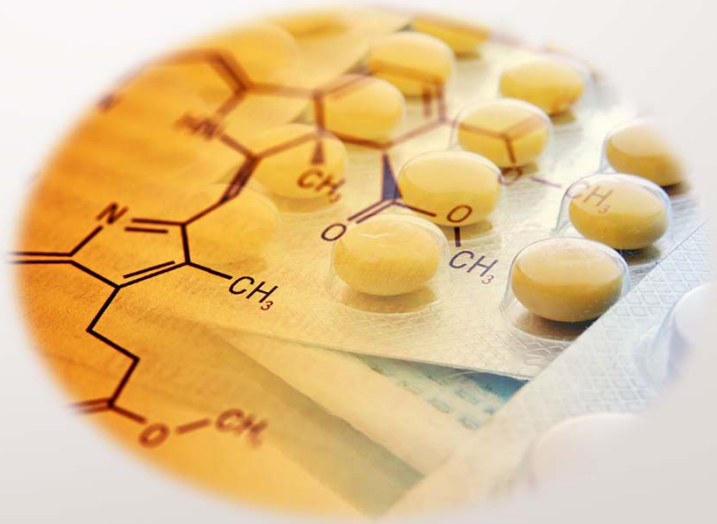
製程中管制(IPC)至最終產品放行(含製程確效) - 以固體劑型為例



吳中凱 (Kyle Wu)

October 3rd (台北) and 7th (台南), 2016

為什麼要對產品執行製程中管制及最終產品放行？

- 確保產品品質及用藥人的安全

- 法規規定 (最終產品)
  - 品質保證是一個廣泛的概念。...該適合於藥品製造的品質保證系統應確保下列事項：vi. ***最終產品***依界定的程序，正確地操作及核對。(PIC/S 1.1)
  - 品質管制是優良製造規範的一部分，涉及抽樣、規格及檢驗，且與組織、文件與放行程序有關，用以確保必要且相關的試驗已確實執行，...品質管制的基本要求是：vi. ...半製品/中間產品...及***最終產品***的檢查與檢驗結果均應予記錄，並對照其規格正式評估之。 (PIC/S 1.3)
  - ***最終產品***規格應包括或提供下列項目：d) 抽樣及檢驗的指示；e) 具有合格標準範圍之定性及定量的要求。(PIC/S 4.16)
  - 品質管制與抽樣、規格與試驗以及組織、文件與放行程序有關，確保必要與相關的檢驗皆已執行，並確保在品質經判斷滿意前，無原物料會被放行供使用，無***產品***會被放行供銷售或供應。品質管制...應涉及可能與該產品品質有關的所有決定。(PIC/S Chapter 6 Quality Control)。
  - ***最終產品***的評價應包含所有相關的因素，包括生產條件、製程中檢驗的結果、製造(包括分/包裝)文件的檢討、符合最終產品規格及最終包裝產品的檢查。(PIC/S 6.3)

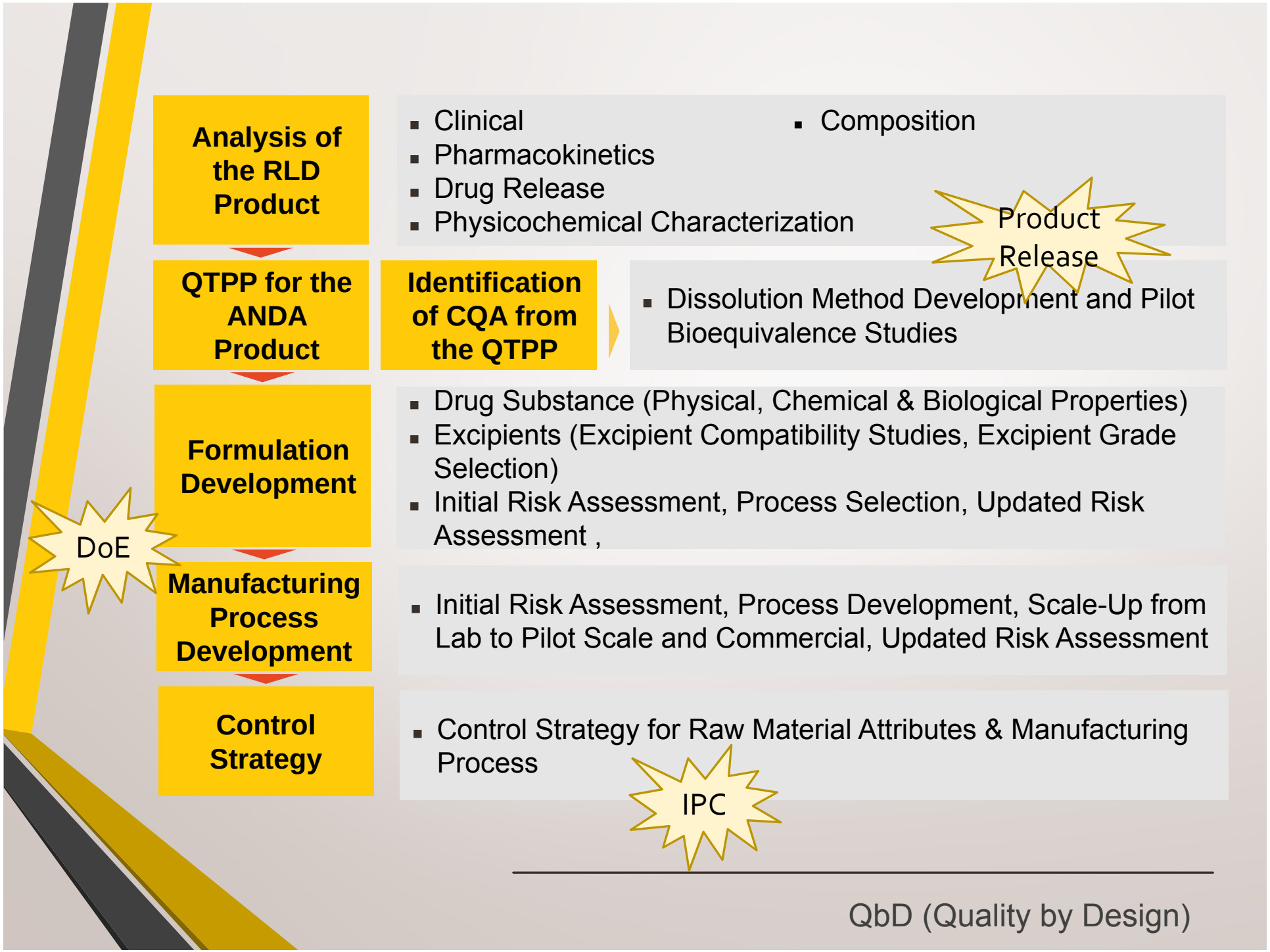
為什麼要對產品執行製程中管制及最終產品放行？

- 法規規定 (製程中管制)
  - 品質保證是一個廣泛的概念。...該適合於藥品製造的品質保證系統應確保下列事項：v. 半製品/中間產品的所有必要管制，以及任何其他***製程中管制***與確效均已執行 。(PIC/S 1.1)
  - 所有經許可的藥品，...其常規定期性或輪動式的品質檢討應以證實既有製程的一致性、現行規格對原料與最終產品的適當性為目標執行之，...通常應每年執行一次並加以文件化，且至少包含下列項目：ii. 關鍵之***製程中管制***及***最終產品結果***的檢討。 (PIC/S 1.4)
  - 製造配方、操作/加工、分/包裝與檢驗的指令：所要使用的***製程中管制***與製程分析技術，連同允收標準（合適時），應該加以規定。(PIC/S Chapter 4 Documentation)
  - 操作指令應包括下列項目：e) 任何***製程中管制***的指令及其範圍。(PIC/S 4.18)
  - Processing operations intermediate and bulk products任何必要的***製程中管制***及環境管制均應執行並予記錄。(PIC/S 5.38)
  - 契約中應清楚載明何方負責採購、測試及放行原物料、承擔生產及品質管制，含***製程中管制***，以及何方負責抽樣及檢驗。(PIC/S 7.12)

