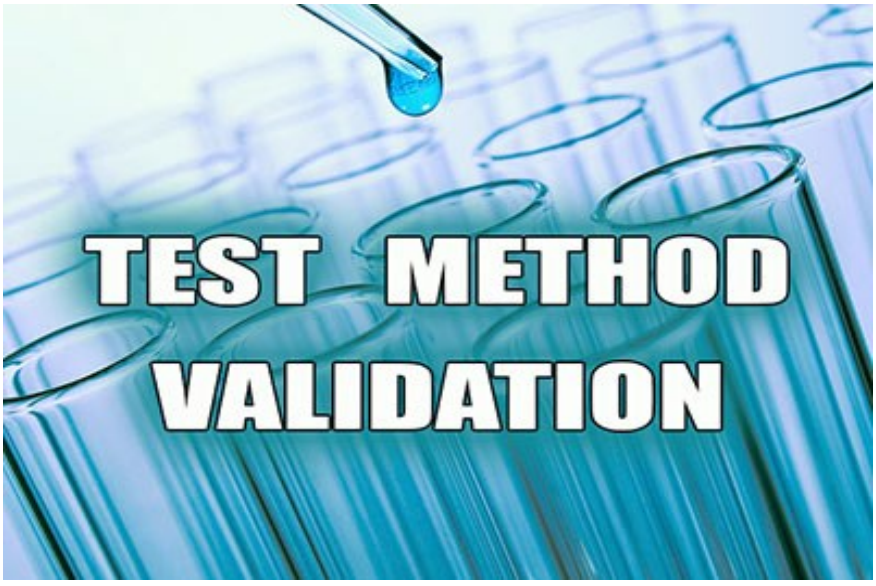
المؤسسة العامة للغذاء و الدواء

Jordan Food and Drug Administration

الدليل الإرشادي لمتطلبات المؤسسة العامة للغذاء و الدواء لدراسات التثبتية لطرق التحليل الخاصة بالأدوية

JFDA Guidelines for Validation of Analytical Procedures for Finished Pharmaceutical Products

Rev 00- August 2021



إعداد : هدى قرعاني – ريما صالح

مديرية المختبرات

الدليل الإرشادي لمتطلبات المؤسسة العامة للغذاء و الدواء لدراسات التثبتية لطرق التحليل الخاصة بالأدوية

مقدمة

- يسمى هذا الدليل بالدليل الأرشادي لمتطلبات المؤسسة العامة للغذاء و الدواء لدراسات التثبتية لطرق التحليل الخاصة بالأدوية

- لغايات هذا الدليل الأرشادي يكون للكلمات والعبارات الواردة فيها المعاني المخصصة لها في المراجع العلمية والدستورية اضافة الى مايلي:

دراسة التثبتية : هو عملية توثيق لأثبات أن طريقة التحليل سوف تؤدي دائما الى تحقيق النتائج المتوقعة

لجنة التثبتية : هي اللجنة الفنية لتقييم دراسة التثبتية لطرق التحليل الخاصة بملفات الأدوية المقدمة لغايات التسجيل في مختبر الرقابة الدوائية المشكلة استنادا لنص المادة رقم (14) والمادة (15) من قانون الدواء والصيدلة رقم (12) لسنة 2013

- تعتمد اللجنة المعايير حسب الدليل الأرشادي وذلك لتقييم طرق التحليل ودراسات التثبتية لغايات اعتماد هذه الطرق بأقل زمن ممكن و تحقيقا لرسالة المؤسسة المتمثلة في ضمان مأمونية وفاعلية الدواء والمواد ذات العلاقة من خلال سياسات وتشريعات تستند الى معايير عالمية و تتسم بالشفافية و التشاركية

- الهدف من هذا الدليل توضيح معايير التقييم و متطلبات دراسة التثبتية في قسم مختبر الدواء في المؤسسة العامة للغذاء و الدواء فيما يتعلق بدراسات التثبتية والتحققية لطرق التحليل الخاصة بالمستحضرات النهائية للأدوية

