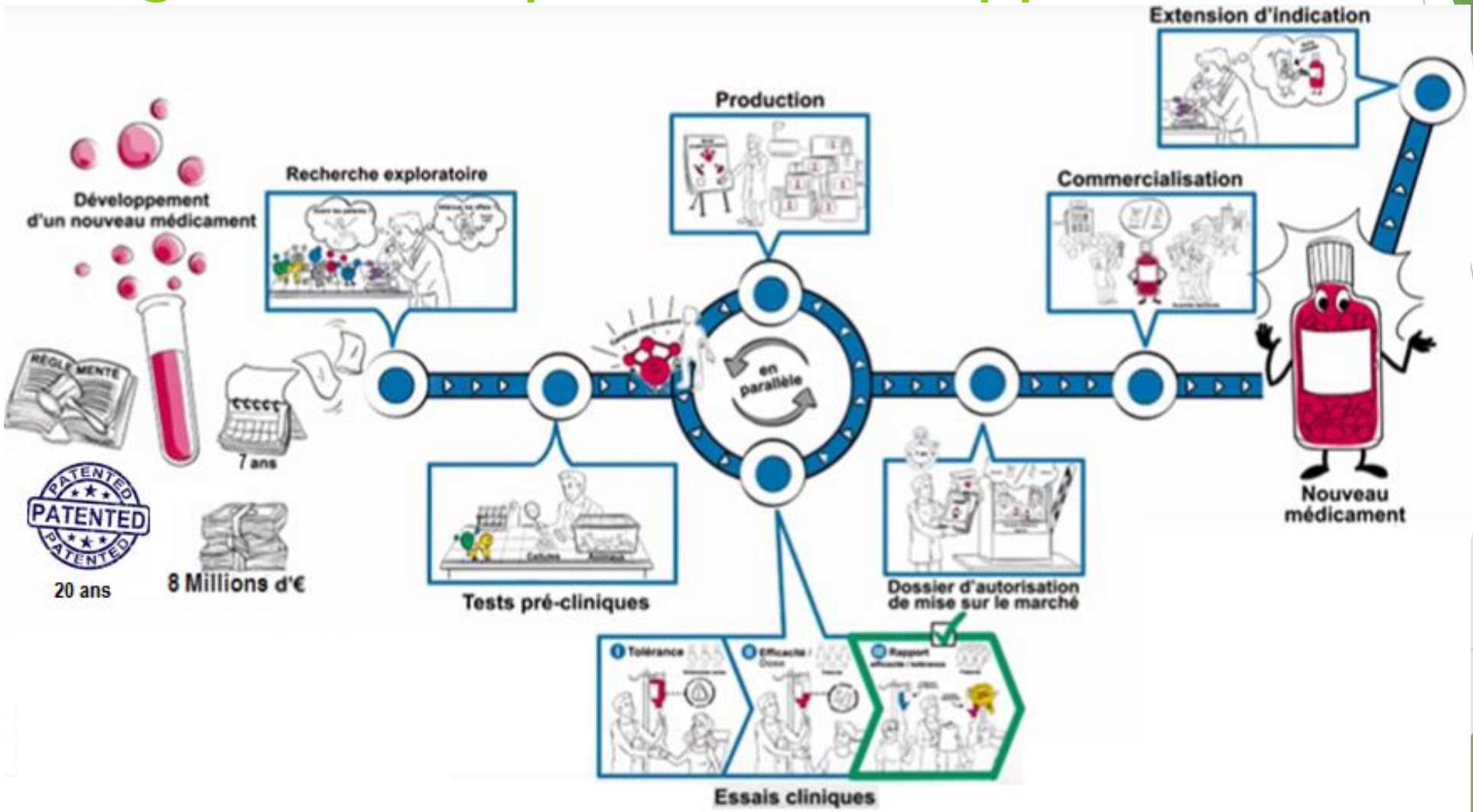
Développement pharmaceutique et Dossier d'AMM
Module 3,

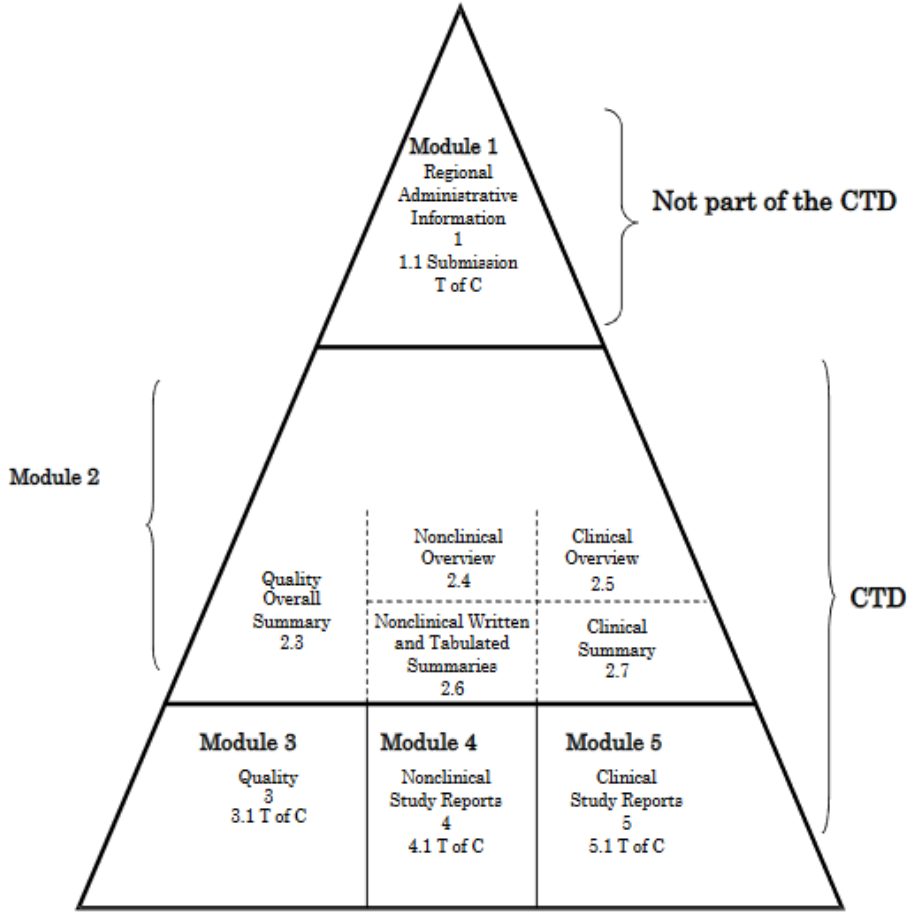
Marinette Moreau

Les grandes étapes du développement



ICH M4: guideline on common technical document (CTD) for the registration of pharmaceuticals for human use organization of CTD :

Diagrammatic Representation of the Organization of the ICH CTD Common Technical Document



PHARMACEUTICAL DEVELOPMENT
Module 3 du dossier AMM

Module 3 :

- 3.2S Drug substance
- 3.2P Drug product

Module 3

- 3.2S va être rapidement présentée

- **Uniquement la Partie P, section 3.2.P.3 : va être particulièrement développée**.