如何設定製程中管制及產品放行的項目及規格？

- Pharmacopeia
- QbD (Quality by Design)
  - Quality, safety, and efficacy are designed or built into the product. Quality cannot be adequately assured merely by in-process and finished-product inspection or testing. (US FDA Guidance for Industry, Process Validation: General Principles and Practices; II. A.)
  - Quality by Design (QbD): A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. (ICH Pharmaceutical Development Q8(R2))

- Examples of QbD (Quality by Design) from US FDA
  - Quality by Design for ANDAs: An Example for Immediate-Release Dosage Forms
  - Quality by Design for ANDAs: An Example for Modified Release Dosage Forms
- List of Abbreviations about QbD
  - ANDA: Abbreviated New Drug Applications
  - RLD: Reference Listed Drug
  - BE: Bioequivalence
  - QTPP: Quality Target Product Profile
  - CPP: Critical Process Parameter
  - CQA: Critical Quality Attribute
  - DOE: Design of Experiments


Analysis of the RLD Product
Clinical
Pharmacokinetics
Drug Release
Physicochemical Characterization
Composition
Product Release
QTPP for the ANDA Product
Identification of CQA from the QTPP
Dissolution Method Development and Pilot Bioequivalence Studies
Formulation Development
Drug Substance (Physical, Chemical & Biological Properties)
Excipients (Excipient Compatibility Studies, Excipient Grade Selection)
Initial Risk Assessment, Process Selection, Updated Risk Assessment ,
DoE
Manufacturing Process Development
Initial Risk Assessment, Process Development, Scale-Up from Lab to Pilot Scale and Commercial, Updated Risk Assessment
Control Strategy
Control Strategy for Raw Material Attributes & Manufacturing Process
IPC
QbD (Quality by Design)

- Analysis of the RLD Product (Development of Generic Acetriptan Tablets, 20 mg)
  - Clinical: Indications & Usage, Dosage & Administration, Adverse Reactions
  - Pharmacokinetics: Tmax, AUC and Cmax
  - Drug Release: Biopharmaceutics Classification System (BCS) Class II, Dissolution profile
  - Physicochemical Characterization

Table. Physicochemical characterization of Brand Acetriptan Tablets, 20 mg

Description	White round tablet debossed with ACE
Batch No.	A6970R
Expiry date	November 2011
Strength (mg)	20
Average weight (mg)	201.2
Score	No
Coating	Uncoated
Diameter (mm)	8.02-8.05
Thickness (mm)	2.95-3.08
Volume (mm^3)	150.02 average measured using image analysis
Hardness (kP)	7.4-10.1
Disintegration time (min)	1.4-1.6
Disintegration observation	Rapidly disintegrates into fine powder
Assay (% w/w of label claim)	99.7-100.2
Related Compound 1 (RC1) (%)	ND
Related Compound 2 (RC2) identified as ACE12345 (%)	0.41-0.44
Related Compound 3 (RC3) (%)	ND
Related Compound 4 (RC4) (%)	ND
Highest individual unknown (%)	0.07-0.09

- Analysis of the RLD Product (Development of Generic Acetriptan Tablets, 20 mg)
  - Composition: Based on the RLD labeling, patent literature and reverse engineering

Table. Composition of Brand Acetriptan Tablets, 20 mg

Component	Function	Unit (mg per tablet)	Unit (% w/w)
Acetriptan, USP	Active	20.0	10
Lactose Monohydrate, NF	Filler	64-86	32-43
Microcrystalline Cellulose (MCC), NF	Filler	72-92	36-46
Croscarmellose Sodium (CCS), NF	Disintegrant	2-10	1-5
Magnesium Stearate, NF*	Lubricant	2-6	1-3
Talc, NF	Glidant/Lubricant	1-10	0.5-5
Total tablet weight		200	100

*Magnesium stearate level estimated by EDTA titration of magnesium.

- QTPP for the ANDA Product

Table. Quality Target Product Profile (QTPP) for Generic Acetriptan Tablets, 20 mg

QTPP Elements		Target	Justification
Dosage form		Tablet	Pharmaceutical equivalence requirement: same dosage form
Dosage design		Immediate release tablet without a score or coating	Immediate release design needed to meet label claims
Route of administration		Oral	Pharmaceutical equivalence requirement: same route of administration
Dosage strength		20 mg	Pharmaceutical equivalence requirement: same strength
Pharmacokinetics		Immediate release enabling T_{max} in 2.5 hours or less; Bioequivalent to RLD	Bioequivalence requirement Needed to ensure rapid onset and efficacy
Stability		At least 24-month shelf-life at room temperature	Equivalent to or better than RLD shelf-life
Drug product quality attributes	Physical Attributes	Pharmaceutical equivalence requirement: Must meet the same compendial or other applicable (quality) standards (i.e., identity, assay, purity, and quality).	
	Identification		
	Assay		
	Content Uniformity		
	Dissolution		
	Degradation Products		
	Residual Solvents		
	Water Content		
	Microbial Limits		
Container closure system		Container closure system qualified as suitable for this drug product	Needed to achieve the target shelf-life and to ensure tablet integrity during shipping
Administration/Concurrence with labeling		Similar food effect as RLD	RLD labeling indicates that a high fat meal increases the AUC and C_{max} by 8-12%. The product can be taken without regard to food.
Alternative methods of administration		None	None are listed in the RLD label.

- CQA for the ANDA Product

Table. Critical Quality Attributes (CQAs) of Generic Acetriptan Tablets, 20 mg

Quality Attributes of the Drug Product		Target	Is this a CQA?	Justification
Physical Attributes	Appearance	Color and shape acceptable to the patient. No visual tablet defects observed.	No	Color, shape and appearance are not directly linked to safety and efficacy. Therefore, they are not critical. The target is set to ensure patient acceptability.
	Odor	No unpleasant odor	No	In general, a noticeable odor is not directly linked to safety and efficacy, but odor can affect patient acceptability. For this product, neither the drug substance nor the excipients have an unpleasant odor. No organic solvents will be used in the drug product manufacturing process.
	Size	Similar to RLD	No	For comparable ease of swallowing as well as patient acceptance and compliance with treatment regimens, the target for tablet dimensions is set similar to the RLD.
	Score configuration	Unscored	No	The RLD is an unscored tablet; therefore, the generic tablet will be unscored. Score configuration is not critical for the acetriptan tablet.
	Friability	NMT 1.0% w/w	No	Friability is a routine test per compendial requirements for tablets. A target of NMT 1.0% w/w of mean weight loss assures a low impact on patient safety and efficacy and minimizes customer complaints.
Identification		Positive for acetriptan	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug product release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay		100% w/w of label claim	Yes	Assay variability will affect safety and efficacy. Process variables may affect the assay of the drug product. Thus, assay will be evaluated throughout product and process development.
Content Uniformity (CU)		Conforms to USP <905> Uniformity of Dosage Units	Yes	Variability in content uniformity will affect safety and efficacy. Both formulation and process variables impact content uniformity, so this CQA will be evaluated throughout product and process development.
Dissolution		NLT 80% at 30 minutes in 900 mL of 0.1 N HCl with 1.0% w/v SLS using USP apparatus 2 at 75 rpm	Yes	Failure to meet the dissolution specification can impact bioavailability. Both formulation and process variables affect the dissolution profile. This CQA will be investigated throughout formulation and process development.