JFDA Guidelines for Validation of Analytical Procedures

General Requirements

1) Composition Certificate Carrying reference No. ,Revision & Date including :
   - Active ingredients: name, quantity, function
   - Inactive ingredients: name, quantity, function
   - Total weight

   If multiple strengths intended to be registered or if validation study performed on different strengths, compositions of strengths under concern are to be submitted

2) Shelf Life Specifications Carrying reference number, Revision & Date and include the following:
   - Physical , Chemical & Microbiological tests
   - Reference for Limits
   - Reference for method
   - Method of analysis Reference number

3) Method of Analysis (MOA)
   - Carrying the reference number As In Specifications
   - Include Procedures for all physical, Chemical and Microbiological tests mentioned in Specifications , in English language only
   - Assay And Related Substances Methods Of Analysis Should Be Stability Indicating Methods. (Chromatographic method)
   - Same methods used in validation report
   - Detailed
     a. Sample, standard, placebo (for Related Substances MOA only), System suitability & impurities preparations in details
     b. System suitability parameters
     c. Conclusion of stability in solution as mentioned in validation report

General Requirements

d. Types of filters with specification, discard volume (if Applicable)
e. Table of RRT & RRF (if applicable)
f. Detailed Calculations including (%assay, %Dissolve, %unknown, %known, Total impurities)
g. Chromatographic conditions for HPLC, UPLC, GC System, including:

- Column specification (length, inner diameter and particle size) with trade name
- Oven temperature (if applicable)
- Detector Type (Ex.: UV-VIS, Refractive index …..)
- Flow rate (ml/min).
- Injection volume (µl)
- Auto sampler cooling temperature (if applicable)
- Mobile phase preparation in details
- Gradient table (if applicable)
- Any precautions or notes (Ex.: protect from light, Needle wash, Water type … etc.).
- Retention time (about not range) and Run time
- Sample Solution: Resolution between main peak and closest impurity >1.3

h. UV-spectrum (Ex.: for dissolution)

- wavelength , cell path length
- System suitability requirement and calculation

General Requirements

i. Modifications on Method of Analysis (MOA) Due to Deficiency letters or any other reasons ,should be added and reflected on the method of analysis ,not only on the validation report , accordingly new revision of MOA should be submitted

4) Copy of the Latest Available Monograph (USP, BP or Any Other) For API & Finished Product, even if the method of analysis is in-house

5) Justification of Specifications (rational and scientific justification) for:

a. Assay Limit for active substances, preservatives and antioxidants
b. Dissolution Limit and parameters
c. Related substances Limit for:
   - Known impurities (Degradation Products): if available, addition of process impurities to specification is not accepted unless justified.
   - Unknown impurities
   - Total impurities

Acceptance criteria should be based on the following in orderly manner

I. International pharmacopeias (USP , British , EP , Japanese) if there is a monograph for the drug product
II. ICH guideline (Ex.: maximum Daily Dose for related substances)/ FDA data base for dissolution parameters
III. General pharmacopeias chapters
IV. Based on RLD /originator if accepted by registration technical committees
V. Case by case discussion with discriminative report for dissolution test

General Requirements

6) Drug Master File (DMF) Impurity Profile
   - Impurity Classification (process or degradation)
   - Method of analysis
   - Acceptance criteria for impurities

7) Real Chromatograms including
   - Specificity Chromatograms (Blank , Placebo , Standard , System Suitability , all Known Impurities injected individually And also as a mixture, Sample ,Process Impurities if have RRT in MOA) for all MOA
   - Forced Degradation Chromatograms : all chromatograms relevant to submitted study including normal sample (s) chromatograms for assay & related MOA
   - LOQ Chromatograms for active & all known imp if study is based on S/N or visual
   - Only one representative chromatogram for other validation parameters (for example one chromatogram for linearity , one chromatogram for accuracy,……. etc) for all MOA
     - ❖ Required Data in the chromatograms
       - ✓ Chromatogram Name : Sample ,STD ,System Suitability ,….etc

