لو رحت ونزلت المنتج تاعك على السوق خلال عملية النقل وكل الظروف راح تتكسر.. المفروض يكون أقل من 1%.. المفروض تخلي الـ Target تاعك أقل من 1%... هاد هو الـ release يلي نحكي عنه.

GENERAL CONCEPTS

In-process Tests

- In-process tests, are tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal series of tests which are conducted prior to release.

➢ In-process tests which are only used for the purpose of adjusting process parameters within an operating range, e.g., hardness and friability of tablet cores which will be coated and individual tablet weights, are not included in the specification.

GENERAL CONCEPTS

In-process Tests

- Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to or tighter than the release requirement, (e.g., pH of a solution) may be sufficient to satisfy specification requirements when the test is included in the specification.
- However, this approach should be validated to show that test results or product performance characteristics do not change from the in-process stage to finished product.

In-process test

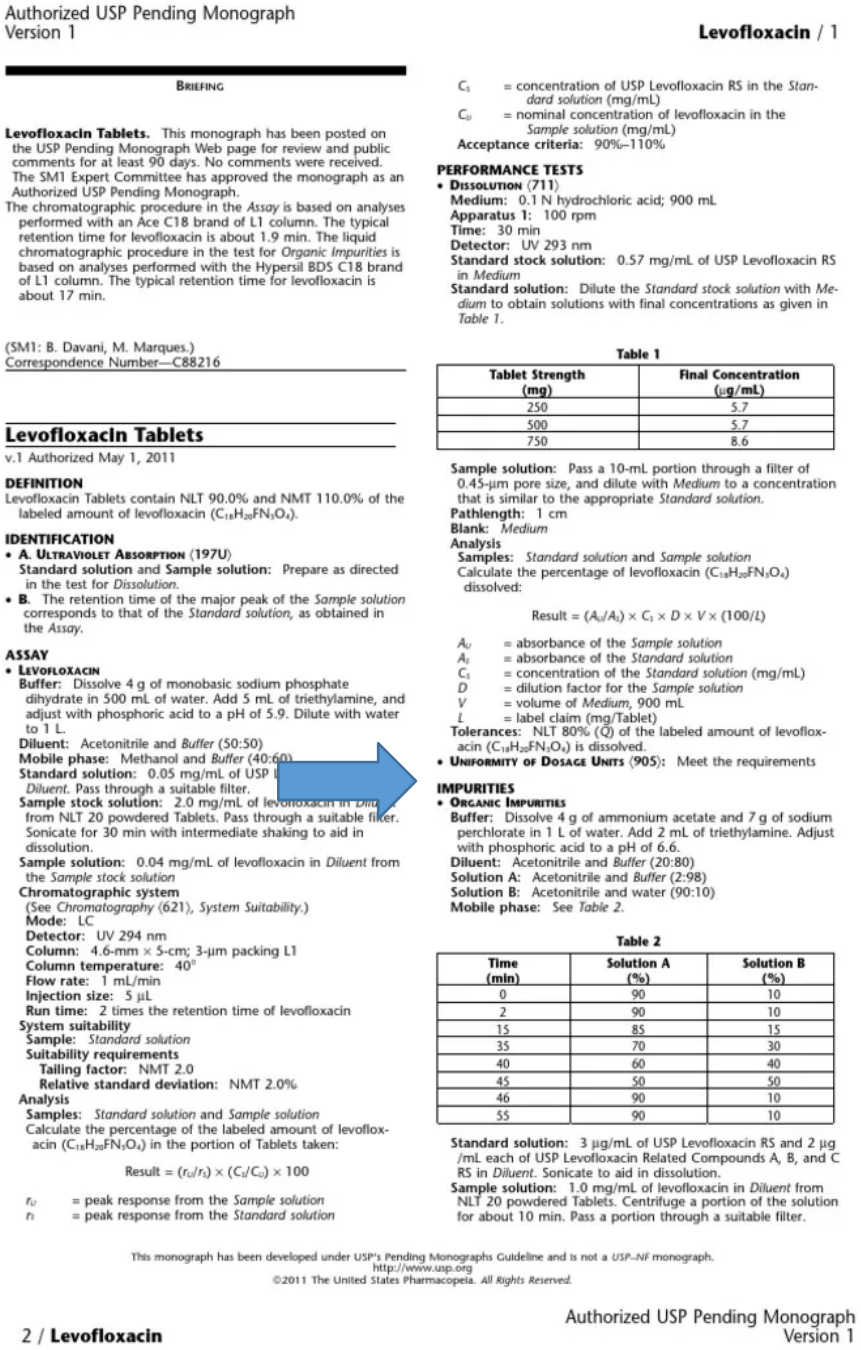
هي عبارة عن إختبارات تُجرى أثناء عملية تصنيع الدواء، سواء المادة
فعالة أو المنتج متكامل .. هاي الإختبارات لحتى نضبط المنتج أثناء
إنتاجه مش حتى أقيم الـ Quality النهائية .. زي مثلاً Hardness
أو Fribility طبعاً مش لحتى أقيم جودة المنتج بالنهاية .. بس طبعاً
لنضبط معايير التصنيع