- CQA for the ANDA Product

Table. Critical Quality Attributes (CQAs) of Generic Acetriptan Tablets, 20 mg

of the Drug Product	Target	Is this a CQA?	Justification
Degradation Products	ACE12345: NMT 0.5%, Any unknown impurity: NMT 0.2%, Total impurities: NMT 1.0%	Yes	Degradation products can impact safety and must be controlled based on compendial/ICH requirements or RLD characterization to limit patient exposure. ACE12345 is a common degradant of acetriptan and its target is based on the level found in near expiry RLD product. The limit for total impurities is also based on RLD analysis. The target for any unknown impurity is set according to the ICH identification threshold for this drug product. Formulation and process variables can impact degradation products. Therefore, degradation products will be assessed during product and process development.
Residual Solvents	USP <467> option 1	Yes*	Residual solvents can impact safety. However, no solvent is used in the drug product manufacturing process and the drug product complies with USP <467> Option 1. Therefore, formulation and process variables are unlikely to impact this CQA.
Water Content	NMT 4.0% w/w	No	Generally, water content may affect degradation and microbial growth of the drug product and can be a potential CQA. However, in this case, acetriptan is not sensitive to hydrolysis and moisture will not impact stability.
Microbial Limits	Meets relevant pharmacopoeia criteria	Yes*	Non-compliance with microbial limits will impact patient safety. However, in this case, the risk of microbial growth is very low because roller compaction (dry granulation) is utilized for this product. Therefore, this CQA will not be discussed in detail during formulation and process development.

*Formulation and process variables are unlikely to impact the CQA. Therefore, the CQA will not be investigated and discussed in detail in subsequent risk assessment and pharmaceutical development. However, the CQA remains a target element of the drug product profile and should be addressed accordingly.

- 一般來說，CQA的項目會是之後最終產品放行檢驗的項目

- Dissolution Method Development and Pilot Bioequivalence Studies
  - The dissolution method may differ from the FDA-recommended dissolution method and the quality control method used for release testing.

Table. Acetriptan solubility in different media

Media	Solubility
--	(mg/mL)
Biorelevant FaSSGF[2]	0.12
Biorelevant FaSSIF-V2[2]	0.18
0.1 N HCl with 0.5% SLS	0.075
0.1 N HCl with 1.0% SLS	0.15
0.1 N HCl with 2.0% SLS	0.3

  - For low solubility drugs, pilot bioequivalence (BE) studies are invaluable to demonstrate that the in vitro dissolution used is appropriate.

- Formulation Development
  - Drug Substance (Physical, Chemical & Biological Properties)

Table. Acetriptan Form III stability under stress conditions

Stress Conditions	Assay (% w/w)	Degradation Products (% w/w)				Solid State Form
		RC1	RC2	RC3	RC4	
Untreated	99.4	ND	ND	ND	ND	Crystalline Form III
Saturated Solution						
0.1 N HCl (RT, 14 days)	96.9	ND	2.3	1.1	ND	N/A
0.1 N NaOH (RT, 14 days)	97.3	ND	2.1	0.9	ND	N/A
3% H_2O_2 (RT, 7 days)	86.7	ND	9.9	1.3	ND	N/A
Purified water (RT, 14 days)	96.8	ND	1.9	1.2	ND	N/A
Photostability (ICH Q1B Option 1)	90.6	ND	7.5	2.1	ND	N/A
Heat (60 °C, 24 h)	93.4	ND	5.2	ND	1.5	N/A
Solid State Material						
Humidity (open container, 90% RH, 25 °C, 7 days)	99.4	ND	0.1	0.1	ND	No change
Humidity and heat (open container, 90% RH, 40 °C, 7 days)	99.9	ND	0.1	0.1	ND	No change
Humidity and heat (open container, 90% RH, 60 °C, 7 days)	95.9	ND	2.7	0.2	1.4	No change
Photostability (ICH Q1B Option 1)	95.5	ND	3.2	1.4	ND	No change
Dry heat (60 °C, 7 days)	95.8	ND	4.1	ND	0.9	No change
Dry heat (105 °C, 96 h)	82.5	ND	3.9	ND	13.7	No change
Mechanical stress (Grinding and compression)	99.2	ND	0.1	0.1	ND	No change

ND: Not Detected; N/A: Not Applicable

- Formulation Development
  - Drug Substance (Physical, Chemical & Biological Properties)

Table. Initial risk assessment of the drug substance attributes

Drug Product CQAs	Drug Substance Attributes								
	Solid State Form	Particle Size Distribution (PSD)	Hygroscopicity	Solubility	Moisture Content	Residual Solvents	Process Impurities	Chemical Stability	Flow Properties
Assay	Low	Medium	Low	Low	Low	Low	Low	High	Medium
Content Uniformity	Low	High	Low	Low	Low	Low	Low	Low	High
Dissolution	High	High	Low	High	Low	Low	Low	Low	Low
Degradation Products	Medium	Low	Low	Low	Low	Low	Low	High	Low

Table. Justification for the initial risk assessment of the drug substance attributes

Drug Substance Attributes	Drug Products CQAs	Justification
Particle Size Distribution (PSD)	Assay	A small particle size and a wide PSD may adversely impact blend flowability. In extreme cases, poor flowability may cause an assay failure. The risk is medium.
	Content Uniformity	Particle size distribution has a direct impact on drug substance flowability and ultimately on CU. Due to the fact that the drug substance is milled, the risk is high.
	Dissolution	The drug substance is a BCS class II compound; therefore, PSD can affect dissolution. The risk is high.
	Degradation Products	The effect of particle size reduction on drug substance stability has been evaluated by the DMF holder. The milled drug substance exhibited similar stability as unmilled drug substance. The risk is low.

- Formulation Development
  - Excipients (Excipient Compatibility Studies, Excipient Grade Selection)

Table. Excipient compatibility (binary mixtures)*

Mixture	Assay (% w/w)	Degradants (% w/w)
Lactose Monohydrate/DS (1:1)	99.8%	ND
Lactose Anhydrous/DS (1:1)	99.6%	ND
Microcrystalline Cellulose (MCC)/DS (1:1)	98.4%	ND
Dibasic Calcium Phosphate/DS (1:1)	99.3%	ND
Mannitol/DS (1:1)	101.1%	ND
Pregelatinized Starch/DS (1:1)	100.5%	ND
Croscarmellose Sodium (CCS)/DS (1:1)	99.7%	ND
Crospovidone (1:1)	99.3%	ND
Sodium Starch Glycolate (1:1)	98.8%	ND
Talc/DS (1:1)	99.5%	ND
Magnesium Stearate/DS (1:1)	95.1%	AD1: 4.4%

*Conditions: 40 °C/75 % RH, open container, 1 month

Table. Excipient compatibility (interaction study)*

Mixture	Assay (% w/w)	Degradants (% w/w)
All excipients	99.4%	ND
All excipients except Lactose Monohydrate	99.2%	ND
All excipients except Microcrystalline Cellulose (MCC)	99.8%	ND
All excipients except Croscarmellose Sodium (CCS)	99.9%	ND
All excipients except Talc	99.3%	ND
All excipients except Magnesium Stearate	99.6%	ND

*Conditions: 40 °C/75 % RH, open container, 1 month

- Formulation Development
  - Initial Risk Assessment of the Formulation Variables

Table. Initial risk assessment of the formulation variables

Drug Product CQA	Formulation Variables				
	Drug Substance PSD	MCC/Lactose Ratio	CCS Level	Talc Level	Magnesium Stearate Level
Assay	Medium	Medium	Low	Low	Low
Content Uniformity	High	High	Low	Low	Low
Dissolution	High	Medium	High	Low	High
Degradation Products	Low	Low	Low	Low	Medium

Table. Justification for the initial risk assessment of the formulation variables

Formulation Variables	Drug Products CQAs	Justification
MCC/Lactose Ratio	Assay	MCC/Lactose ratio can impact the flow properties of the blend. This, in turn, can impact tablet CU. The risk is high. Occasionally, poor CU can also adversely impact assay. The risk is medium.
	Content Uniformity	
	Dissolution	MCC/lactose ratio can impact dissolution via tablet hardness. However, hardness can be controlled during compression. The risk is medium.
	Degradation Products	Since both MCC and lactose are compatible with the drug substance and will not impact drug product degradation, the risk is low.