  ****Développement Formule ,**
  ****Développement et validation du procédé de fabrication**

- Les sections 3.2.P.4, 3.2.P.5 , 3.2P.6 , 3.2P.7 et 3.2.P.8 vont être présentées

3.2S Drug substance

- 32s1-gen-info
- 32s2-manuf
- 32s3-charac
- 32s4-contr-drug-sub
- 32s5-ref-stand
- 32s6-cont-closure-sys
- 32s7-stab

Module 1: Administrative Information and Prescribing Information
- This module should contain documents specific to each region

Module 2: Common Technical Document Summaries
- 2.3: QUALITY OVERALL SUMMARY (QOS)

Module 3: Quality

- **3.1. TABLE OF CONTENTS OF MODULE 3**
- **3.2. BODY OF DATA**
- **3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)**
- **3.2.S.1 General Information (name, manufacturer)**
  - 3.2.S.1.1 Nomenclature (name, manufacturer)
  - 3.2.S.1.2 Structure (name, manufacturer)
  - 3.2.S.1.3 General Properties (name, manufacturer)
- **3.2.S.2 Manufacture (name, manufacturer)**
  - 3.2.S.2.1 Manufacturer(s) (name, manufacturer)
  - 3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)
  - 3.2.S.2.3 Control of Materials (name, manufacturer)
  - 3.2.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)
  - 3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)
  - 3.2.S.2.6 Manufacturing Process Development (name, manufacturer)
- **3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)**
- **3.2.S.3 Characterisation (name, manufacturer)**
- 3.2.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)
- 3.2.S.3.2 Impurities (name, manufacturer)
- **3.2.S.4 Control of Drug Substance (name, manufacturer)**
- 3.2.S.4.1 Specification (name, manufacturer)
- 3.2.S.4.2 Analytical Procedures (name, manufacturer)
- 3.2.S.4.3 Validation of Analytical Procedures (name, manufacturer)
- 3.2.S.4.4 Batch Analyses (name, manufacturer)
- 3.2.S.4.5 Justification of Specification (name, manufacturer)
- **3.2.S.5 Reference Standards or Materials (name, manufacturer)**
- **3.2.S.6 Container Closure System (name, manufacturer)**
- **3.2.S.7 Stability (name, manufacturer)**
- 3.2.S.7.1 Stability Summary and Conclusions (name, manufacturer)
- 3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)
- 3.2.S.7.3 Stability Data (name, manufacturer)

3.2P Drug Product

- 32p1-desc-comp
- 32p2-pharm-dev
- 32p3-manuf
- 32p4-contr-excip
- 32p5-contr-drug-prod
- 32p6-ref-stand
- 32p7-cont-closure-sys
- 32p8-stab

3.2.P Drug product :

Description and composition of the drug product :3.2.P.1

- Example of table of composition :

Ingredients	Fonction	Reference	Unit formula x mg/ 1 ml	Percentage formula
xxxxxx	Active substance	Ph. Eur.	x	100X
Excipient 1	Preservative	Ph. Eur.	X1	100X1
Excipient 2	Solvant	Ph. Eur.	X2	100X2
Excipient 3…	…	Ph. Eur.	QS 1ml	Qs 100ml

Section 3.2.P.2: Développement pharmaceutique : formule et procédé de fabrication: la directive ICH Q8

ICH Q8 guideline describes the suggested contents for the 3.2.P.2 (Pharmaceutical Development)

Formulation Development:3.2.P.2

A summary should be provided describing the development of the formulation, including identification of those attributes that are critical to the quality of the drug product, taking into consideration intended usage and route of administration

Les Grandes lignes de la directive ICH Q8

Components of the Drug Product

- Drug Substance
  - The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability: solid state properties solubility, water content, particle size, crystal properties, biological activity, and permeability.
  - The compatibility of the drug substance with excipients should be evaluated
- Excipients
  - The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed
  - justify the choice and quality attributes of the excipient and to support the justification of the drug product specification

Les Grandes lignes de la directive ICH Q8

Manufacturing Process Development

- It is important to consider the critical formulation attributes, together with the available manufacturing process options, in order to address the selection of the manufacturing process and confirm the appropriateness of the components. Appropriateness of the equipment used for the intended products should be discussed. Process development studies should provide the basis for process improvement, process validation, continuous process verification

Les Grandes lignes de la directive ICH Q8

Manufacturing Process Development

- An assessment of the ability of the process to reliably produce a product of the intended quality (e.g., the performance of the manufacturing process under different operating conditions, at different scales, or with different equipment) can be provided. An understanding of process robustness can be useful in risk assessment and risk reduction (see ICH Q9 Quality Risk Management glossary for definition) and to support future manufacturing and process improvement, especially in conjunction with the use of risk management tools (see ICH Q9)

Les Grandes lignes de la directive ICH Q8

- **Container Closure System**: Primary Packaging selection , compatibility and stability studies
- **Microbiological Attributes**
  - the microbiological attributes of the components as active substance should be addressed
  - the microbiological attributes of the finished drug product
  - The selection and effectiveness of preservative systems : antimicrobial preservative effectiveness should be demonstrated during development. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using an antimicrobial preservative effectiveness test.

Cas Pratiques exemple de Contenu d'un Rapport de développement

Développement d'un comprimé :

Cas Pratiques: exemple de Contenu d'un Rapport de développement
Active ingredient

- Structure chimique de la molécule
- Propriétés physicochimiques telle la solubilité , la stabilité à la lumière , l'oxygène etc…
. - DMF fournisseur

The particle size distributions of batches used during the development are shown in the following table.

Batch number	Mean (µm)	d10 (µm)	d25 (µm)	d50 (µm)	d75 (µm)	d90 (µm)
3841105	21,5	4,4	7,5	13,6	29,8	52,1
1002	21,9	4,9	10,6	18,8	29,7	43,9
1012	28,8	4,9	10,6	18,8	29,7	43,9
TM0040409	33,6	6,7	14,2	25,8	44,3	70,7
TM0050409	32,5	6,6	14,3	25,6	42,6	66,6

Table 1: Particle size distributions after analysis by a laser method

Cas Pratiques: exemple de Contenu d'un Rapport de développement
la formule

Composition	References	Function	Supplier
Active ingredient	Current Ph.Eur.	Active Ingredient	XXXXXX
Lactose monohydrate	Current Ph.Eur.	Filler	Meggle
Povidone K30	Current Ph.Eur.	Binder	BASF
Sodium Laurylsulphate	Current Ph.Eur.	Wetting agent	Tensachem
Crospovidone	Current Ph.Eur.	Disintegrant	BASF
Microcrystalline cellulose PH200	Current Ph.Eur.	Filler	FMC
XXX flavour	Current Ph.Eur.	Aroma	Firmenich
Sodium Stearylfumarate	Current Ph.Eur.	Lubricant	Rettenmaier France

Cas Pratiques : exemple de Contenu d'un Rapport de développement Conditionnement primaire

1.1 Primary packaging

The tablets are packaged in Alu/Alu or in Alu/Aclar blisters.

The composition of the primary packaging is presented below:

Packaging	Composition		References
Alu/Alu Blisters	Thermoformable material	OPA25/ALU45/PVC60	Internal monograph
	Sealing material	Aluminium 20 µm	Internal monograph
Alu/Aclar Blisters	Thermoformable material	Aclar 76 µm / PVC 191 µm	LC² Internal monograph
	Sealing material	Aluminium 20 µm	LC² Internal monograph

Cas Pratiques Rapport de développement justification de la formule Exemples pour un diluant , et un liant
La même démarche est appliquée pour la justification du choix et de la teneur de chaque excipient

1.1.1 Binder

A commonly used binder (Povidone K30) was assessed. It was added to the wetting granulation liquid. Different percentages of binder were tested.

All the formula tested were equivalent. The proportion of binder was modified.

Components	080717	080718	080719	080725	080726
Acive ingredient	1,25	1,25	1,25	1,25	1,25
Pharmatose® DCL11	88,75	83,75	78,75	63,75	63,75
Povidone K30	5,00	10,00	15,00	15,00	20,00
Sodium Laurylsulphate	1,00	0,28	0,17	0,50	0,66
External phase	*QS 100%*				

Table 1: Composition of different batches with different proportions of binder in internal phase

Batch number	Binder quantity (% m/m)	Flowability (s)	d50 (µm)
080717	5	None	125
080718	10	None	180
080719	15	8	250
080725	15	10	250
080726	20	10	250

Table 2: Rheological properties of different batches with different ratios of binder

Cas Pratiques Rapport de developement justification de la formule

- With 5% or 10% of binder, a bad granules quality had been obtained. The granules were too brittle and too fine.
- With 15% or 20% of binder, the granules had a suitable quality for tabletting.
- But better tabletting properties were obtained with 20% of binder.