         For Example: Sample 40/ 12.5 mg label claim-Assay

         For Example: Sample 40/ 12.5 mg label claim-Assay- 0.1 N HCL Stress

       - ✓ Wave Length , Injection volume
       - ✓ Date of acquisition
       - ✓ Full Run Time According to MOA
       - ✓ Zoomed especially for Related MOA & FD studies
       - ✓ Data Table including all necessary data ,for example system suitability parameters, for LOQ study based on S/N , S/N data should be present , for FD peak purity should be submitted,etc

General Requirements

8) Transfer of analytical procedures (TAP /AMT) If applicable

If different companies mentioned in validation file, relationship between these companies should be mentioned

Requirements for TAP

- Declaration of Relationship Between Sending Unit (SU) & Receiving Unit (RU)
- Declaration whether RU Analyze drug product or not , if RU do not analyze then no TAP Required
- Protocol of TAP including what type of TAP Applied, responsibilities of transferring and receiving laboratories , Acceptance Criteria and how deviations will be handled
- TAP Report include Data / Results from both SU & RU
- Report should be signed by both sending and receiving units as evidence to TAP
- If Comparative Testing TAP Adopted all previous requirements in addition to the following regarding samples and acceptance criteria

Samples & Acceptance Criteria

❖ Assay

Samples: At each site 1 Analyst, 3 lots or 1 lot*3 samples
Acceptance Criteria: Mean @RU within ± 2 % of mean @SU

❖ Dissolution

Samples: At each site 1 Analyst, 1 lot * 6 Units
Acceptance Criteria: According to Intermediate Precision

❖ Related Substances

Samples: At each site 1 Analyst, 3 lots or 1 lot * 3 samples
Acceptance Criteria: According to Submitted Protocol, comparison of profiles (Chromatograms Required)

General Requirements

9) Validation / Verification Report in details report According to ICH guideline and USP for all active substances ,preservatives, antioxidants ,all known/unknown impurities mentioned in shelf life specifications

Validation /Verification parameters

Parameter	Required for	Assay	Related substances	Titration	Dissolution
Accuracy	Validation	√	√	√	√
	Verification	√	√	√	X
Linearity	Validation	√	√	√	√
	Verification*	X	X	X	X
Precision	Validation	√	√	√	√
	Verification	X	X	X	√
Specificity	Validation	√	√	√	√
	Verification	√	√	√	√
Robustness	Validation	√	√	X	√ (analytical finish only)
	Verification	X	X	X	X
System suitability	Validation	√	√	X	√
	Verification	√	√	X	√
Stability in solution	Validation	√	√	X	√
	Verification	X	X	X	X
Filter compatibility	Validation	√	√	X	√
	verification	√	√	X	√
LOQ	Validation	X	√	X	X
	Verification	X	√	X	X

* Linearity is required if concentration is not determined in the monograph

Validation /Verification parameters Assessment

Accuracy	**Concept***	Assay/ Titration	Related Substances	Dissolution
		add known quantity of analyte to drug product (spiked placebo or sample product)	sample spiked with known amounts of impurities(spiked placebo or sample product)	(spiked placebo or sample product)
		Constant Placebo concentration @100 % in all levels		
	Assessments	Min.9 determination (9 different preparations) Covering Range Three concentration level ,each level 3 different preparations		
	Requirements	1. % Recovery [% Recovery= 100* (actual conc./ Theoretical conc.)] 2. Actual &theoretical Concentrations values 3. Sample preparation in details (placebo amount ,active amount and dilution) 4. Quantity of placebo added in each level 5. 100% level should be assessed **Optional:** a) Difference between mean and accepted true value b) Confidence interval		
	Limits	average Recovery for each level (98-102)% individual Recovery (97-103)%	average Recovery for each level (80-120)% individual Recovery (70-130)%	average Recovery for each level (95-105)% individual Recovery (95-105)%