- Formulation Development
  - DoE for the Formulation Variables

Table. Design of the 2^3 full factorial DOE to study intragranular excipients and drug substance PSD

Factors: Formulation Variables			Levels		
			-1	0	+1
A	Drug substance PSD (d_{90}, µm)		10	20	30
B	Disintegrant (%)		1	3	5
C	% MCC in MCC/Lactose combination		33.3	50.0	66.7
Responses		Goal	Acceptable Ranges		
Y_1	Dissolution at 30 min (%) (with hardness of 12.0 kP)	Maximize	≥ 80%		
Y_2	Disintegration time (min) (with hardness of 12.0 kP)	Minimize	< 5 min		
Y_3	Tablet content uniformity (% RSD)	Minimize % RSD	< 5%		
Y_4	Assay (% w/w)	Target at 100% w/w	95.0-105.0% w/w		
Y_5	Powder blend flow function coefficient (ffc)	Maximize	> 6		
Y_6	Tablet hardness@ 5 kN (kP)	Maximize	> 5.0 kP		
Y_7	Tablet hardness @ 10 kN (kP)	Maximize	> 9.0 kP		
Y_8	Tablet hardness @ 15 kN (kP)	Maximize	> 12.0 kP		
Y_9	Friability @ 5 kN (%)	Minimize	< 1.0%		
Y_{10}	Friability @ 10 kN (%)	Minimize	< 1.0%		
Y_{11}	Friability @ 15 kN (%)	Minimize	< 1.0%		
Y_{12}	Degradation products (%) (observed at 3 months, 40 °C/75% RH)	Minimize	ACE12345: NMT 0.5% Any unknown impurity: NMT 0.2% Total impurities: NMT 1.0%		

- Formulation Development
  - DoE for the Formulation Variables

Table. Experimental results of the DOE to study intragranular excipients and drug substance PSD

Batch No.	Factors: Formulation Variables			Responses			
	A: Drug substance PSD	B: Disintegrant level	C: % MCC in MCC/Lactose combination	Y_1: Dissolution at 30 min	Y_3: CU	Y_5: ffc value	Y_7: Tablet hardness @ 10 kN
	(d_{90}, µm)	(%)	(%)	(%)	(% RSD)	--	(kP)
1	30	1	66.7	76.0	3.8	7.56	12.5
2	30	5	66.7	84.0	4.0	7.25	13.2
3	20	3	50.0	91.0	4.0	6.62	10.6
4	20	3	50.0	89.4	3.9	6.66	10.9
5	30	1	33.3	77.0	2.9	8.46	8.3
6	10	5	66.7	99.0	5.1	4.77	12.9
7	10	1	66.7	99.0	5.0	4.97	13.5
8	20	3	50.0	92.0	4.1	6.46	11.3
9	30	5	33.3	86.0	3.2	8.46	8.6
10	10	1	33.3	99.5	4.1	6.16	9.1
11	10	5	33.3	98.7	4.0	6.09	9.1

- Formulation Development
  - DoE for the Formulation Variables

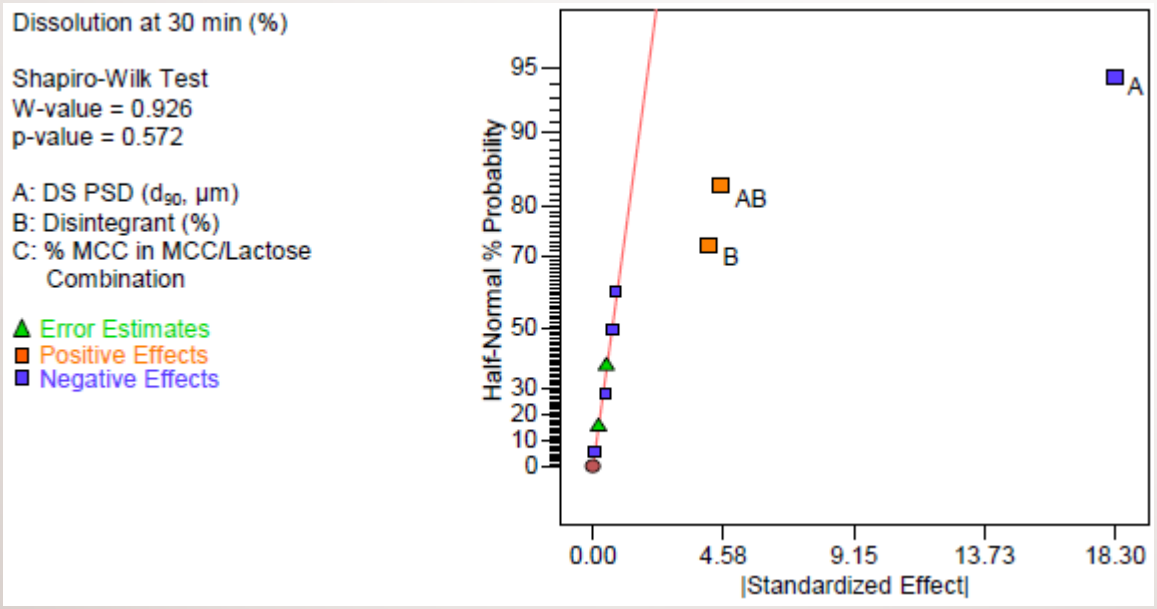


Figure. Half-normal plot of the formulation variable effects on dissolution at 30 min (tablet target hardness of 12.0 kP)

- Formulation Development
  - DoE for the Formulation Variables
  - Design space

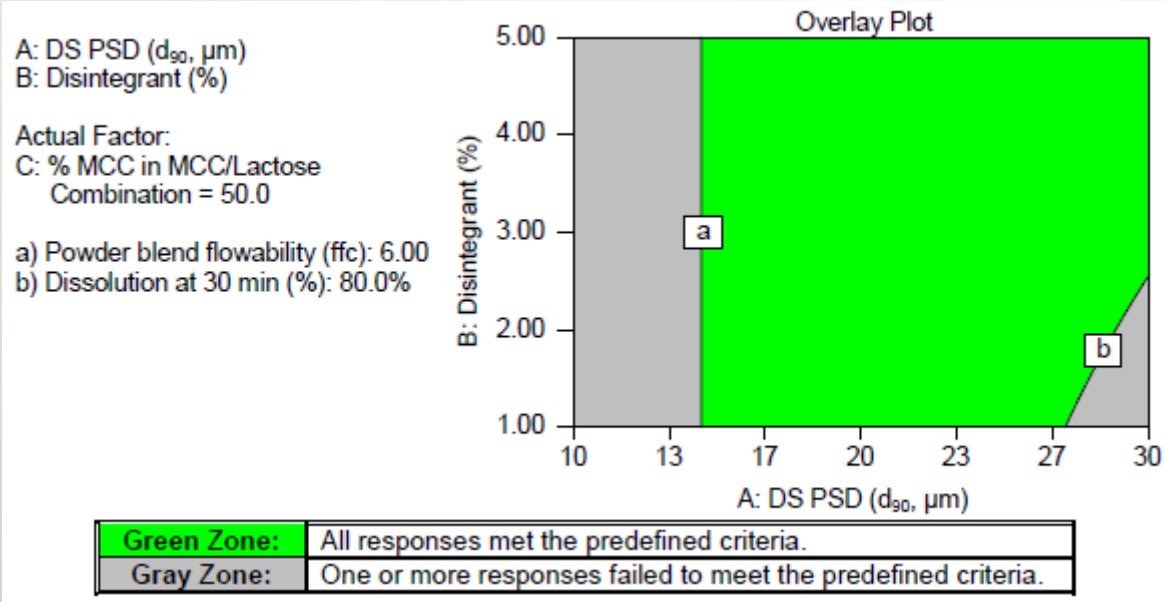


Figure. Overlay plot – effect of acetriptan formulation variables on responses

- Formulation Development
  - Updated Risk Assessment of the Formulation Variables

Table. Updated risk assessment of the formulation variables

Drug Product CQAs	Formulation Attributes			
	Drug Substance PSD	MCC/Lactose Ratio	CCS Level	Magnesium Stearate Level
Assay	Low	Low*	Low*	Low*
Content Uniformity	Low	Low	Low*	Low*
Dissolution	Low	Low	Low	Low
Degradation Products	Low*	Low*	Low*	Low

*The level of risk was not reduced from the initial risk assessment.