Cas Pratiques Rapport de développement justification de la formule

1.1.1 Filler

Three different fillers were tested. These fillers are commonly used: lactose monohydrate and microcrystalline cellulose (Avicel® PH102). Two different quality of lactose have been evaluated: Pharmatose® DCL 11 and Spherolac®.

The formula is equivalent from batch to batch. Only the type of filler is modified.

Components	080726	080732	080736
Active ingredient	1,46	1,46	1,46
Pharmatose® DCL11	74,42	/	/
Spherolac® 100	/	/	74,42
Avicel® PH102	/	74,42	/
Povidone K30	23,35	23,35	23,35
Sodium Laurylsulphate	0,77	0,77	0,77

Table 1 : Composition of different batches with different fillers in internal phase

Batch number	Diluents	Ability to settle V_{10}-V_{500} (ml)	Bulk density (g/ml)	Flowability (s)
080726	Lactose monohydrate (Pharmatose® DCL 11)	11	0.43	10
080732	Microcrystalline Cellulose (Avicel® PH102)	11	0.26	14
080736	Lactose monohydrate (Spherolac® 100)	12	0.46	11

Table 2: Rheological properties of different batches with different fillers in internal phase

	080726	080732	080736
d10 (µm)	90	90	125
d50 (µm)	250	250	250
d90 (µ)	500	500	500

Table 3: Particle size of different batches with different fillers in internal phase

With microcrystalline cellulose, a bad granule quality had been obtained (brittleness, high percentage of fine particles, very low density). However, lactose monohydrate had a suitable quality for tabletting

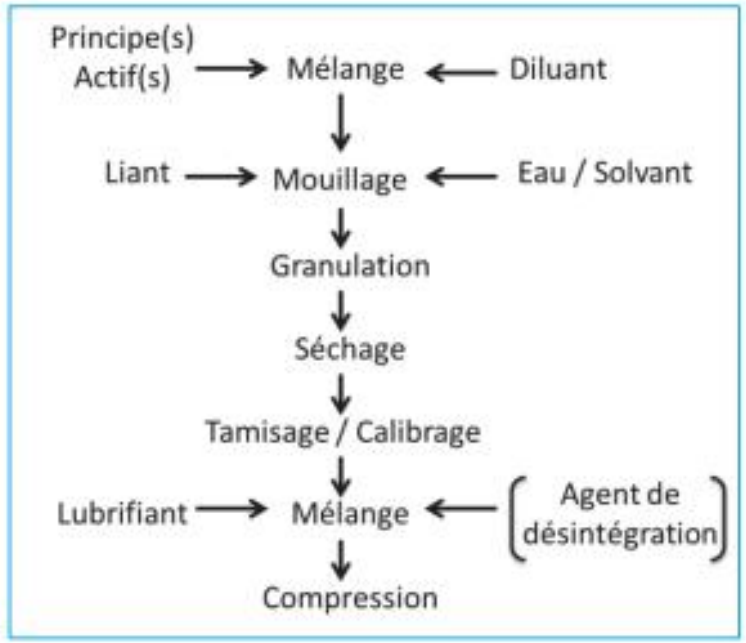
Manufacturing process devlopment

Exemple de développement d'un procédé de fabrication

- Voir slides suivantes : cas pratique d'un procédé de fabrication par granulation humide High shear et Lit d'Air Fluidisé (LAF)

Rappel :
Etapes principales de la fabrication d'un comprimé

- Procédé de fabrication par granulation humide :
  - Pesée des différents ingrédients
  - Mélange
  - Granulation
  - Calibration humide
  - Séchage
  - Calibration à sec
  - Mélange
  - Compression



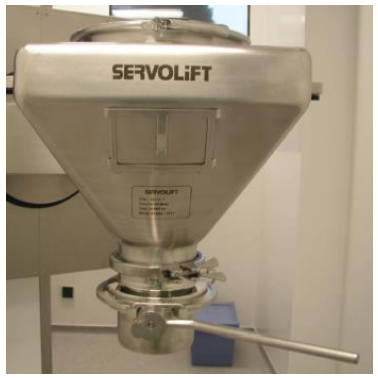
Rappel :
Etapes principales de la fabrication d'un comprimé

Mélangeurs: différents designs

Cet appareil est un mélangeur de type rotatif de marque Servolift® .

10 l

35 l



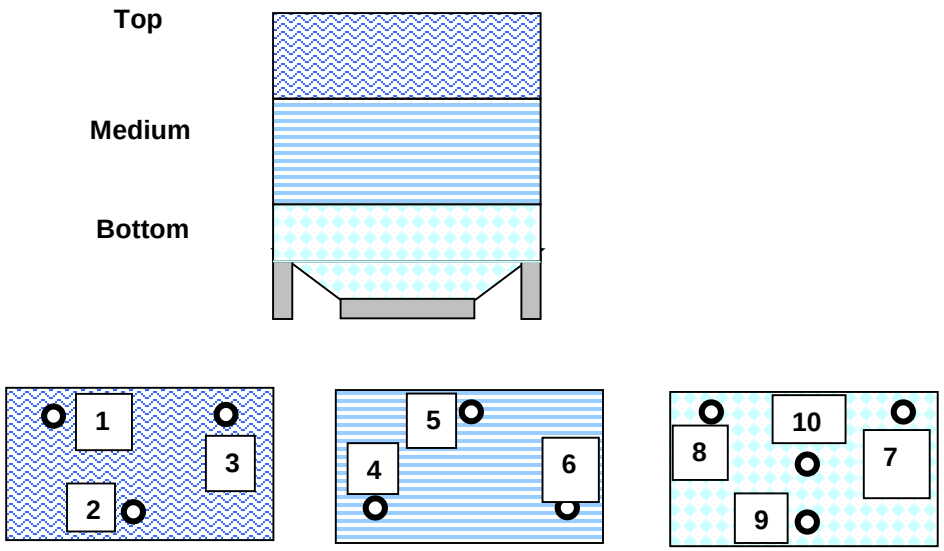
60 l

Rappel :

Etapes principales de la fabrication d’un comprimé:
Contrôle d’homogénéité

- Ce contrôle est très important , il permet de s ’assurer que le mélange est homogène .
- des cannes d’échantillonnages qui permettent de faire des prélèvements de même quantité que ce soit au fond, au milieu et en haut de la cuve.
- Puis ces échantillons seront analysés pour vérifier que la teneur en actif à plusieurs emplacements dans le mélangeur

Points de prélèvements au niveau d'un mélangeur



Level 1: Top level

Samples no. 1 – 3

–1 back left

–2 front middle

–3 back right

Level 2:Medium Level

Samples no.4 – 6

- 4 front left

– 5 back middle

– 6 front right

Level 3: Bottom level *Sample no. 7-10*

– 8 back left

– 9 front middle

– 7 back right

– 10 middle center

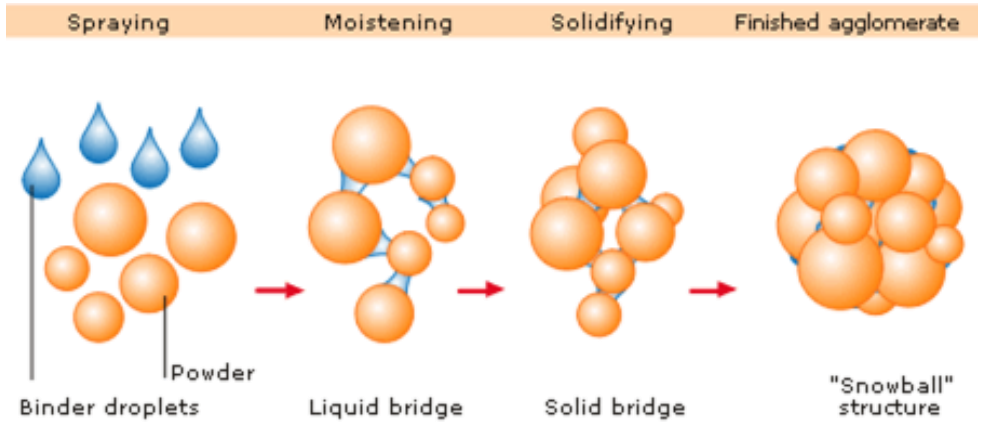
Rappel :La granulation humide

Quoi ? => transformer la poudre en grain,

Pourquoi ? => maitriser les propriétés physiques des poudres, afin de leur donner les caractéristiques nécessaires et satisfaisantes aux différentes étapes de procédés de mise en forme : sachet, gélules, comprimés...