برضه pH لل solut نفس الشي

GENERAL CONCEPTS

Limited Data Available at Filing

- It is recognized that only a limited amount of data may be available at the time of filing, which can influence the process of setting acceptance criteria.
- As a result it may be necessary to propose revised acceptance criteria as additional experience is gained with the manufacture of a particular drug substance or drug product (example: acceptance limits for a specific impurity).



Authorized USP Pending Monograph
Version 1

Levofloxacin / 1

BRIEFING

Levofloxacin Tablets. This monograph has been posted on the USP Pending Monograph Web page for review and public comments for at least 90 days. No comments were received. The SM1 Expert Committee has approved the monograph as an Authorized USP Pending Monograph.
The chromatographic procedure in the *Assay* is based on analyses performed with an Ace C18 brand of L1 column. The typical retention time for levofloxacin is about 1.9 min. The liquid chromatographic procedure in the test for *Organic Impurities* is based on analyses performed with the Hypersil BDS C18 brand of L1 column. The typical retention time for levofloxacin is about 17 min.

(SM1: B. Davani, M. Marques.)
Correspondence Number—C88216

Levofloxacin Tablets

v.1 Authorized May 1, 2011

DEFINITION
Levofloxacin Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of levofloxacin ($C_{18}H_{20}FN_3O_4$).

IDENTIFICATION
- **A. ULTRAVIOLET ABSORPTION** ⟨197U⟩
  Standard solution and **Sample solution:** Prepare as directed in the test for *Dissolution*.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
- **LEVOFLOXACIN**
  Buffer: Dissolve 4 g of monobasic sodium phosphate dihydrate in 500 mL of water. Add 5 mL of triethylamine, and adjust with phosphoric acid to a pH of 5.9. Dilute with water to 1 L.
  Diluent: Acetonitrile and *Buffer* (50:50)
  Mobile phase: Methanol and *Buffer* (40:60)
  Standard solution: 0.05 mg/mL of USP L... *Diluent*. Pass through a suitable filter.
  Sample stock solution: 2.0 mg/mL of levofloxacin in *Dil...* from NLT 20 powdered Tablets. Pass through a suitable filter. Sonicate for 30 min with intermediate shaking to aid in dissolution.
  Sample solution: 0.04 mg/mL of levofloxacin in *Diluent* from the *Sample stock solution*
  Chromatographic system
  (See *Chromatography* ⟨621⟩, *System Suitability*.)
  Mode: LC
  Detector: UV 294 nm
  Column: 4.6-mm × 5-cm; 3-µm packing L1
  Column temperature: 40°
  Flow rate: 1 mL/min
  Injection size: 5 µL
  Run time: 2 times the retention time of levofloxacin
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Tailing factor: NMT 2.0
  Relative standard deviation: NMT 2.0%
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of the labeled amount of levofloxacin ($C_{18}H_{20}FN_3O_4$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Levofloxacin RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of levofloxacin in the *Sample solution* (mg/mL)
Acceptance criteria: 90%–110%

PERFORMANCE TESTS
- **DISSOLUTION** ⟨711⟩
  Medium: 0.1 N hydrochloric acid; 900 mL
  Apparatus 1: 100 rpm
  Time: 30 min
  Detector: UV 293 nm
  Standard stock solution: 0.57 mg/mL of USP Levofloxacin RS in *Medium*
  Standard solution: Dilute the *Standard stock solution* with *Medium* to obtain solutions with final concentrations as given in *Table 1*.