Table. Justification for the reduced risks of the formulation variables

Formulation Variables	Drug Product CQAs	Justification
Drug Substance PSD	Assay	All tablets showed acceptable assay. The risk is reduced from medium to low.
	Content Uniformity	The poor flow of the drug substance is mitigated by using a roller compaction process, low drug load and fillers that have good flowability. The risk is reduced from high to low.
	Dissolution	The risk is reduced from high to low by controlling drug substance PSD and optimizing intragranular superdisintegrant.

- Manufacturing Process Development

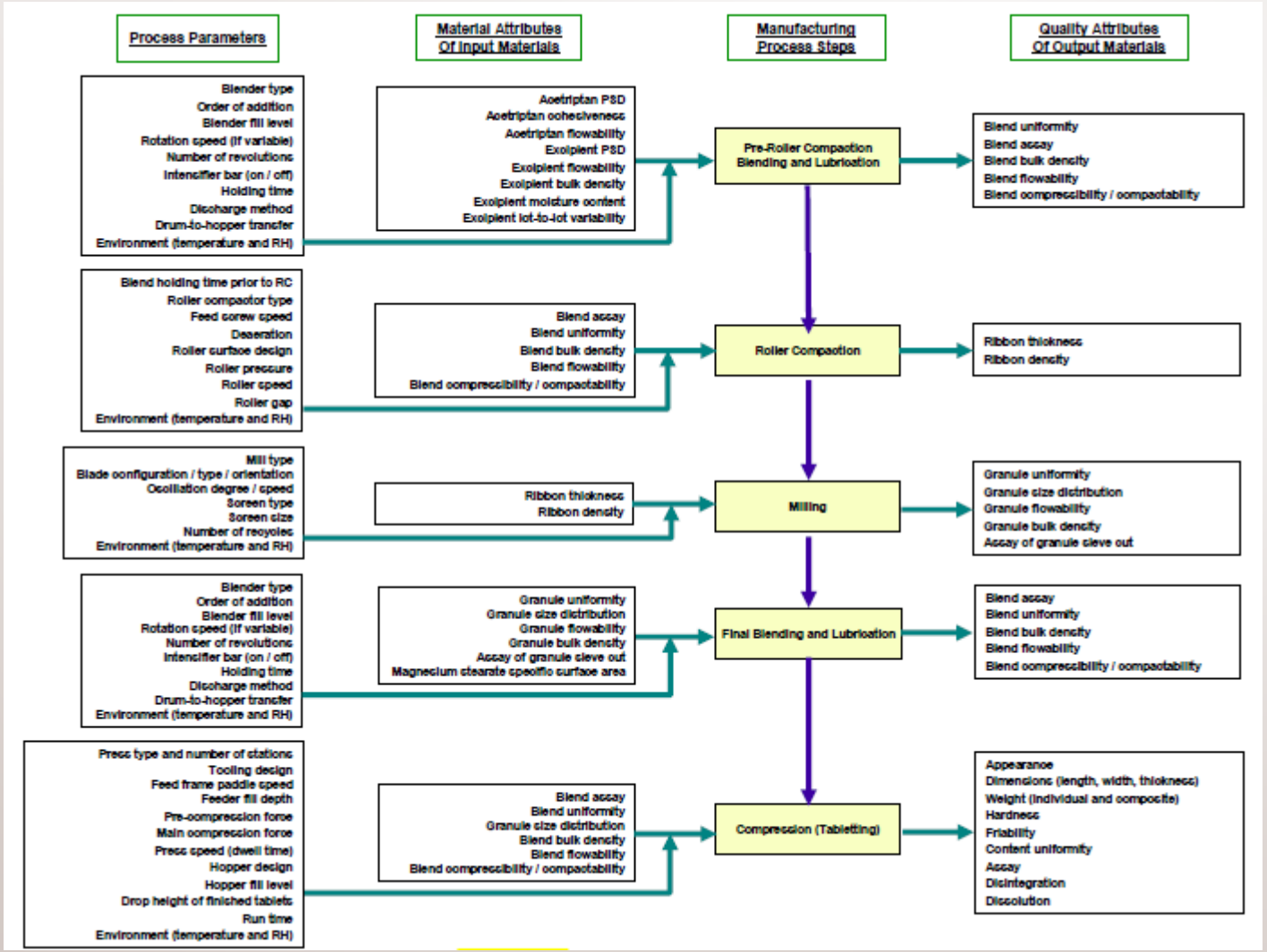


Figure. Process map for Generic Acetriptan Tablets, 20 mg

- Manufacturing Process Development

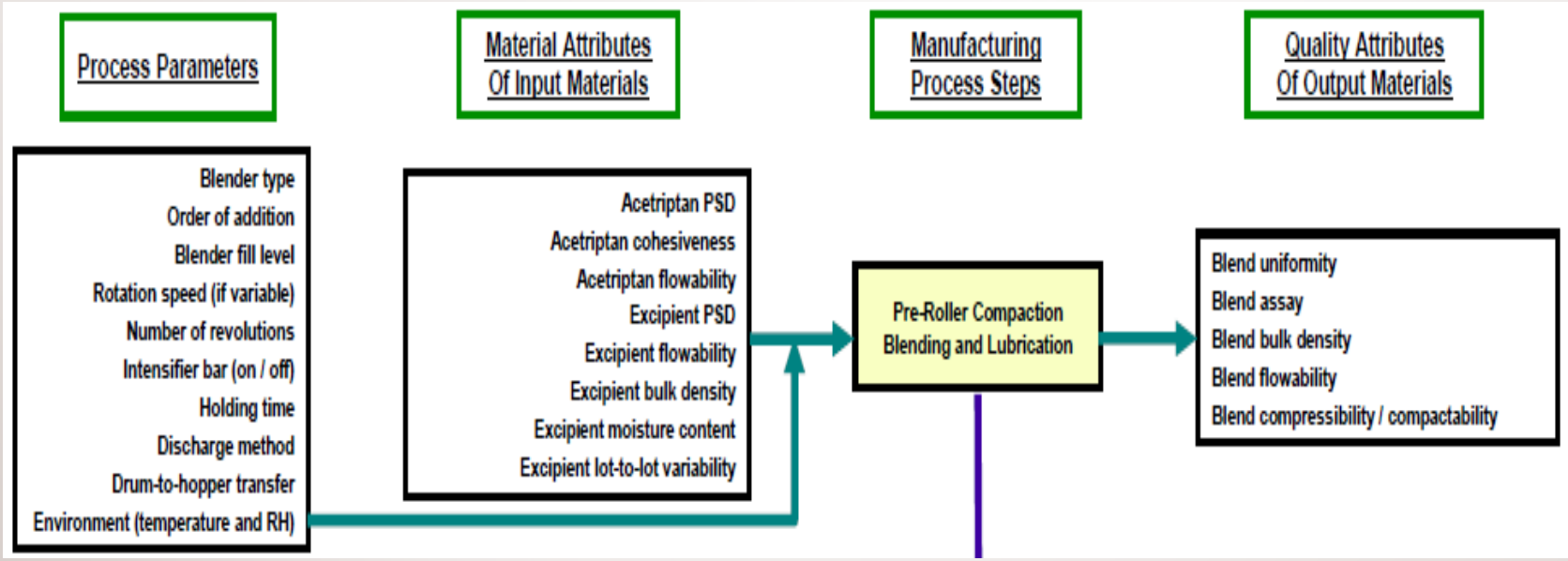


Figure. Process map for Generic Acetriptan Tablets, 20 mg

- Manufacturing Process Development
  - Initial Risk Assessment of the Drug Product Manufacturing Process