Comment ? => par transfert d'énergie, améliorer leur écoulement, leur plasticité, leur porosité

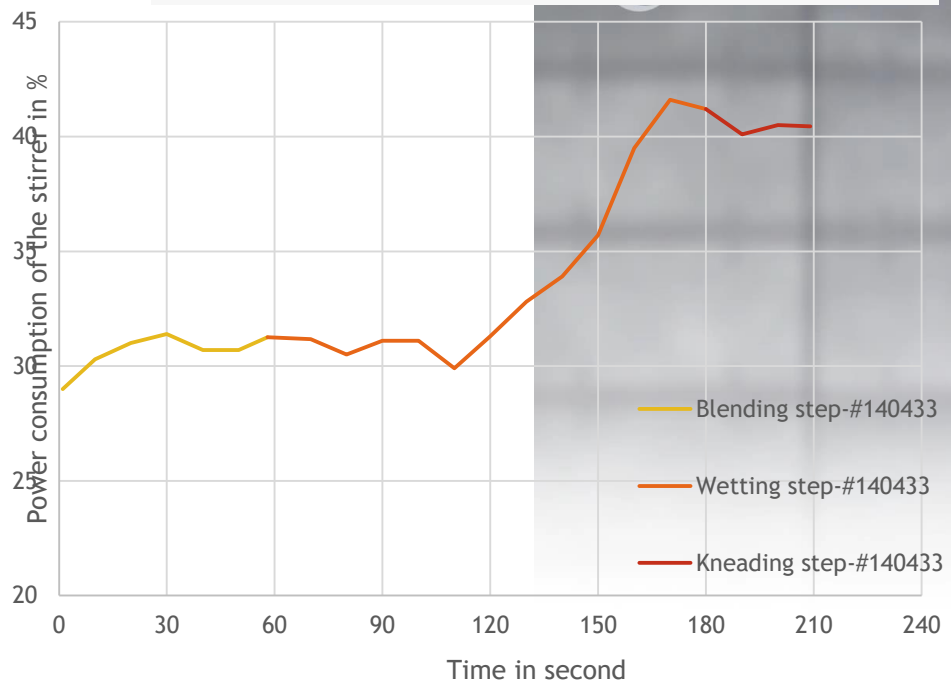
Il existe plusieurs procédés de granulation, principalement on distingue les procédés par voie sèche [compacteur] et par voie humide [Lit d'air fluidisé] ou [high shear Mixer].

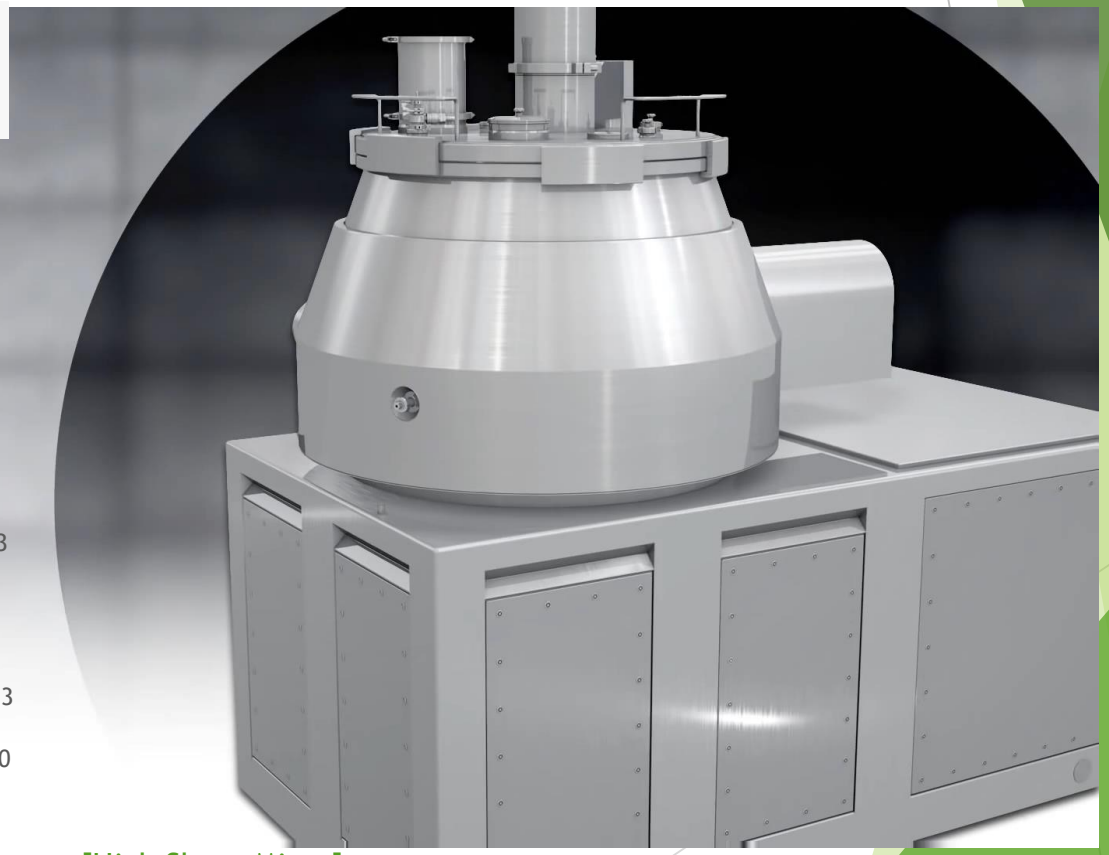


La granulation humide en high shear

Curve of power consumption batch Nr. 140433

(8% PVP K30)



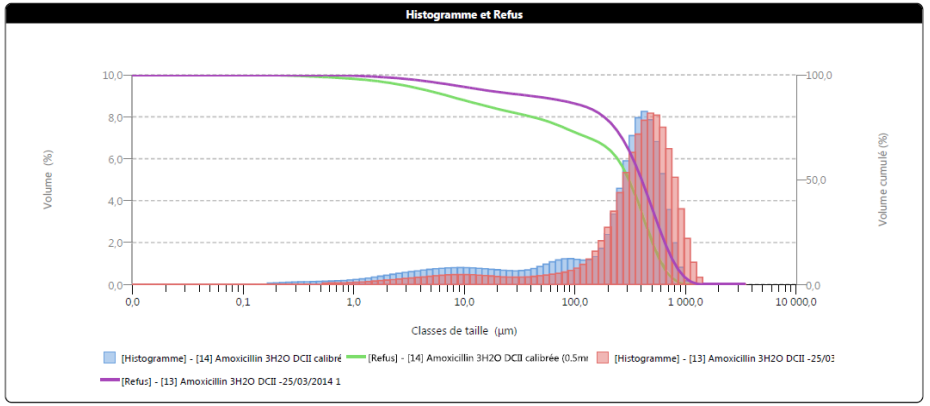


Le procédé de granulation en mélangeur à haut taux de ciscaillements [High Shear Mixer]

La calibration grain humide : une option en cas de granulation high shear

Le procédé de calibration permet de maitriser la taille des particules en minimisant leurs disparités. On parle de population de particules , distribution particulaire.
Le principe de fonctionnement d'un calibreur est la réduction de la taille particulaire obtenu par friction/cisaillement du grain à l'aide d'un rotor/stator, le rotor peut être rotatif ou oscillant.

