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Regulatory affairs to elaborate a pharmaceutical marketing autorization application for microencapsulated drug delivery systems

Thierry Vandamme, Jean-Yves Pabst

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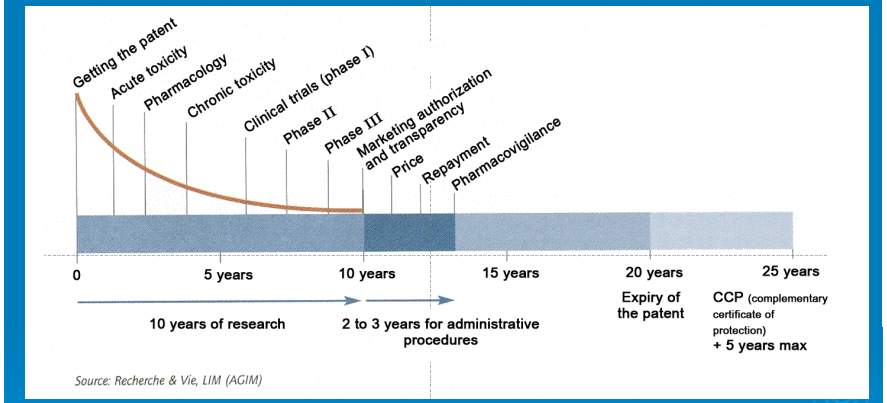


Marketing autorization

1. General aims of a request for a marketing autorization (considering (2) et (3) of community code relating to the drugs of human use)

2. Field of application:

   Products being the subject of a request of a marketing autorization

   Products not being the subject of a request of a marketing autorization

2. Products being the subject of a request of a marketing autorization

(L.5121-8 du CSP)

- Industrially prepared drugs
- Marketing autorisation delivered for 5 years, renewable
- Any modification of the marketing autorisation must be autorized beforehand
- The marketing autorisation can be modified, supended or withdrawn by the european agency or by the agency of the government

3. Conditions of granting of a marketing autorization

- Conditions of funds
- Formal requirements
- Means:

  Standards and protocols for the execution of the tests on the drugs (*Dir.2003/63/CE modified)*

4. The lawful corpus applicable to the health products

- Community Sources
- National Sources
- International Sources

The rules Governing Medicinal Products in European Union

Pharmaceuticals►EudraLex

Volume 1 Pharmaceutical Legislation
Volume 2 Notice to Applicants
Volume 3 Guidelines
Volume 4 Good Manufacturing Practices
Human and veterinary

The rules Governing Medicinal Products in European Union

Volume 5 Pharmaceutical Legislation
Veterinary Medicinal Products
Volume 6 Notice to Applicants
Veterinary Medicinal Products
Volume 7 Guidelines
Veterinary Medicinal Products
Volume 8 Maximum residue limits
Volume 9 Pharmacovigilance Human+ Veterinary

Pharmaceutical Legislation

- Directives
- Regulations
- Miscellaneous (opinion with the applicants, explanatory notes, recommendations)

Lawful Sources

- Public health code
- Code of the social security
- Code of the intellectual property
- Good practices (published in Official Journal)
- Pharmacopeias
- Other regulations (environment, Genetically Modified Organism,…)

…*ISO, HACCP*…?

Para-legal standards

- ICH: guiding lines
- Standards resulting from the knowledge of the state of the art
- Learned Societies (SFSTP,…)

4. Presentation and structure of the request file of the marketing autorization

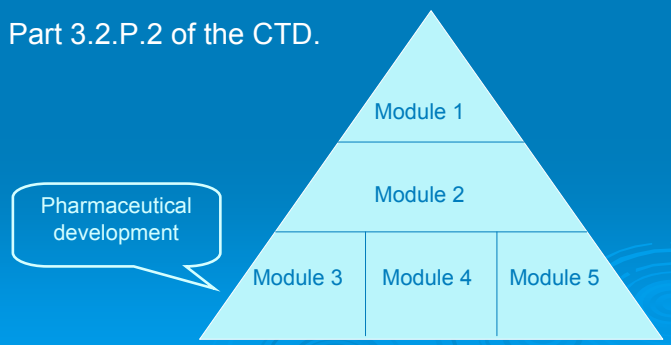
- Format of request: CTD
- Complete record (*full application*)
- Shortened file (*abridged application*)

Common technical document

- Modules
- Contents of the modules
- Opinions of the applicants
- Standards and analytical protocols, pharmaco-toxicological and clinical applicable as regards tests of drugs

INTRODUCTION

- Part 3.2.P.2 of the CTD.