Table. Initial risk assessment of the manufacturing process for Generic Acetriptan Tablets, 20 mg

Drug Product CQAs	Process Steps				
	Pre-RC* Blending and Lubrication	Roller Compaction	Milling	Final Blending and Lubrication	Compression
Assay	Medium	Low	Medium	Low	Medium
Content Uniformity	High	High	High	Low	High
Dissolution	Medium	High	Medium	High	High
Degradation Products	Low	Low	Low	Low	Low

*RC: roller compaction

Table. Justification for the initial risk assessment of the manufacturing process

Process Steps	Drug Product CQAs	Justification
Pre-Roller Compaction Blending and Lubrication	Assay	Suboptimal pre-roller compaction blending and lubrication may cause variable flowability of the blend. The risk is medium.
	Content Uniformity	The PSD and cohesiveness of the drug substance adversely impact its flowability which, in turn, affects CU. The risk is high.
	Dissolution	Blending process variables may impact the distribution of CCS in the blend which could impact disintegration of the granules and, ultimately, dissolution of the tablets. The risk is medium.

- Manufacturing Process Development
  - Initial Risk Assessment of the Drug Product Manufacturing Process

Table. Initial risk assessment of the process variables

Process Step: Pre-Roller Compaction Blending and Lubrication		
Output Material CQA: Blend Uniformity		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
Input Material Attributes		
Acetriptan PSD	High	The pilot BE study indicated that a $d_{90} \leq 30$ µm is needed for bioequivalence. Based on several lots of acetriptan analyzed during preformulation, the drug substance meeting this d_{90} criterion has poor flowability (ffc < 3.50) which may impact BU. The risk is high.
Acetriptan cohesiveness	Medium	The specific energy of acetriptan Lot #1-4 indicated that acetriptan is moderately to highly cohesive which will make achieving BU more challenging. The risk is medium.
Acetriptan flowability	Medium	The ffc value of acetriptan Lot #1-4 suggested poor flow which could impact BU. The risk is medium.
Excipient flowability	Low	Filler comprises the majority (~ 80%) of the formulation. MCC grade B02 and lactose monohydrate grade A01 are used in a 1:1 ratio because this ratio demonstrated good flowability (ffc ≈ 7). Glidant and lubricant are used in small quantities and are unlikely to impact BU. The risk is low.

- Manufacturing Process Development
  - Initial Risk Assessment of the Drug Product Manufacturing Process

Table. Initial risk assessment of the process variables

Process Step: Pre-Roller Compaction Blending and Lubrication		
Output Material CQA: Blend Uniformity		
Variables	**Risk Assessment**	**Justification and Initial Strategy**
Blending Variables		
Blender type	Low	Different blender types have different mixing dynamics. V-blender is selected based on equipment availability. The risk is low. However, if the blender type is changed during scale-up or commercialization, the risk should be re-evaluated.
Order of addition	Low	Order of addition may impact the ease of evenly dispersing ingredients charged in lower quantities. Materials are added in the following order: lactose monohydrate, CCS, acetriptan, talc, and MCC. The risk is low.
Rotation speed (rpm)	Medium	Rotation speed is often fixed by equipment constraint. Different size blenders have different rotation speeds. The rotation speed for the 16 qt blender is fixed at 20 rpm. The risk is medium.
Number of revolutions	High	Under- or over-blending will result in suboptimal BU. The risk is high.

- Manufacturing Process Development
  - Process Development (DoE)

Table. Design of the 3^2 study to investigate pre-RC blending and lubrication process variables

Factors: Process Variables			Levels		
			0	1	2
A	Number of revolutions (N_{rev})		100	200	300
B	Acetriptan d_{90} (µm)		10	20	30
Responses		Goal	Acceptable Ranges		
Y_1	Blend Assay (% w/w)	Achieve 100% w/w	Assay mean of all locations: 95.0-105.0% w/w		
Y_2	Blend Uniformity (% RSD)	Minimize % RSD	% RSD of all locations: ≤ 5%		

Table. Results of the pre-RC blending and lubrication optimization study

Batch No.	Factors: Process Variables		Response
	A: N_{rev}	B: Acetriptan d_{90}	Y_2: BU
	--	(µm)	(% RSD)
21	100	10	8.9
22	100	30	5.4
23	300	20	2.5
24	100	20	6.8
25	200	20	3.0
26	300	10	3.2
27	300	30	2.3
28	200	30	2.8
29	200	10	4.3

- Manufacturing Process Development
  - Updated Risk Assessment of the Drug Product Manufacturing Process

Table. Updated risk assessment of the process variables

Process Step: Pre-Roller Compaction Blending and Lubrication		
Output Material CQA: Blend Uniformity		
Variables	**Risk Assessment**	**Justification for the Reduced Risk**
Acetriptan PSD	Low	In order for the blending process to be robust enough to accommodate different acetriptan PSD, an in-line NIR method was developed for blending endpoint determination. Blender fill levels from 35-75% had no impact on blending endpoint. The risk was reduced from high to low.
Number of revolutions	Low	
Blender fill level	Low	

Table. Updated risk assessment of the manufacturing process for Generic Acetriptan Tablets, 20 mg

Drug Product CQAs	**Process Steps**				
	Pre-RC Blending and Lubrication	**Roller Compaction**	**Milling**	**Final Blending and Lubrication**	**Compression**
Assay	Low	Low*	Low	Low*	Low
Content Uniformity	Low	Low	Low	Low*	Low
Dissolution	Low	Low	Low	Low	Low
Degradation Products	Low*	Low*	Low*	Low*	Low*

*The level of risk was not reduced from the initial risk assessment.

- Approach to Process Validation
  (US FDA Guidance for Industry, Process Validation: General Principles and Practices; II. B.)
  - Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
  - Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
  - Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

- 由Process Design所定義出來之CPP在製程確效時必須被確認。(一般是Risk Assessment中，評估為中、高風險的項目或是DoE中確定會影響產品CQA的項目)。