Table 1

Tablet Strength (mg)	Final Concentration (µg/mL)
250	5.7
500	5.7
750	8.6

  Sample solution: Pass a 10-mL portion through a filter of 0.45-µm pore size, and dilute with *Medium* to a concentration that is similar to the appropriate *Standard solution*.
  Pathlength: 1 cm
  Blank: *Medium*
  Analysis
  Samples: *Standard solution* and *Sample solution*
  Calculate the percentage of levofloxacin ($C_{18}H_{20}FN_3O_4$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times D \times V \times (100/L)$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of the *Standard solution* (mg/mL)
D = dilution factor for the *Sample solution*
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)
Tolerances: NLT 80% (Q) of the labeled amount of levofloxacin ($C_{18}H_{20}FN_3O_4$) is dissolved.
- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩: Meet the requirements

IMPURITIES
- **ORGANIC IMPURITIES**
  Buffer: Dissolve 4 g of ammonium acetate and 7 g of sodium perchlorate in 1 L of water. Add 2 mL of triethylamine. Adjust with phosphoric acid to a pH of 6.6.
  Diluent: Acetonitrile and *Buffer* (20:80)
  Solution A: Acetonitrile and *Buffer* (2:98)
  Solution B: Acetonitrile and water (90:10)
  Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	90	10
2	90	10
15	85	15
35	70	30
40	60	40
45	50	50
46	90	10
55	90	10

  Standard solution: 3 µg/mL of USP Levofloxacin RS and 2 µg /mL each of USP Levofloxacin Related Compounds A, B, and C RS in *Diluent*. Sonicate to aid in dissolution.
  Sample solution: 1.0 mg/mL of levofloxacin in *Diluent* from NLT 20 powdered Tablets. Centrifuge a portion of the solution for about 10 min. Pass a portion through a suitable filter.

GENERAL CONCEPTS

Limited Data Available at Filing

- When only limited data are available, the initially approved tests and acceptance criteria should be reviewed as more information is collected, with a view towards possible modification.
- This could involve loosening, as well as tightening, acceptance criteria as appropriate.

Limited Data Available at Filing

← لما تقدم طلب لل FDA لحتى تعتمد دواء معيّن، ممكن هاد الدواء
مش ماشي على الحابيز تاعت القبول بشكل دقيق
مثال، إذا كان في شوائب داخل الدواء، ما حددوا صوتها بدقة في البداية.
ممكن بعدين يصدوا هاد الشي بعدين مع الخبرة بالتصنيع.

← مع الوقت، لما يصير في خبرة بتصنيع الدواء والخبرة تزداد، ممكن يعدلوا
معايير الجودة لحتى تصير أكثر دقة حسب الحاجة.
يعني ممكن تكون صارمة إذا ما كان في دقة، وممكن تكون أقل صرامة
إذا المنتج مخالك وآمن، Tightening or Loosening.

GENERAL CONCEPTS

Parametric Release

- Parametric release can be used as an operational alternative to routine release testing for the drug product in certain cases when approved by the regulatory authority.
- Sterility testing for terminally sterilized drug products is one example. In this case, the release of each batch is based on satisfactory results from monitoring specific parameters, e.g., temperature, pressure, and time during the terminal sterilization phase(s) of drug product manufacturing.
- These parameters can generally be more accurately controlled and measured, so that they are more reliable in predicting sterility assurance than is end-product sterility testing.