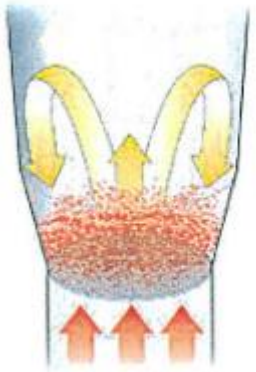
Principe de fonctionnement du calibreur conique :



	Numéro d'enregistrement :	Nom de l'échantillon	Dx (10) (µm)	Dx (50) (µm)	Dx (90) (µm)	Obscuration du laser (%)
	14	Amoxicillin 3H2O DCII calibrée (0,5mm)	7,14	309	613	5,60
	13	Amoxicillin 3H2O DCII	39,6	402	802	3,48
Moyenne			**23,3**	**356**	**707**	**4,54**
1xEcart type			**22,9**	**65,9**	**133**	**1,50**
1xRSD			**98,2**	**18,5**	**18,8**	**33,05**

Le séchage en LAF

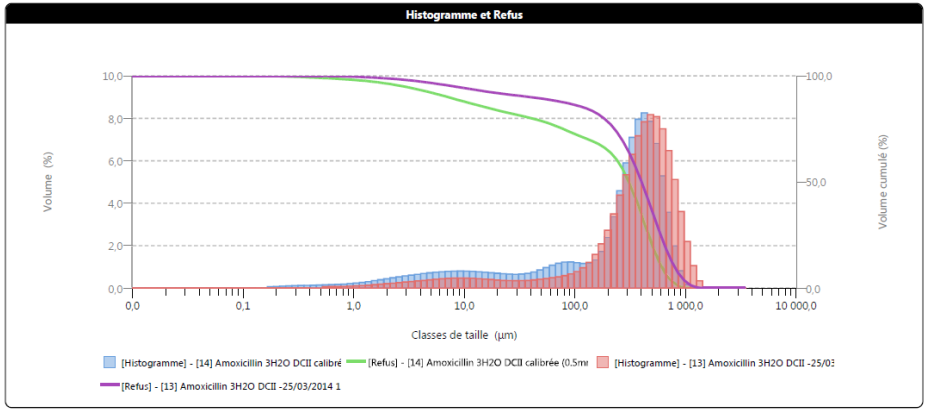
Le séchage du grain est primordiale pour garantir un taux d'humidité résiduelle nécessaire et suffisant pour garantir la qualité du produit final.



La calibration du grain sec

Le procédé de calibration permet de maitriser la taille des particules en minimisant leurs disparités. On parle de population de particules , distribution particulaire.
Le principe de fonctionnement d'un calibreur est la réduction de la taille particulaire obtenu par friction/cisaillement du grain à l'aide d'un rotor/stator, le rotor peut être rotatif ou oscillant

Principe de fonctionnement du calibreur oscillant :



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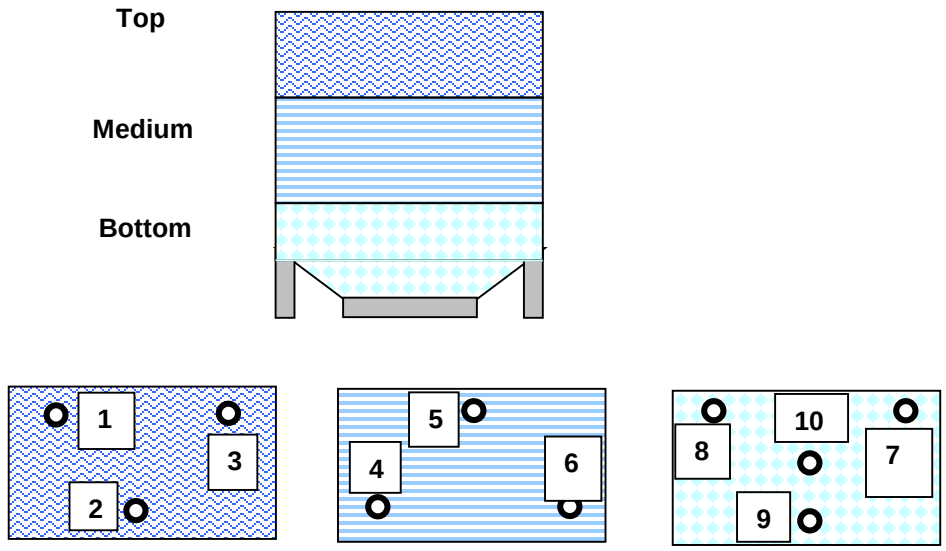
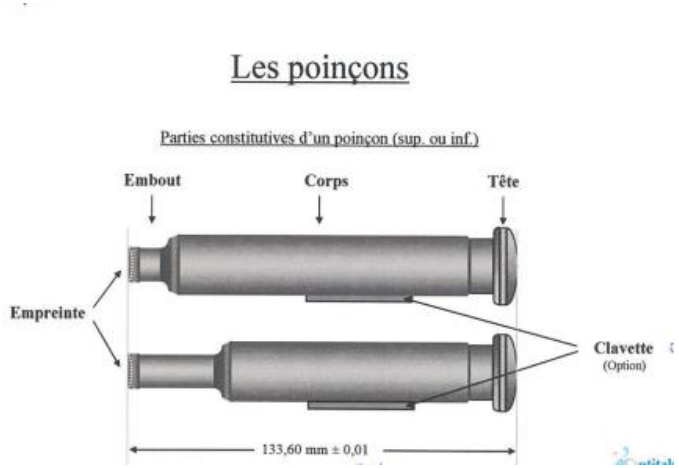
Moyenne			**23,3**	**356**	**707**	**4,54**
1xEcart type			**22,9**	**65,9**	**133**	**1,50**
1xRSD			**98,2**	**18,5**	**18,8**	**33,05**

Mélange Final et compression





La granulation en LAF

En position « Top Spray » le lit d’air fluidisé est utilisé pour la granulation en voie humide, la calibration se fait uniquement sur grain sec , puis mélange et compression

Cas pratiques d'optimisation de procédé exemple de granulation humide à lit d'air fluidisé 1/6

- ***Plan d'expériences***
  - **Domaine expérimental**
- Un grand nombre de paramètres critiques interviennent sur la qualité du grain obtenu par granulation humide en lit d'air fluidisé (débit de pulvérisation, pression d'atomisation, température de l'air entrant, débit d'air de fluidisation…). Le plan d'expériences utilisé permet d'apprécier les effets de deux variables contrôlées : le débit de pulvérisation du liquide de granulation, et la pression d'atomisation. Seules ces deux variables ont été suivies

Cas pratiques d'optimisation de procédé exemple de granulation humide à lit d'air fluidisé 2/6

Un débit de 240 g/min et une pression de 3 bars ont été choisies comme valeurs centrales. Les valeurs extrêmes qui ont été sélectionnées sont les suivantes :

(a) débit : 200 à 280 g/min,

(b) pression : 2,5 à 3,5 bars ;

Tous les autres paramètres étaient constants pour chaque expérience.