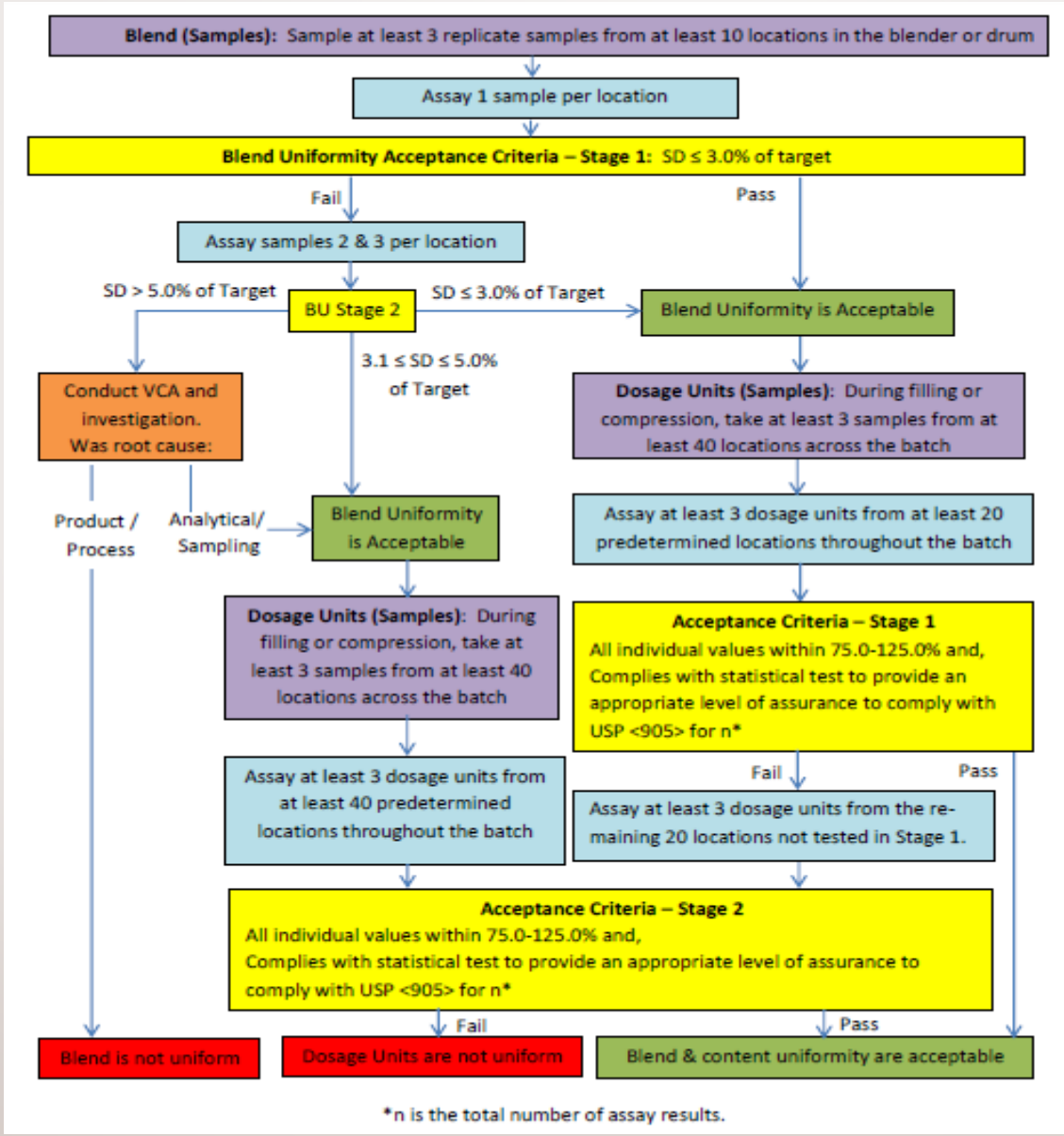
- 由Process Design所定義出來之CQA在製程確效及市售批的生產時必須被確認。(一般是製程中管制或產品放行的項目)。

- 產品申請查驗登記前，需確定製程的CPP及產品的CQA，之後的製程確效及市售批的生產，CPP與CQA必須前後一致。

如何實際執行製程中管制及最終產品放行(如何抽樣？抽樣數目？)

- Pharmacopeia
- Guidance from Agency or related Association (ICH, WHO, ISPE…)
  - Recommended Changes to Withdrawn FDA Draft Stratified Sampling Guidance Document

    (ISPE (International Society for Pharmaceutical Engineering) Blend and Content Uniformity Group December, 2014)
  - ANSI/ASQC Z1.4 Sampling Procedures and Tables Package (American National Standards Institute (ANSI))



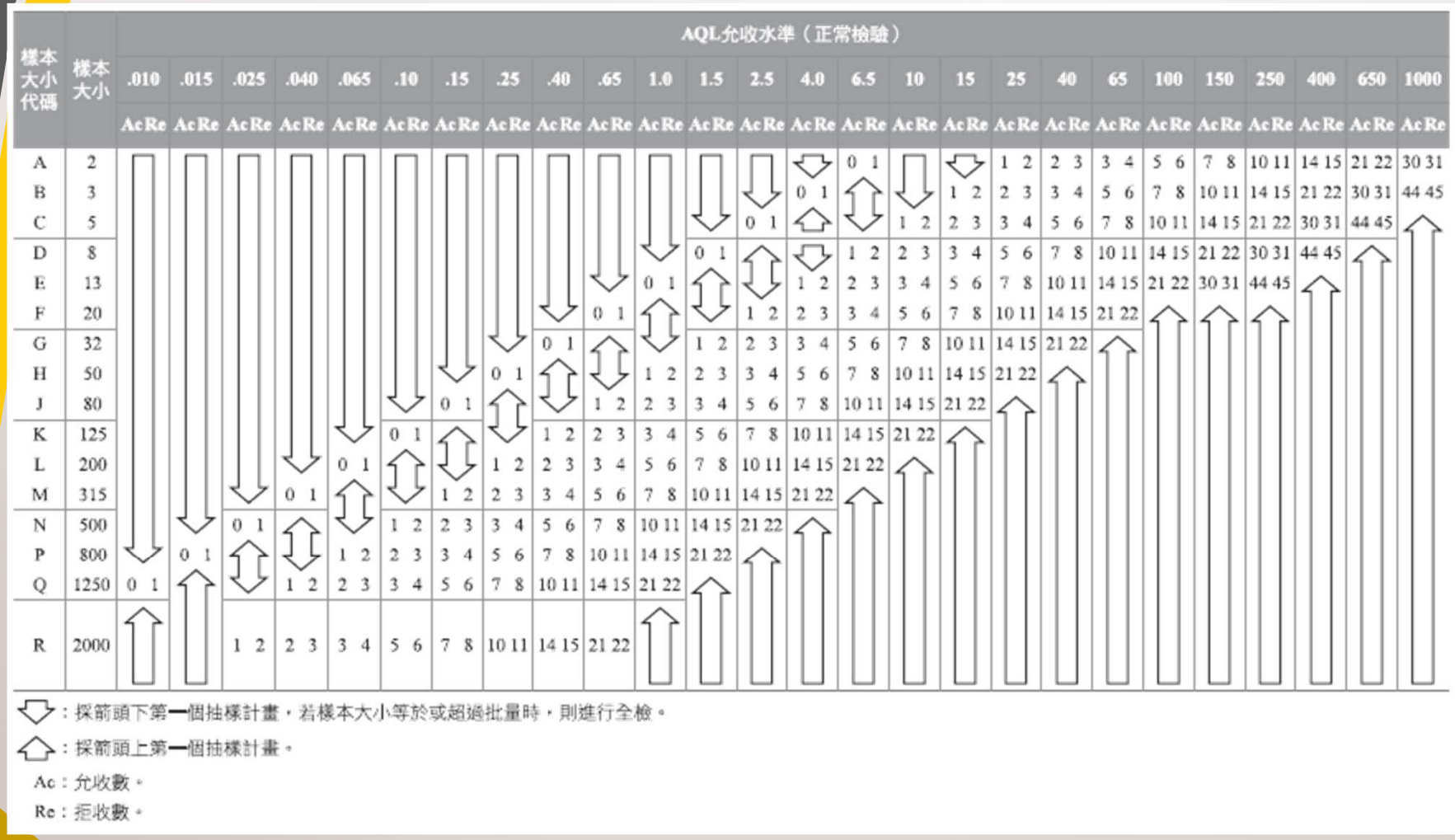
From ISPE Blend and Content Uniformity Group December, 2014