Module 1

Administrative Information and Prescribing information

Module 1.1- Comprehensive Table of Contents

Module 1.2- Application Form

Module 1.3- Summary of Product Characteristics

Module 1.4- Information about the Experts

Module 1.5- Specific requirements for different types of applications

Module 2

- 2.1 Overall CTD table of contents of modules 2,3,4&5
- 2.2 Introduction
- 2.3 Quality overall summary
- 2.4 Nonclinical overview
- 2.5 Clinical overview
- 2.6 Content of nonclinical written and tabulated summaries
- 2.7 Clinical summary

Module 3

- 3.1 Module 3 table of contents
- 3.2 Body of data
  - 3.2.S Drug substance
  - 3.2.P Drug product
  - 3.2.A Appendices
- 3.3 Literature references

Module 4

- 4.1 Module 4 table of contents
- 4.2 Study report
  - 4.2.1 Pharmacology
  - 4.2.2 Pharmacokinetics
  - 4.2.3 Toxicology
- 4.3 Literature references

Module 5

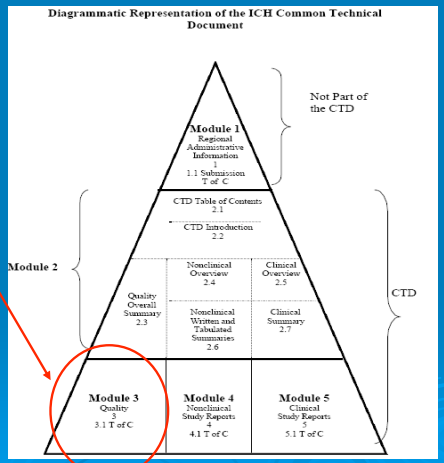
- 5.1 Module 5 table of contents
- 5.2 Tabular listings of all clinical studies
- 5.3 Clinical study reports
- 5.4 Literature references

Marketing autorization

Guideline: Chemistry of active substances

- Explanatory note part 2, section C of the directive 75/318/EEC relates to the chemistry of the active substance.
- Goal: to highlight the necessary informations for the control of a substance activates lately used when this one does not have a monograph in the pharmacopeias.
- Field of application: CTD module 3 part 3.2.S active ingredient

Module 3 of the CTD
Field of application of the explanatory note



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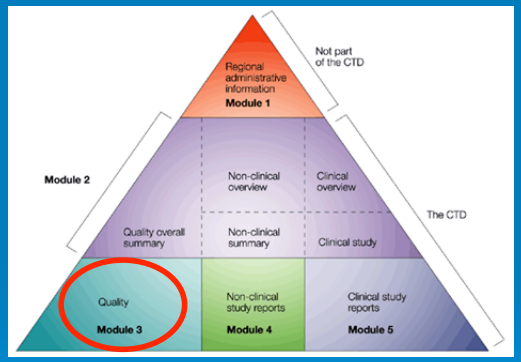
Note for guidance on pharmaceutical development ICH Q8

EMEA/CHMP/1670468/2004-ICH

Note for Guidance on Pharmaceutical Development (ICH Q8)



Part 3.2.P.2 Pharmaceutical Development of the module 3 of the CTD

Marketed product

- Development of a formulation :
  - To provide a summary of the manufacturing process with the identified critical points
  - To describe any change in the formulation
- Overdoses :
  - Overdose in active substance disadvised.
  - If overdose: ⇨ to justify
- Physicochemical and biological properties :
  - To identify if affect safety, performance, manufacture.
  - Tests carried out to justify

Other characteristics

- Development of the manufacturing process :
  - Steps and choices to be described and to be justified
- System of closing of the container :
  - To determine according to the use, the preservation, the transport and the characteristics of the product
- Microbiological data:
  - To provide the limits of contamination, the data on the choice and the effectiveness of the preservatives
  - To show the absence of the contamination of the sterile products