GENERAL CONCEPTS

Parametric Release

- Appropriate laboratory tests (e.g., chemical or physical indicator) may be included in the parametric release program.
- It is important to note that the sterilization process should be adequately validated before parametric release is proposed and maintenance of a validated state should be demonstrated by revalidation at established intervals.
- When parametric release is performed, the attribute which is indirectly controlled (e.g., sterility), together with a reference to the associated test procedure, still should be included in the specifications.

* parametric realese.

هو صعب، بس مش مخيف، اسمه parametric يعني إله دخل بالحرارة وهاي الأمور.. عندي معايير (الحرارة، الوقت، الضغط) بقدر أتحكم فيها عند التعقيم.. عشان هيك بعتمد عليها لأنه موثوقيتها عالية جدًا..
بدل ما أروح أعمل اختبار تعقيم على كل دفعة للمنتج النهائي.

GENERAL CONCEPTS

Alternative Procedures

- Alternative procedures are those which may be used to measure an attribute when such procedures control the quality of the drug substance or drug product to an extent that is comparable or superior to the official procedure.

Example:

- For tablets that have been shown not to degrade during manufacture, it may be permissible to use a spectrophotometric procedure for release as opposed to the official procedure, which is chromatographic.
- However, the chromatographic procedure should still be used to demonstrate compliance with the acceptance criteria during the shelf-life of the product.

GENERAL CONCEPTS

Pharmacopoeial Tests and Acceptance Criteria

- References to certain procedures are found in pharmacopoeias in each region. Wherever they are appropriate, pharmacopoeial procedures should be utilized.

Evolving Technologies

- New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when they are considered to offer additional assurance of quality, or are otherwise justified.

GENERAL CONCEPTS

Impact of Drug Substance on Drug Product Specifications

- In general, it should not be necessary to test the drug product for quality attributes uniquely associated with the drug substance.

Example:

- It is normally not considered necessary to test the drug product for synthesis impurities which are controlled in the drug substance and are not degradation products.

- Alternative procedures

← مثلًا الـ Drug Assay لدواء الـ paracetamol بتبع Hplc الـ method
ولكن خلال عملية التصنيع أنا بدي قرار سريع .. الـ Hplc الـ process
كتير طويل .. أنا بدي يا ها تيجي خلال نصف ساعة مثلًا .. يروحوا
يستخدموا alternative method مثلًا الـ UV بعطي نتيجة سريعة جدًا .. مثلًا
هل الـ rang للدواء هاد بين 80-90 مثلًا؟ هو هاد ما بغني عن الـ Hplc
method ولكن في حالات لطارئ بحتاجه .. زي Test صباحي.

=

* Impact Drug Substance

← الـ Synthesis impurity بقيسها بس للـ Drug Substance ولكن إذا كانت
نفسها Degradation لازم بصيرها quantification طول ولحتى لـ
Limit .. يعني أنا عندي impurite للبنزين مثلًا وكان لـ Finshed product
تاعتها 0.1 وسموح وناجحة .. خلص هلي بتركها .. هاد
المسموح إلكي .. بس لازم تقدم إثباتات لو سألوك .. إنه هاي
Degradation مش prosess

القصد إنه إذا كان الشوائب الناتجة من عملية تصنيع المادة الفعالة
مراقبة ومتحكم فيها .. مفش من الضروري اختبر لمنتج عندي .. بس
لو المادة تحتوي على Degradation هون لازم اختبر لمنتج تاعي
لأنه التحلل حبخرب لدواء عندي.

GENERAL CONCEPTS

Reference Standard

- A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test.
- It should have a quality appropriate to its use.
- It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing.
- For new drug substance reference standards intended for use in assays, the impurities should be adequately identified and / or controlled, and purity should be measured by a quantitative procedure.

* Referance Standard

هي مواد impure بنسبة 99.99٪ من paracetamol

بسيل لمثال .. اسمها المعيار الرئيسي .. أو المرجعي .. بضيف أي شي بدك تعمله للـ paracetamol بدك تعمل إله Standaisitional

للـ referance standard .. تبيعك يا ن إد FDA مختوم مع شهادة .. فهو 100٪ paracetamol .. هو معيار تقارن فيه .. بكل شي.