Facteurs	Unité	Centre	Pas de variation
X1 Débit de pulvérisation	g/min	240	40,0
X2 Pression d'atomisation	bars	3,00	0,5

Tableau 1 : Variables contrôlées

Cas pratiques d'optimisation de procédé exemple de granulation humide à lit d'air fluidisé3/6

Un plan à 3 niveaux (plan 3k) a été choisi, permettant de déterminer les effets linéaires des variables prises séparément, leur interaction (effet rectangle), ainsi que les effets du second ordre (effets quadratiques) *(cf. figure 1)*.

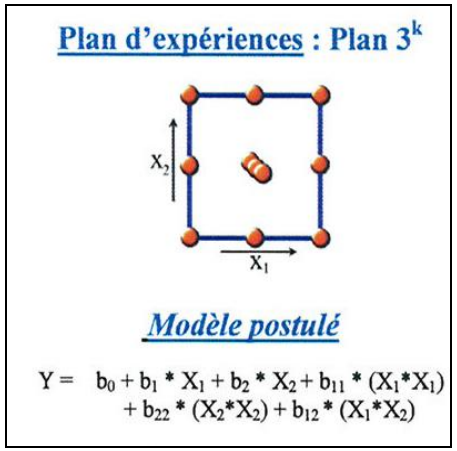


Figure 1 : Modélisation du plan d'expériences 3^k

Cas pratiques d'optimisation de procédé exemple de granulation humide à lit d'air fluidisé 4/6

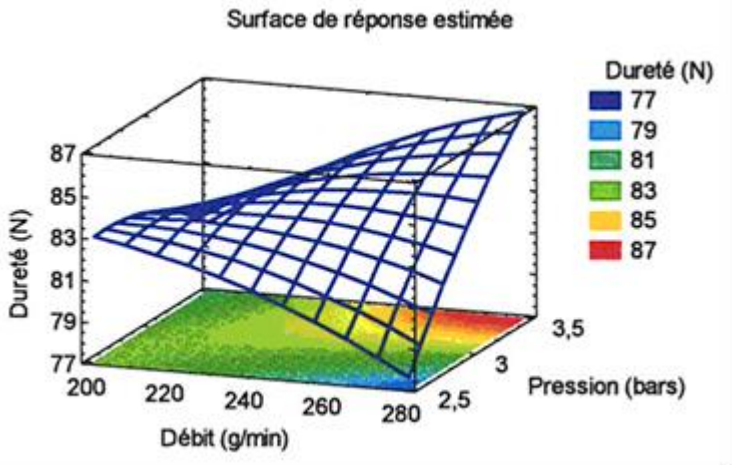


Figure : Surface de réponse estimée pour la dureté des comprimés de format 150 mg

Cas pratiques d'optimisation de procédé exemple de granulation humide à lit d'air fluidisé 5/6

- **CONCLUSION**
- Un plan d'expériences visant à déterminer l'influence de deux facteurs essentiels (débit de pulvérisation et pression d'atomisation) sur la qualité du granulé obtenu et des comprimés réalisés avec celui-ci, a été mis en œuvre. Les intervalles de variation des facteurs ont volontairement été fixés pour correspondre aux conditions opératoires adaptées à l'outil de production. La reproduction (triplicat) de l'expérience au centre du domaine investigué a permis d'évaluer la significativité statistique des effets calculés. De l'ensemble des résultats et de leur traitement statistique il ressort que

Cas pratiques d'optimisation de procédé exemple de granulation humide à lit d'air fluidisé 6/6

- Le procédé de granulation est très robuste dans les intervalles de débit de pulvérisation et de pression d'atomisation étudiés.
- **Les paramètres retenus pour la suite du développement sont les suivants :**
- **Débit de pulvérisation : 260 g/min (± 10 g/min)**
- **Pression d'atomisation : 3,0 bars (± 0,5 bars)**

3.2.P.3.1: Manufacturer (s) of the finished product: The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided

3.2.P.3.2 Batch Formula

A batch formula should be providedfor each batch size that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

Section 3.2.P.3.3: maufacturing process

- A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests, or final product controls are conducted should be identified.
- A narrative description of the manufacturing process including packaging that represents the sequence of steps undertaken and the scale of production, should also be provided. Steps in the process should have the appropriate process parameters identified, such as time, stirring speeds , pressure, temperature, or pH…. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified based on development and validation outcomes
- Equipment , filters ..should be described in this section.
- Any Holding time durations should be stated in particular for sterile production, based on validation outcomes and Media Fill Test for sterile aseptic process

Section 3.2.P.3.4 Controls of Critical Steps and Intermediates

3.2.P.3.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process should be provided to ensure that the process is controlled

Exemple de Contrôles en cours de fabrications: IPCs

S. No.	In -process tests	Sampling quantity	Method	Specification/requirement
Stage –Drying of Granules (After Drying)				
1.	Loss on Drying *(% m/m)*	Approximately 5g (pooled sample)#	**Moisture Balance**	Between 1 – 2
Stage – Lubricated blend (After Lubrication)				
1.	Description	Approximately 25g (pooled sample)#	**Visual**	White to off-white granular powder
2.	Water *(% m/m, By KF)*		**As Per Ph.Eur.**	Not more than 4
3.	Assay *(% Labeled amount)*		**By HPLC***	Mean Value: 95.0 – 105.0
Stage – Compression# (At regular intervals during compression)				
1.	Description	----	**By Physical examination**	White to off white, oval, biconvex, uncoated tablets, debossed with 'HC' on one side and '200' on other side.
2.	Average mass *(mg)*	10 Tablets	**By weighing**	310.00 ± 3%
3.	Hardness *(Newton)*	10 Tablets	**By Hardness tester**	60 – 120
4.	Disintegration time *(min)*	6 Tablets	**As Per Ph.Eur.**	Not more than 15
5.	Friability*(% m/m)*	Equivalent to 6.5g	**As Per Ph.Eur.**	Not more than 1.0
6.	Uniformity of Mass *(% m/m)*	20 Tablets	**As Per Ph.Eur.**	±5 % of Average Mass
Stage – Packaging (At start and at regular intervals)				
1.	Leak Test	---	**By Vacuum Leak test***	Should pass the test

Regulatory requirements for manufacturing Process Validation :section 3.2.P.3.5

Guidelines and ICH :

- •EU Annex 15 and EU PV Guideline
- •FDA process validation guide
- ICH Q10
- Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., Homogenization step, validation of the sterilization process or aseptic processing or filling…).
- Validation of filters (i.e: bacterial challenge, extractable , leachable compatibility) should be also provided.

Section 3.2.P.3.5
Validation du procédé de fabrication
Directives et ICH

Regulatory requirements for Process Validation

- **ICH Q10 Pharmaceutical Quality System : Technology transfer**

The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realisation. This knowledge forms the basis for the manufacturing process, *control strategy*, process validation approach and ongoing continual improvement.