*Injectables that do not contain placebo, accuracy study is not required

Validation /Verification parameters Assessment

Linearity &Range		Assay/ Titration	Related Substances	Dissolution
	Concept	Concentration – response relationship Should be established across the range of analytical procedure		
	Assessments*	Minimum five concentration levels across the range either by (1) dilution standard stock solution Or (2) preparation of Separate synthetic mixtures, taking into consideration that 100% concentration level should be included		
	Requirements	1. Linear relationship, or model should be established 2. Correlation coefficient 3. Y-intercept 4. Slope of regression 5. Visual Plot (plot for concentration & response)		
	Limits	Range: (80-120) % of the test Conc. Linearity: % intercept @ Target conc.: NMT 5% R: ≥ 0.999	Range: (50 or LOQ - 120or 150) % of the acceptance criteria Linearity: % intercept @ Target conc.: NMT 10% R: ≥ 0.99	Range: ± 20% over the specified range Linearity: % intercept @ Target conc.: NMT 5% R^2: ≥ 0.98

*Example: - Assay Specs limit (90-110 %), Recommended % Levels (80, 90, 100, 110, 120)
-Dissolution Specs limit (Q=75%), Recommended % Levels (60, 70, 80, 90,100)
-Unspecified Impurity limit 0.2 %, Recommended % Levels (LOQ, 0.1, 0.2, 0.22, 0.24)

Other levels could be studied taking into consideration increasing number of levels (more than 5) to Bracket Different concentration dosages, or to account for any future changes in specification limits

Validation /Verification parameters Assessment

Precision Repeatability **A. System precision** system suitability for standard **B. Method precision** Assaying homogenous authentic sample (drug product)		Assay/ Titration	Related Substances	Dissolution
	Assessments	Min.9 determination (9 different preparations): Three concentration level ,each level 3 different preparations OR 6 determinations (different preparations) at 100% level of test concentration		
	Requirements	• Relative standard deviation RSD %		
	Limits	RSD <2%	-Limit <0.1 % ,RSD ≤20% -Limit(≥ 0.1- <1.0) % ,RSD ≤10% - Limit (≥1.0- <10.0) % ,RSD ≤5% -Limit ≥ 10 % ,RSD ≤2%	RSD for authentic sample: < 5% RSD for Synthetic sample: < 2%
Precision **Intermediate Precision (ruggedness)**		Assay	Related Substances	Dissolution
	Concept	To study the effect of: • Different equipment • Different analyst • Different days Note: it's not necessary to study these effects individually		
	Assessments	2X6 determinations (different preparations) at 100% level of test concentration		
	Requirements	• Relative standard deviation RSD For RS if authentic sample results ND or below LOQ spiked sample at specification limit required		
	Limits	RSD <2 %	-Limit <0.1 % ,RSD ≤20% -Limit(≥ 0.1- <1.0) % ,RSD ≤10% - Limit (≥1.0- <10.0) % ,RSD ≤5% -Limit ≥ 10 % ,RSD ≤2%	RSD ≤ Absolute 10 % (@ time points < 85% dissolved) RSD ≤ Absolute 5 % (@ time points > 85% dissolved)