Guidelines

Specifications

- A specification may list, in addition to release tests in-process tests and periodic (skip) tests,.
- In such cases the applicant should specify which tests are routinely conducted batch-by-batch, and which tests are not, with an indication and justification of the actual testing frequency.
- In this situation, the drug substance and / or drug product should meet the acceptance criteria if tested.

Justification of Specifications

- When a specification is first proposed, justification should be presented for each procedure and each acceptance criterion included.
- The justification should refer, as appropriate, to:
  - relevant development data,
  - pharmacopoeial standards,
  - test data for drug substances and drug products used in toxicology and clinical studies,
  - results from accelerated and long term stability studies.

عند وضع مواصفات لأي منتج دوائي لأول مرة، يجب شرح سبب اختيار كل اختبار ومعيار قبول لهذه المواصفات. هذا الشرح يعتمد على بيانات التطوير والمعايير الدوائية، وكذلك نتائج الاختبارات السابقة مثل تلك المتعلقة بالأمان والفعالية والثباتية للمنتج الدوائي.

Justification of Specifications

- Test results from stability and scale-up / validation batches, with emphasis on the primary stability batches, should be considered in setting and justifying specifications.
- It should be noted that changes in the specification after approval of the application may need prior approval by the regulatory authority.

يجب أخذ نتائج اختبارات الثباتية والدفعات الكبيرة/دفعات التحقق بعين الاعتبار عند تحديد وتبرير المواصفات، خاصة الدفعات الأساسية. ويجب الانتباه إلى أن أي تغييرات في المواصفات بعد الموافقة على التطبيق قد تتطلب موافقة مسبقة من الجهات التنظيمية.

بإستثناء ال hardness و fribility مش مطلوب منك تحطهم على ال specification

هون عامل ملخص الفرق بين ال universal test وال specific

Universal Tests			
New Drug Substances	**New Drug products**		
Description			
Identification			
Assay			
Impurities			
Specific Tests			
New Drug Substances	**New Drug products**		
	Solid oral drug products	**Oral liquids**	**Parenteral Drug Products**
Water content	Water content	Water content	Water content
Particle size		Particle size distribution	Particle size distribution
			Particulate matter
	Uniformity of dosage units	Uniformity of dosage units	Uniformity of dosage units
	Dissolution	Dissolution	
	Disintegration		
Physicochemical properties		pH	Osmolarity
Polymorphic forms	Hardness/friability		
		Extractables	
Tests for chiral new drug substances			
Microbial limits	Microbial limits	Microbial limits	Sterility
		Antimicrobial preservative content	Antimicrobial preservative content
			Endotoxins/Pyrogens
		Redispersibility	Redispersibility
Inorganic impurities			
		Reconstitution time	Reconstitution time
		Antioxidant preservative content	Extractables

Universal Tests / Criteria : New Drug Substances & Products

a) ***Description***:

For drug substance: a qualitative statement about the state (e.g. solid, liquid) and color of the new drug substance.

For drug product: A qualitative description of the dosage form should be provided (e.g., size, shape, and color).

- If any of these characteristics change during storage, this change should be investigated and appropriate action taken.

Universal Tests / Criteria : New Drug Substances & products

b) Identification

- Identification testing should optimally be able to discriminate between compounds of closely related structure which are likely to be present.
- Identification tests should be specific for the new drug substance, e.g., infrared spectroscopy.
- Identification solely by a single chromatographic retention time, for example, is not regarded as being specific.

Universal Tests / Criteria : New Drug Substances

b) Identification

- However, the use of two chromatographic procedures, where the separation is based on different principles or a combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS is generally acceptable.
- If the new drug substance is a salt, identification testing should be specific for the individual ions. An identification test that is specific for the salt itself should suffice.

e.g. to distinguish between diclofenac sodium and diclofenac potassium

Universal Tests / Criteria : New Drug Substances

b) Identification

- New drug substances which are optically active may also need specific identification testing or performance of a chiral assay.