Marketing autorization

Impurities Testing : Impurities in New Drug Substance Guideline ICH Q3A (R2)

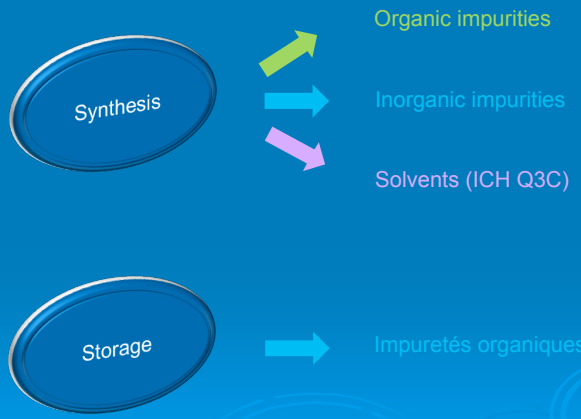
Impurity testing: impurities in New Drug Substance Guideline ICH Q3A (R2)

- Part concerned : Module 3 of the CTD, active substance part
- Type of document : guiding line (Guideline)

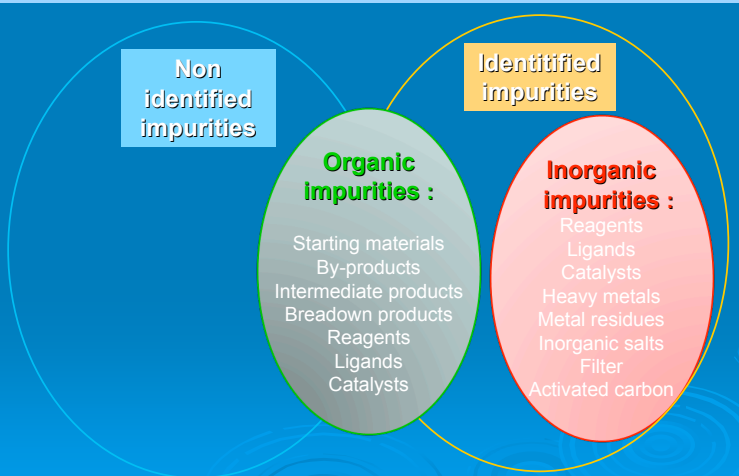
Subject : Determination and quantitation of the impurities for a New Active Substance (NAS)

Goal: drafting of the impurity part of the certificate analysis of batch of NAS

Classification of the impurities



Classification of the impurities



Description and control of the impurities

- Report of analysis of batches. → Real and potential impurities

Maximum amount per day	Threshold of description	Threshold of identification	Threshold of qualification
≤ 2 g / day	0.05%	The more less amount between 0,10% and 1,0 mg per day	The more less amount between 0,15% and 1,0 mg per day
> 2 g / day	0.03%	0.05%	0.05%

Indexed impurity — Characterized structure — Harmlessness of the proven impurity

Note : precision of the analysis and the values
value < 1.0% → 2 decimals
value > 1.0% → 1 decimal

Qualification of the impurities

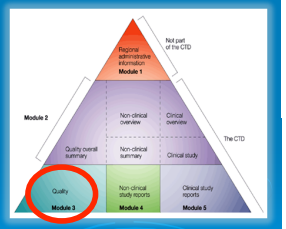
- Process of acquisition and evaluation of the data
  → **Biological safety of the impurity**
  Example: clinical and preclinical studies
- Comparison NAS with individually qualified impurities
- Si threshold exceeded and data insufficient
  → **Complementary studies**
- Flexible threshold of qualification

Marketing autorization

CPMP/QWP/130/90 Rev. 1: GUIDELINE ON THE CHEMISTRY OF NEW ACTIVE SUBSTANCES

NATURE of the DOCUMENT

- Adopted in December 2003
- Coming into effect in February 2004
- Application of the directive 2001/83/EEC
- **Part of the CTD concerned: 3.2.S**
- Goal of the revision: displacement of the définition of the active substance from 3.2.S.2.2 to 3.2.S.2.3