Validation /Verification parameters Assessment

Specificity * If known impurities are available	**Concept**	Assay/ Titration	Related Substances	Dissolution For UV-VIS spectroscopy method
		spiking the drug products (or drug substances + placebo) with all known impurities @5 % level and demonstrating that the assay result is unaffected by the presence of these extraneous materials (impurities)	spiking the drug products (or drug substances + placebo) with all known impurities @Specification limit and demonstrating that these impurities are determined with appropriate accuracy and precision	to demonstrate that the results are not unduly affected by dissolution medium blank, placebo constituents, other active drug substances or potential degradation products from the dissolved drug substance in the dissolution medium **Placebo** consists of all excipients and coating with ink and capsule shells included without the active ingredients **Blank** is dissolution medium
	Assessments	The assay results of three samples before and after spike should be compared(if assay method of analysis is selective to all known impurities spiking is not required only chromatogram)	The impurity profile should be compared If process impurities mentioned in MOA (RRT included) chromatogram for these impurities should be submitted to verify RRT	Placebo interference can be evaluated by using a spiked placebo that is prepared by weighing samples of the placebo blend, dissolving or dispersing them in dissolution medium at concentrations that would be encountered during testing, it prefers to be at 37°C Comparing the solution to standard solution at concentration expected The result = 100*[(Absorbance placebo/ Absorbance standard) *Conc. standard *Media Volume] /label Claim

Specificity *(Cont)* If known impurities are available	**Requirements**	• % Assay before & after adding imp. • Real chromatograms with peak purity • Sample preparation in details	• Representative chromatograms to demonstrate the degree of selectivity • Peaks should be appropriately labeled • Peak purity ;only needed if assay & related MOA are the same • Sample preparation in details	
	Limits	± 2 %	NA	Placebo interference should not exceed 2% Blank interference should not exceed 1%

* This approach only applicable if there are 3 or more impurities mentioned in specification, if less number of impurities present FD should be submitted

Specificity (Cont) If known impurities are not available:	**Concept**	Assay/ Titration	Related Substances	Dissolution
		1- Comparing the test results of samples containing imp. Or degradation products to 2nd well characterized procedure (phamacopieal or validated procedure). **Or** **2-Forced degradation study**		Same as above

Validation /Verification parameters Assessment

Relative Response Factor (RRF)	**Concept**	Related Substances -RRF is used to correct the difference in detector response of impurities with analyte peak -RRF study is only required for In-house MOA that mention RRF -RRF study is not required for Pharmacopeia methods (Verification) , RRF values -if mentioned- are adopted as is from applicable monograph
	Assessment	RRF is established by slope method with linear range of solutions Relative response factor of impurity = [Slope of impurity solution in curve/ Slope of standard solution in curve] Note: If the impurity slope value is in numerator, Relative Response factor (RRF) value appears in the denominator (OR) The Relative Response Factor of the Impurity with respect to drug will appear as divide factor in the formula of impurity determination. Relative response factor of impurity = [Slope of Standard solution in curve/ Slope of Impurity solution in curve] Note: If the impurity slope value is in denominator, Relative Response factor (RRF) value appears in the numerator (OR) The Relative Response Factor of the drug substance with respect to impurity will appear as multiplication factor in the formula of impurity determination.
	Requirements	-Linearity study for active and all Known impurities mentioned in MOA -Slope Values & RRF Calculations
	Limits	-If RRF value between (0.8 – 1.2) the RRF Can be considered as 1 , other values are added to MOA according to the study -If RRF value (< 0.2 or > 5) method is not suitable to analyze corresponding imp , justification or other MOA submitted for that imp

Validation /Verification parameters Assessment

Assessment & Requirements

For

Forced Degradation (FD)

***Typical Stress Conditions**

Type of Study	Condition	Time	Extreme Condition
Acid Hydrolysis	(0.1 – 1.0)N HCL ,RT-70°C	Few hrs – 7 Days	7 Days/1.0 N @70°C
Base Hydrolysis	(0.1 – 1.0)N NaOH ,RT-70°C	Few hrs – 7 Days	7 Days/1.0 N @70°C
Oxidation	0.3 – 3 % H2O2 ,RT in Dark	Few hrs – 7 Days	7 Days /3 % H2O2
**Thermal	70°C	Up to 3 weeks	3 weeks@70°C
**Thermal / humidity	70°C/75% RH	Up to 3 weeks	3 weeks@70°C/75% RH
***Photo	Fluorescent & UV Light	> 2 * ICH	4 * ICH

*other conditions could be selected , selecting stress conditions should depend upon the decomposition of the product under normal manufacturing, uses condition and storage specifications which are specific and different for each drug product