Examples:
L-Dopa (D-dopa is inactive)
Levofloxacin is the active optical isomer of ofloxacin
Levocetirizine is the active enantiomer of cetirizine

Identification testing for drug product should establish the identity of the new drug substance(s) in the new drug product

Universal Tests / Criteria : New Drug Substances and products

c) *Assay*

A specific, stability-indicating procedure should be included to determine the content of the drug in new drug substance and new drug products.

In many cases it is possible to employ the same procedure (e.g., HPLC) for both assay of the new drug substance/product and quantitation of impurities.

- Results of content uniformity testing for new drug products can be used for quantitation of drug product strength, if the methods used for content uniformity are also appropriate as assays.

Universal Tests / Criteria : New Drug Substances and products

c) *Assay*

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, the combination of the assay and a suitable test for impurities should be used.

- A specific procedure should be used when there is evidence of excipient interference with the non-specific assay.

Universal Tests / Criteria : New Drug Substances

d) Impurities:

Impurities in new drug subsances can be classified into the following categories (ICH Q3A):

1. Organic impurities
   - Starting materials
   - By-products
   - Intermediates
   - Degradation products
   - Reagents, ligands and catalysts
2. Inorganic impurities
   - Reagents, ligands and catalysts
   - Heavy metals or other residual metals
   - Inorganic salts
   - Other materials (e.g., filter aids, charcoal)

Universal Tests / Criteria : New Drug Substances

d) ***Impurities:***

3. Residual solvents

Class 1 solvents: Solvents to be avoided

- Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.
- E.g. Benzene, CCl4

Class 2 solvents: Solvents to be limited

- Non-genotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity.
- Solvents suspected of other significant but reversible toxicities.
- E.g. Acetonitrile, Chloroform, Methanol, Dichloromethane, hexane

Class 3 solvents: Solvents with low toxic potential

- Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have permitted daily exposure (PDE)s of 50 mg or more per day.
- E.g. Acetic acid, Ethanol, Ethyl acetate, Dimethyl sulfoxide, Acetone

Universal Tests / Criteria : New Drug products

d) impurities:

- Organic and inorganic impurities (degradation products) and residual solvents are included in this category.
- Organic impurities arising from degradation of the new drug substance and impurities that arise during the manufacturing process for the drug product should be monitored in the new drug product.
- Process impurities from the new drug substance synthesis are normally controlled during drug substance testing, and therefore are not included in the total impurities limit.
- However, when a synthesis impurity is also a degradation product, its level should be monitored and included in the total degradation product limit.

Universal Tests / Criteria : New Drug products

d) impurities:

- Acceptance limits should be stated for individual specified degradation products, which may include both identified and unidentified degradation products as appropriate, and total degradation products.
- When it has been conclusively demonstrated via appropriate analytical methodology, that the drug substance does not degrade in the specific formulation, and under the specific storage conditions proposed in the new drug application:

-→ degradation product testing may be reduced or eliminated upon approval by the regulatory authorities.

Specific Tests / Criteria : New Drug Substances

The following tests may be considered on a case by case basis for drug substances.

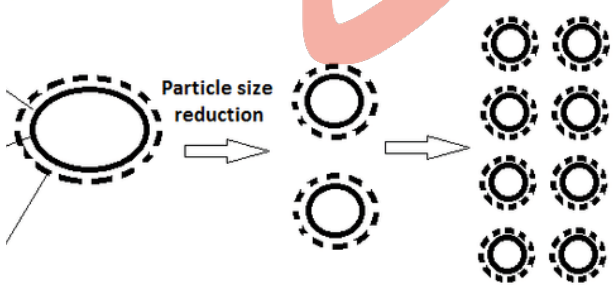
***a) Physicochemical properties*:**

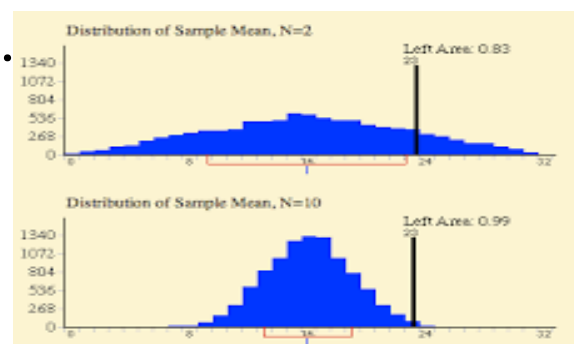
e.g. pH of an aqueous solution, melting point / range, and refractive index.