FDA PV Guidance: January 2011

Guidance for Industry

Process Validation: General Principles and Practices

FDA Guidance, 2011

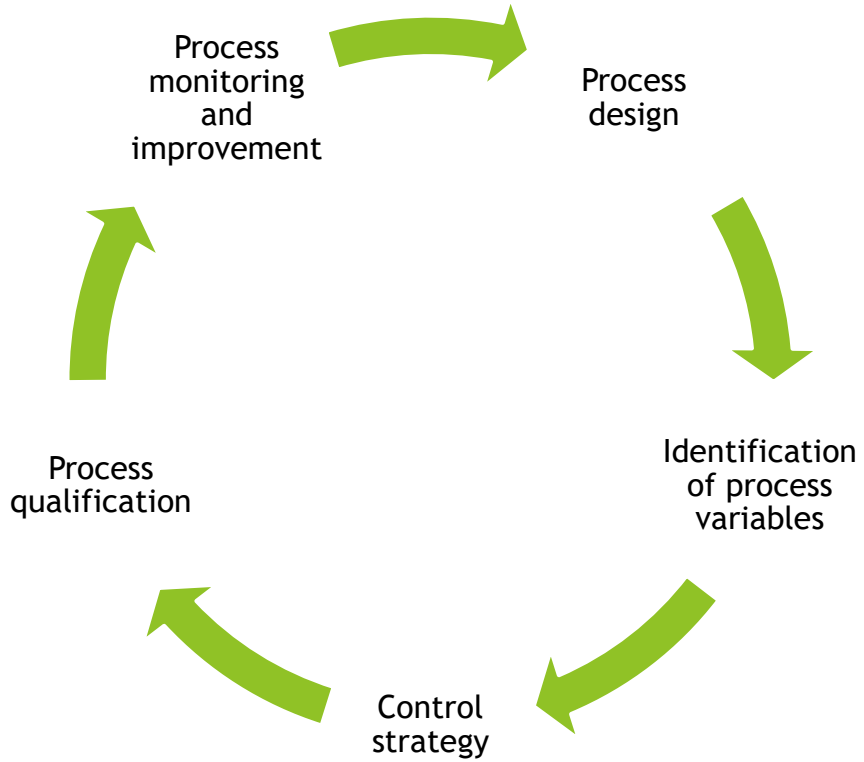
- Process validation definition
- •…the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering (product meeting its CQAs and intended use) quality product

•…involves a series of activities taking place over the lifecycle of the product and process

PROCESS VALIDTAION:

- Process validation involves a series of activities taking place over the lifecycleof the product and process. This guidance describes process validation activities in three stages.
- Process validation should **not** be viewed as **a one-off event**

PROCESS VALIDTAION



PROCESS VALIDATION

- Stage 1 –*Process Design*: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- -Demonstrate a Understanding of the Process
- •Stage 2 –*Process Performance Qualification (PPQ)* or *traditional Process Validation*: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.
- -Demonstrate Process Robustness at Commercial-scale
- •Stage 3 –Continued Process Verification (CPV): Assuring that during routine production the process remains in a state of control.
- -Demonstrate Understanding of Process Variability at Commercial

PROCESS VALIDATION

- **La règlementation pharmaceutique internationale**, en particulier américaine et européenne définit la validation de process en 3 phases ou stages.

  Le stage 1 correspond au design du produit et du procédé de fabrication (couramment appelé développement).

  Le stage 2 couvre la qualification des équipements, QI, QO, QP (stage 2a) et la validation de process (stage 2b). Une fois le procédé validé, il est attendu que la mise en œuvre d'une surveillance soit réalisée, dans un premier temps de manière renforcée (stage 3a), puis de manière routinière (stage 3b).

- L'application de la **guideline CPV** sur des produits « anciens » nécessite de faire une évaluation des résultats passés et la capabilité du procédé de production. Si ce travail met en évidence des lacunes lors du développement une stratégie doit être mise en place.

- **Le stage 3** permet de s'assurer du maintien de l'état validé du procédé ou au contraire d'identifier des dérives de procédé afin de mettre en place des actions correctives au plus tôt. Il requiert la mise en place d'un protocole couvrant les paramètres et contrôles à suivre, ainsi que des critères d'acceptation. Il intègre des notions de statistiques.

PROCESS VALIDATION

- **Establishing a Strategy for Process Control**
- **Control Strategy –**A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to active substance and finished product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

- **Proven Acceptable Range (PAR) –**A characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria. (ICH Q8 R2)
- **Normal Operating Range (NOR) –**A region around the target operating conditions that contains typical operational variability and is within the claimed acceptable ranges. (EMA 25Apr2014 *Draft guideline on process validation for the manufacture of biotechnology-derived active substances*17

La nouvelle philosophie de validation des procédés

- La validation industrielle traditionnelle s'appliquait
  - généralement à 3 lots consécutifs à échelle industrielle,
  - puis aux lots de revalidation via « change control »

- Aujourd'hui les directives Européennes et FDA:
  - la validation d'un procédé n'est pas un évènement temporel dans le développement du produit mais plutôt une validation qui dure tout le long de la vie du produit.
  - Comprend différentes étapes : la conception, et le développement, la fabrication à échelle industrielle, la commercialisation jusqu'à l'arrêt de cette dernière

La nouvelle philosophie de validation des procédés

- Cette approche de monitoring des procédés lors des fabrications de routine intégrant l'analyse de tendance ainsi que les actions correctives et préventives (système CAPA), permet de renforcer les connaissances scientifiques du procédé acquises lors du développement
- le rapport du CPV pourrait être annexé à l'APR (revue annuelle qualité produit)

Etapes du processus de la validation des procédés dans les réglementations Européennes et FDA