** Study can be either conducted with or without Humidity

*** ICH condition Fluorescent=1.2 million lux hours,UV=200Watthours/m2

Typical Recommended Degradation
(5 – 20) %

Validation /Verification parameters Assessment

Assessment & Requirements For Forced Degradation (FD)	**Data to be Submitted** 1. Study Conducted On Authentic Sample / justification if Synthetic Sample used 2. Detailed Sample Preparation for Each Stress Condition 3. Summary Table including 3.1 Study Conditions normal (Unstressed) , Basic , Acidic ,Oxidation , Heat, Photolysis Example 5 ml 0.1 N HcL ,70 ° C , 5 hrs 3.2 Area Values for Active under Concern 3.3 % Active Recovery or % Active Assay 3.4 RRT , % Imp calculated according to Related substances method of analysis (% Area not accepted) 3.5 Mass Balance for Related Substances Forced Degradation Study , and for assay when assay method is the same method for Related Substances 3.6 Peak Purity 4. Example of Calculation for Active Recovery & Mass Balance 5. Real Chromatograms Containing data table, date of acquisition, properly labeled for each condition in the study including relevant unstressed samples chromatograms, with peak purity data for active peak 6. Interpretation & Justification of Results ✓ Proper justification for the lack of mass balance (Scientific evidence and not just speculations) ✓ Forced degradation studies should be conducted with gentle conditions, starting with harsh conditions may cause lack of mass balance ✓ General justifications are not accepted (for example volatile degradants) ✓ Proper justification for not achieving active degradation (5 – 20) % ✓ To prove stability of molecule gradual forced degradation studies from gentle to more harsh conditions **(Extreme Conditions**)are submitted along with supporting data from literature ✓ Proper justification for Peak purity if below 980, conditions with impure Active peaks are rejected

Validation /Verification parameters Assessment

<table>
<tr><td rowspan="3"><u>Limit of Quantitation LOQ</u></td><td rowspan="2">Concept</td><td>Assay/ Titration</td><td>Related Substances</td><td>Dissolution</td></tr>
<tr><td>Not required</td><td>The lowest amount of analyte in sample that can be determined with acceptable accuracy and precision.
Expressed as the concentration of analyte (%.ppm) in the sample
Reporting threshold or disregard value must be mentioned in the method of analysis</td><td>Not required</td></tr>
<tr><td>Assessments</td><td colspan="3">1. Visual OR
2. S/N ratio (10:1) OR
3. SD of response and slope: QL=10σ/S
σ: the SD of the response
S: The slope of the calibration curve</td></tr>
<tr><td>Requirements</td><td colspan="3">1. Value of the LOQ
2. Method of determination in details (Visual ,S/N, etc)
3. Real Chromatograms
4. Accuracy & method Precision @LOQ (intermediate precision not required @LOQ)</td></tr>
</table>

Validation /Verification parameters Assessment

<table>
<tr><td rowspan="5"><u>Robustness</u></td><td>Concept</td><td colspan="3">Assay/ Titration | Related Substances | Dissolution
robustness should be assessed through variations in the analytical procedure

Variations
• Stability of analytical solutions
• Different equipment
• Different analysts

HPLC (according to USP chapter 621)
• Influence of PH in mobile phase
• Variations in mobile phase
• Different column , Temperature, Flow Rate</td></tr>
<tr><td>Requirements</td><td colspan="3">- System suitability data should be submitted clearly in accordance with method of analysis
- If measurements are susceptible to variations in analytical conditions, the analytical conditions should be suitably controlled or a precautionary statement should be included in the procedure
- Result for samples for Related Substances Test only (% impurities & allowable acceptance criteria)</td></tr>
<tr><td>Assessments</td><td colspan="3">Standard & System Suitability Solutions& samples for Related Substances</td></tr>
<tr><td rowspan="2">Limits*</td><td>Assay/ Titration</td><td>Related Substances</td><td>Dissolution</td></tr>
<tr><td>• % RSD ≤ 2%for 5 replicates
• Resolution NLT 2
• Number of theoretical plates ≥2000
• Asymmetry ≤ 2</td><td>• % RSD ≤ 10% for minimum 3 replicates
• Resolution NLT 2
• Number of theoretical plates≥2000
• Asymmetry ≤ 2</td><td>• % RSD ≤ 2%
• Resolution NLT 2
• Number of theoretical plates≥2000
• Asymmetry ≤ 2</td></tr>
</table>