***b) Particle size*:**

For some new drug substances intended for use in solid or suspension drug products, particle size can have a significant effect on dissolution rates, bioavailability, and / or stability.

In such instances, procedure for testing of size distribution and acceptance criteria should be provided.

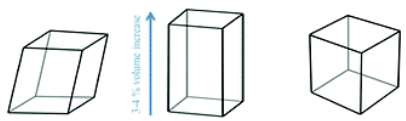




Specific Tests / Criteria : New Drug Substances

c) Polymorphic forms:

In cases where different crystal forms exist which have been shown to affect drug product performance, bioavailability or stability, then the appropriate solid state should be specified.



Example: Part of Chloramphenicol monograph in USP

Melting range ⟨741⟩: between 149° and 153°.

Specific rotation ⟨781S⟩: between +17.0° and +20.0°.

Test solution: 50 mg, undried, per mL, in dehydrated alcohol.

Crystallinity ⟨695⟩: meets the requirements.

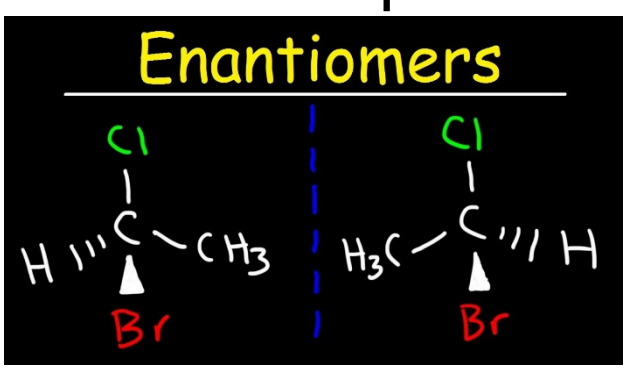
Bacterial endotoxins ⟨85⟩—Where Chloramphenicol is intended for use in preparing injectable dosage forms, it contains

Specific Tests / Criteria : New Drug Substances

d) Tests for chiral new drug substances:

For a drug substance developed as a single enantiomer:

1. The identity test(s) should be capable of distinguishing both enantiomers and the racemic mixture.
2. An enantioselective determination of the drug substance should be part of the specification.
3. Control of the other enantiomer should be considered in the same manner as for other impurities.



Specific Tests / Criteria : New Drug Substances

***e) Water content*:** This test is important in cases where the new drug substance is known to be:

1. hygroscopic
2. degraded by moisture
3. is a hydrate.

The acceptance criteria may be justified with data on the effects of hydration or moisture absorption.

In some cases, a Loss on Drying procedure may be considered adequate; however, a detection procedure that is specific for water (e.g., Karl Fischer titration) is preferred.

Specific Tests / Criteria : New Drug Substances

***f) Inorganic impurities*:**

The need for inclusion of tests and acceptance criteria for inorganic impurities (e.g., catalysts) should be studied during development and based on knowledge of the manufacturing process.

Procedures and acceptance criteria for:

A. sulfated ash / residue on ignition should follow pharmacopoeial precedents;

B. other inorganic impurities may be determined by other appropriate procedures, e.g., atomic absorption spectroscopy.

Specific Tests / Criteria : New Drug Substances

g) ***Microbial limits*****:** There may be a need to specify:

- 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 suitably determined using pharmacopoeial procedures.

➢ 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:
   - sterility testing may be appropriate for drug substances manufactured as sterile
   - endotoxin testing may be appropriate for drug substances used to formulate an injectable drug product.