CPV Definition

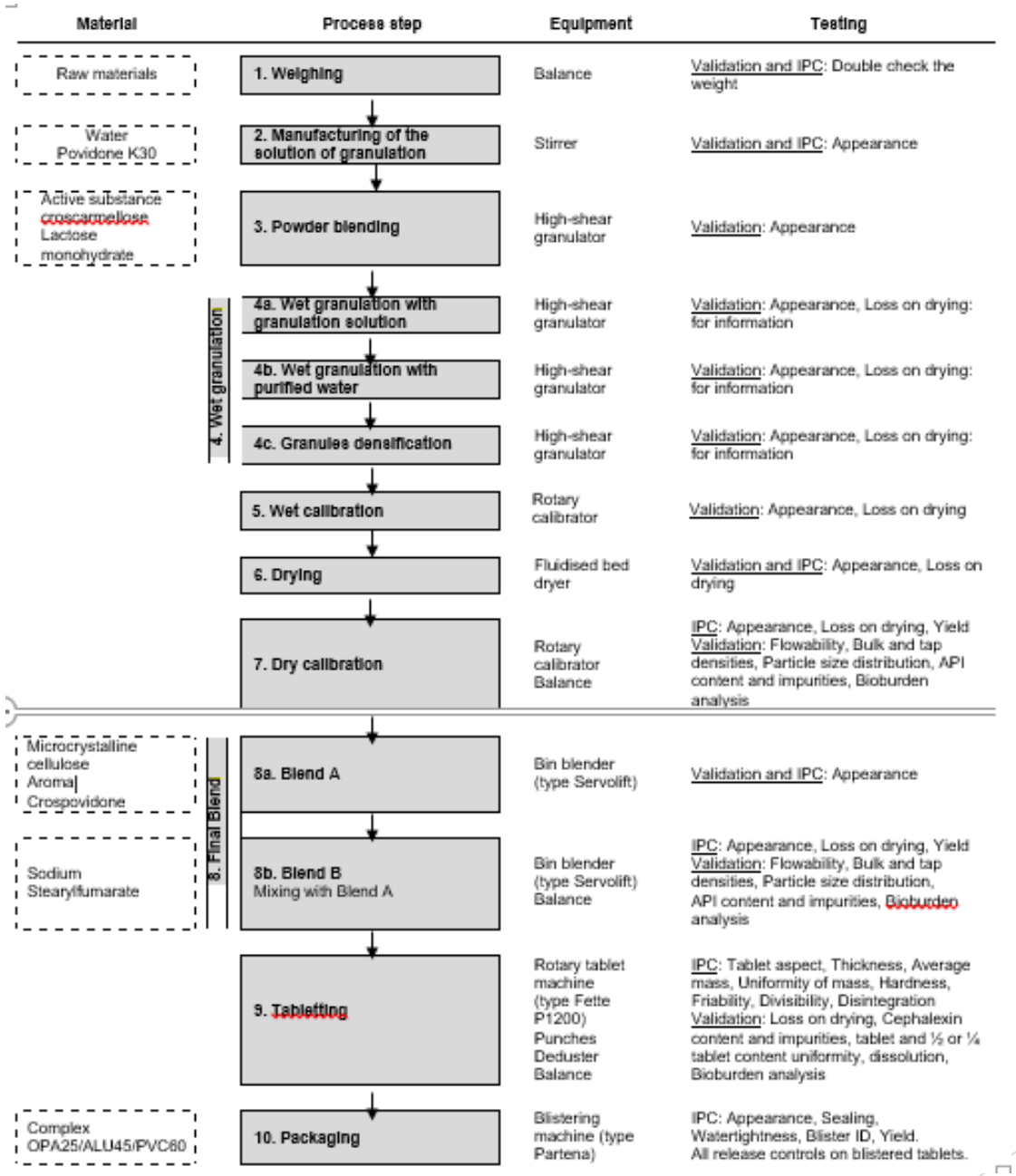
Product Life Cycle

FDA	**Stage 1**	**Stage 2**		**Stage 3**	
	Process design	Process Qualification		Continued Process Verification CPV	
		2.1	2.2	3 (a)	3 (b)
		Utilities & Equipment Design & Qualification (IQ, OQ, PQ)	Process Performance Qualification (PPQ)	Heightened monitoring & sampling until understanding of the process variability	Routine monitoring program
EU	Process Development	Utilities & Equipment Design & Qualification (IQ, OQ, PQ)	Process Validation (traditional)	On-going Process Verification	
			Continuous Process Verification		On-going Process Verification

EU Guidelines for GMP for Medical Products - Annex 15: Qualification & Validation; March, 2015
US FDA, Process Validation: General Principles & Practices; Jan, 2011

Définition des termes

- **« Continous process verification »** est une approche alternative pour la validation de procédé dans laquelle les performances du procédé sont monitorées et évaluées en continu lors de la fabrication. Cette évaluation continue correspond au PAT : process analytical technology (ICHQ 8).
- **« Continued Process Verification »** correspond à l'étape 3 de la validation des procédés décrite dans les directives FDA (*Guidance for Industry Process Validation: General Principles)* et aussi à l'étape **On Going Process Verification** décrite dans les directives Européennes.


Material
Process step
Equipment
Testing
Raw materials
1. Weighing
Balance
Validation and IPC: Double check the weight
Water
Povidone K30
2. Manufacturing of the solution of granulation
Stirrer
Validation and IPC: Appearance
Active substance
croscarmellose
Lactose monohydrate
3. Powder blending
High-shear granulator
Validation: Appearance
4. Wet granulation
4a. Wet granulation with granulation solution
High-shear granulator
Validation: Appearance, Loss on drying: for information
4b. Wet granulation with purified water
High-shear granulator
Validation: Appearance, Loss on drying: for information
4c. Granules densification
High-shear granulator
Validation: Appearance, Loss on drying: for information
5. Wet calibration
Rotary calibrator
Validation: Appearance, Loss on drying
6. Drying
Fluidised bed dryer
Validation and IPC: Appearance, Loss on drying
7. Dry calibration
Rotary calibrator
Balance
IPC: Appearance, Loss on drying, Yield
Validation: Flowability, Bulk and tap densities, Particle size distribution, API content and impurities, Bioburden analysis
Microcrystalline cellulose
Aroma
Crospovidone
8. Final Blend
8a. Blend A
Bin blender (type Servolift)
Validation and IPC: Appearance
Sodium Stearylfumarate
8b. Blend B
Mixing with Blend A
Bin blender (type Servolift)
Balance
IPC: Appearance, Loss on drying, Yield
Validation: Flowability, Bulk and tap densities, Particle size distribution, API content and impurities, Bioburden analysis
9. Tabletting
Rotary tablet machine (type Fette P1200)
Punches
Deduster
Balance
IPC: Tablet aspect, Thickness, Average mass, Uniformity of mass, Hardness, Friability, Divisibility, Disintegration
Validation: Loss on drying, Cephalexin content and impurities, tablet and ½ or ¼ tablet content uniformity, dissolution, Bioburden analysis
Complex
OPA25/ALU45/PVC60
10. Packaging
Blistering machine (type Partena)
IPC: Appearance, Sealing, Watertightness, Blister ID, Yield.
All release controls on blistered tablets.

Le rapport de validation du procédé de fabrication est versé dans le Module 3, section 3.2.P.3.5 du dossier d'AMM

3.2.P.4 Control of Excipients

-3.2.P.4.1 Specifications: The specifications for excipients should be provided and if needed FRC. Reference ICH Guideline: Q6A and Q6B

- 3.2.P.4.2 Analytical Procedures
The analytical procedures used for testing the excipients should be provided, where appropriate, Reference ICH Guidelines: Q2A and Q6B

- 3.2.P.4.3 Validation of Analytical Procedures
Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.
Reference ICH Guidelines: Q2A, Q2B, and Q6B
- 3.2.P.4.4 Justification of Specifications
Justification for the proposed excipient specifications should be provided, where appropriate.
Reference ICH Guidelines: Q3C and Q6B
- 3.2.P.4.5 Excipients of Human or Animal Origin
For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications; description of the testing performed; viral safety data). Reference ICH Guidelines: Q5A, Q5D, and Q6B
-3.2.P.4.6 Novel Excipients
For excipient(s) used for the first time in a drug product or by a new route of administration,

3.2.P.5 Control of Drug Product:

- 3.2.P.5.1 Specification(s)
- 3.2.P.5.2 Analytical Procedures
-3.2.P.5.3 Validation of Analytical Procedures
- 3.2.P.5.4 Batch Analyses
- 3.2.P.5.5 Characterization of Impurities, Reference ICH Guidelines: Q3B, Q5C, Q6A, and Q6B
- 3.2.P.5.6 Justification of Specification(s), Reference ICH Guidelines: Q3B, Q6A, and Q6B

Exemple de spécifications de produit fini

Controls	65 mg Tablet strength	References
Characteristic of tablet	white oblong tablet with 1 breaking line on both sides	
Average mass (mg/tablet)	201.9 - 223.1	
Uniformity of mass	Complies	(Ph. Eur. 2.9.5)
Disintegration	≤ 15 min	(Ph. Eur. 2.9.1)
Content uniformity of tablets	Complies with Ph. Eur. 2.9.40	(Ph. Eur. 2.9.40)
Content uniformity of half tablets	Complies with Ph. Eur. 2.9.40	(Ph. Eur. 2.9.40)
Content uniformity of ¼ tablets		(Ph. Eur. 2.9.40)
Active substance identification	Assay UV spectrum # reference UV spectrum	(Ph. Eur. 2.2.29)
Active substance identity (	Rt assay # Rt reference	Ph. Eur. 2.2.29)
Active substance content (mg/cp)	61.3 - 68.8	(Ph. Eur. 2.2.29)
Impurity A	≤ 0.5%	
Each unspecified impurity (% m/m)	≤ 1.0	
Total unspecified impurities (%m/m)	≤ 1.0	
Total impurities (%m/m)	≤ 3.0	
Dissolution	Complies with Ph. Eur. 2.9.3. with Q = 80% in 15 min	(Ph. Eur. 2.9.3)
TAGC* (cfu/g) (	≤ 10^3	Ph. Eur. 2.6.12)
TMYC* (cfu/g)	≤ 10^2	(Ph. Eur. 2.6.12)
Escherichia coli	None/g	(Ph. Eur. 2.6.13)

3.2.P.6 Reference Standards or Materials:

Information on the reference standards or reference materials used for testing of the drug product should be provided

3.2.P.7 Container Closure System: Conditionnement Primaire

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate.

3.2.P.8 Stability

- 3.2.P.8.1 Stability Summary and Conclusion :
The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life.

- 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

- 3.2.P.8.3 Stability Data
Results of the stability studies should be presented in an appropriate format (e.g. tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included