*If MOA pharmacopeial, limit according to monograph

*For in-house method Minimum requirements for SST is %RSD, not necessary to include all parameters

*For in-house method other limit could be adopted if justified

Validation /Verification parameters Assessment

Stability In Solution		Assay/ Titration	Related Substances	Dissolution
	Concept	The changes in stability study should be within the Acceptance Criteria other wise a precautionary statement should be included in the test procedure		
	Assessments	standard & Sample		
	Requirements	• Area or absorbance or % Assay or difference • Conclusion Of The Study		
	Limits	% Recovery or % Assay (98-102)%	% Recovery or % Assay (80-120)%	% Recovery or % Assay (98-102)%

Filter Compatibility		Assay/ Titration	Related Substances	Dissolution
	Assessments	• Comparing with unfiltered or centrifuged solution • Discard Volume		
	Requirements	• Type of Filters Used • Area or absorbance • % Assay or difference • Conclusion Of The Study		
	Limits	% Recovery or % Assay (98-102)%	% Recovery or % Assay (80-120)%	% Recovery or % Assay (98-102)%

Recommendation

Validation Study should be done with the following considerations to minimize variation

1. Well-characterized reference materials, with documented purity, should be used.
2. High grade of chemical materials
3. The use of one instrument through the whole validation Study , except for intermediate precision study
4. Study should be conducted by the same senior analyst , except for intermediate precision study second senior analyst can be involved in the study
5. For pharmacopeia MOA (Verification) , Reference standards from Related pharmacopeia should be used through the whole study (for example if British pharmacopeia monograph adopted as MOA ,then BP Reference standards should be used if available)

References

1. ICH Q1A – Stability Testing of New Drug Substances and Products
2. ICH Q1B – Photostability Testing of New Drug Substances and Products
3. ICH Q2B – Validation of Analytical Procedures: Methodology
4. ICH Q3A – Impurities in New Drug Substances
5. ICH Q3B – Impurities in New Products
6. M4Q (R1) – The common Technical Document (CTD): Module 3: Quality
7. EMA guidelines / FDA guidelines /Pharmacopoeia (USP, BP, WHO)
8. ANVISA Resolution RDC-53/2015 on Pharmaceutical Small Molecule Forced Degradation Study Requirements (The National Health Surveillance Agency (ANVISA) (Brazil))
9. JFDA Validation Committee

Recognition

Prepared By	الإعداد
Huda Khalil Qurani MSc. Toxicology Head Of Validation Committee/Lab Directorate	هدى خليل قرعاني ماجستير علم السموم المخبري رئيس لجنة التثبتية
Rima Adanan Saleh BSc. Chemical Engineering Validation Committee Member/Lab directorate	ريما عدنان صالح بكالوريوس هندسة كيماوية عضو في لجنة التثبتية
Reviewed by Dr. Khaleel Ghanem Head Of Drug Lab Division	المراجعة د.خليل يوسف غانم رئيس قسم مختبر الدواء
Approved by: Dr. Maha Al-Jaghbeer Director of Lab Directorate	الأشراف : د. مها بشير الجغبير مدير مديرية المختبرات
Authorized by : Prof. Nizar Mhaidat Director of Jordan Drug & Food Administration	المصادقة : الأستاذ الدكتور نزار محمود مهيدات مدير عام المؤسسة العامة للغذاء والدواء

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