Example of Sampling Plan

批量大小			特殊檢驗水準				一般檢驗水準		
			S-1	S-2	S-3	S-4	I	II	III
2	to	8	A	A	A	A	A	A	B
9	to	15	A	A	A	A	A	B	C
16	to	25	A	A	B	B	B	C	D
26	to	50	A	B	B	C	C	D	E
51	to	90	B	B	C	C	C	E	F
91	to	150	B	B	C	D	D	F	G
151	to	280	B	C	D	E	E	G	H
281	to	500	B	C	D	E	F	H	J
501	to	1200	C	C	E	F	G	J	K
1201	to	3200	C	D	E	G	H	K	L
3201	to	10000	C	D	F	G	J	L	M
10001	to	35000	C	D	F	H	K	M	N
35001	to	150000	D	E	G	J	L	N	P
150001	to	500000	D	E	G	J	M	P	Q
500001	to	over	D	E	H	K	N	Q	R

From ANSI/ASQC Z1.4

Example of Sampling Plan



樣本大小代碼	樣本大小	AQL允收水準（正常檢驗）																										
		.010	.015	.025	.040	.065	.10	.15	.25	.40	.65	1.0	1.5	2.5	4.0	6.5	10	15	25	40	65	100	150	250	400	650	1000
		Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re	Ac Re
A	2	⇩	⇩	⇩	⇩	⇩	⇩	⇩	⇩	⇩	⇩	⇩	⇩	⇩	⇩	0 1	⇩	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31
B	3														0 1	⇕		1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45
C	5													0 1	⇧	⇕	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45	⇧
D	8												0 1	⇩	⇩	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45	⇩
E	13											0 1	⇕	⇕	⇧	2 3	3 4	5 6	7 8	10 11	14 15	21 22	30 31	44 45	⇧	⇕	
F	20										0 1	⇧	⇧	⇧	2 3	3 4	5 6	7 8	10 11	14 15	21 22	⇧	⇧	⇧	⇧	⇧	
G	32									0 1	⇩	⇩	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	⇩	⇩	⇩	⇩	⇩	⇩	
H	50								0 1	⇕	⇕	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	⇧	⇧	⇧	⇧	⇧	⇧	⇧	
J	80							0 1	⇕	⇕	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	⇩	⇩	⇩	⇩	⇩	⇩	⇩	⇩	
K	125						0 1	⇩	⇕	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	
L	200					0 1	⇕	⇕	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	
M	315				0 1	⇕	⇕	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	
N	500			0 1	⇕	⇕	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	
P	800		0 1	⇕	⇕	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	
Q	1250	0 1	⇧	⇕	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	
R	2000	⇧	⇧	1 2	2 3	3 4	5 6	7 8	10 11	14 15	21 22	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧	⇧

⇩：採箭頭下第一個抽樣計畫，若樣本大小等於或超過批量時，則進行全檢。

⇧：採箭頭上第一個抽樣計畫。

Ac：允收數。

Re：拒收數。

From ANSI/ASQC Z1.4

Example of Sampling Plan

執行製程中管制(IPC)至最終產品放行(含製程確效) 時需注意的事項

- 管控點或項目的設定(CPP或CQA)
- CPP的範圍(range)與CQA的規格(specification)
- 查驗登記、製程確效及市售批的生產，CPP與CQA必須前後一致
- 抽樣的工具(如採樣棒、藥勺等)於實際取樣前，需明訂且固定下來。
- 取樣樣品的代表性(數量、位置、時間點)
- Blend Uniformity (BU)的樣品，無論在取樣或化驗時須避免分稱。一般取樣量為1~3倍的單位劑量。
- 可能的話，盡量從生產設備上直接抽取樣品。

Process Analytical Technology (PAT)

- A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance
- A system for:
  - Designing, analyzing, and controlling manufacturing
  - Timely measurements (i.e., during processing)
  - Critical quality and performance attributes
  - Raw and in-process materials
  - Processes

  (US FDA Guidance for Industry, PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance)

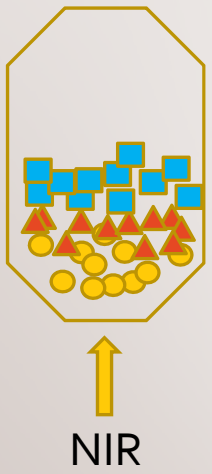
Process Analytical Technology (PAT)

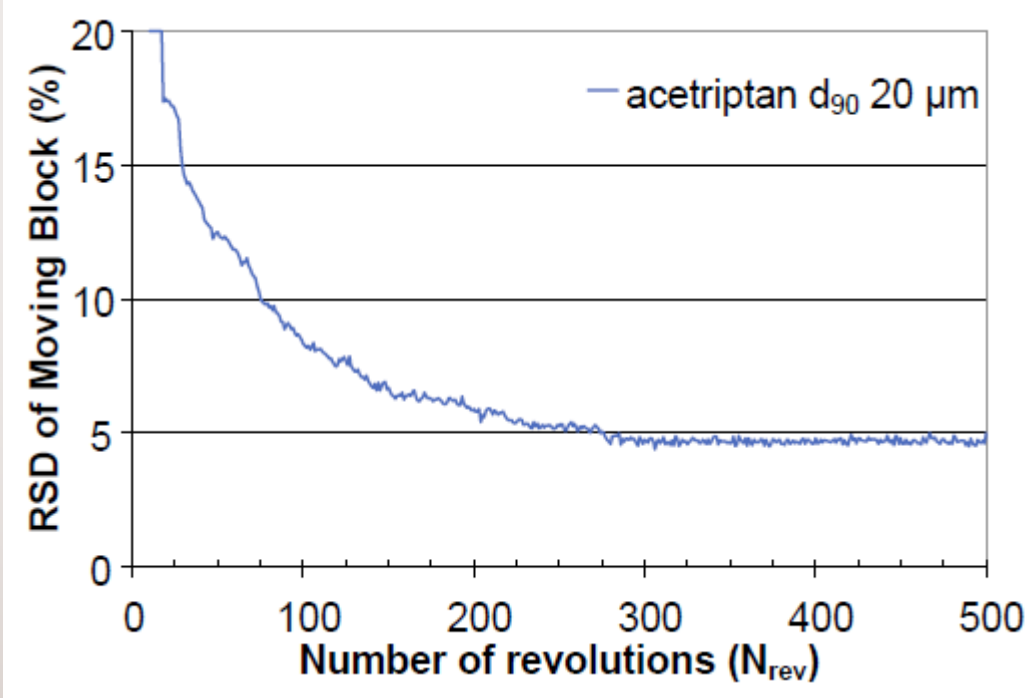
Off-line	Analysis performed in Laboratory	Days
At-line	Analysis performed on factory floor	Minutes
On-line	Automated sampling and analysis	Seconds
In-line	No sampling – instrument in process	< 1 second

From US FDA Guidance for Industry, PAT - A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance

Development of In-line NIR for Blending Endpoint Determination

- To assess the homogeneity of the blend, % RSD was calculated for each moving block of ten consecutive spectra and plotted as a function of number of revolutions.





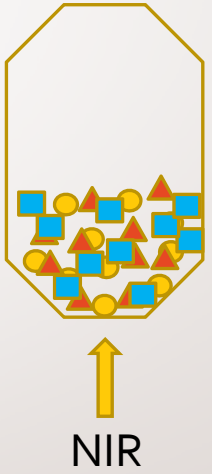


Figure. % RSD of the moving block of the NIR spectra for acetriptan d90 of 20 µm blended for 500 revolutions

- 為什麼要對產品執行製程中管制及最終產品放行？
  - 確保產品品質及用藥人的安全
  - 法規規定
- 如何設定製程中管制及產品放行的項目及規格？
  - QbD (Quality by Design)
  - DoE (Design of Experiment)
  - CPP, CQA
- 如何實際執行製程中管制及最終產品放行(如何抽樣？抽樣數目？)
  - Pharmacopeia
  - Guidance from Agency or related Association (ICH, WHO, ISPE)
- Process Analytical Technology (PAT)


Thank you


Question