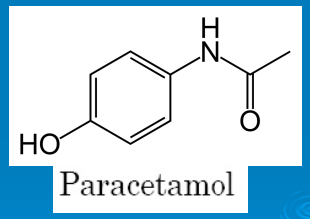


FIELD of APPLICATION

- Present the type of informations required for the new chemical entities
- Applicable to the semi-synthetic substances
- Non applicable to:
  - The biological products
  - The products resulting from the biotechnologies
  - The radiopharmaceutical and radiolabelled products

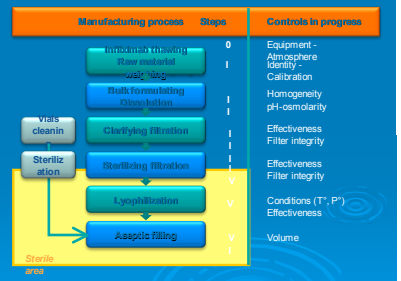
CORPS DU DOCUMENT: 3.2.S.1

- **3.2.S.1 General informations**
  - Identity
  - Nomenclature
  - Chemical structure
  - Pharmaceutical application
- *3.2.S.1.1 Nomenclature*
  - INN
  - Names
  - CAS
- *3.2.S.1.2 Structure*
- *3.2.S.1.3 General properties*



MAIN PART OF THE DOCUMENT: 3.2.S.2

- **3.2.S.2. Manufacturing**
- *3.2.S.2.1 Manufacturers*
- *3.2.S.2.2 Control and process of manufacturing*
  - Diagram of the stages of the manufacturing
  - Written description
  - Output manufacturing, scale
  - Alternative process



MAIN PART OF THE DOCUMENT: 3.2.S.2

- *3.2.S.2.3 Control of the materials*
- *3.2.S.2.4 Control of critical stages*
  - Critical stages: tests and tolerance, definition of a critical stage
  - Intermediary: identity et control
- *3.2.S.2.5 Validation and evaluation*
- *3.2.S.2.6 Development of the manufacturing process*

MAIN PART OF THE DOCUMENT: 3.2.S.3

- **3.2.S.3 Caracterization**
- *3.2.S.3.1 Structure and other characteristics*
  - Description of the chemical structure
  - Physico-chemical characteristics *(Solubility, polymorphism, pK, pH,…)*
- *3.2.S.3.2 Impurities*

MAIN PART OF THE DOCUMENT: 3.2.S.4

- **3.2.S.4 Control of the active substance**
- *3.2.S.4.1. Specificity*
  - Description
  - Identification
  - Impurities
  - Trials
- *3.2.S.4.2. Analytical procedures*
  - Développement analytique
- *3.2.S.4.3. Validation of the analytical processes*
- *3.2.S.4.4 Control*
- *3.2.S.4.5 Justification of the specifications*

MAIN PART OF THE DOCUMENT: 3.2.S.5

- **3.2.S.5 Standard references and materials**
- Information concerning materials of reference
  - Specifications
  - Physicochemical characteristics
  - Caracteristics of the impurities
  - Criteria used to establish the substances of references for the rapid analyses

MAIN PART OF THE DOCUMENT: 3.2.S.6

- **3.2.S.6 Container**
- Description of the storage systems
  - Materials
  - Protection
  - Justification of the choices
  - Primairy and secondairy packgging

ICH HARMONISED TRIPARTITE GUIDELINE

IMPURITIES: GUIDELINES FOR RESIDUAL SOLVENTS Q3C (R3)

❖Goal :

To define the acceptable limits for the residual solvents ➞ Safety for the patients

❖Definition :

Residual solvent:
Volatile organic chemical substance

Product Used } during the synthesis of the drugs (active ingredients), excipients, end-products

❖Choice of the residual solvent :

According to the toxicity

Influence on : The yield (↗)
The form
The purity } of the crystal
The solubility

Any therapeutic effect

❖Extension of the directive :

✓ Measure of the content of solvent

➢ End-product analysis

➢ Analysis of the raw materials ➞ Amount of residual solvents into the end-product

• Result < or = to the defined limits ➞ Any additional test

• Result > to the defined limits ➞ Trial to the end-product

↓

Manufacturing process has allowed to ↘ the amount of residual solvents

✓Field of application

Application to:
• all proportionings
• all shapes } of a drug

No application:
• to the drugs under development
• to the excipients and products used for clinical research
• to the already marketed drugs

✓Exceptions

Local application
Duration of use < 30 days } Amount > accepted ➞ Justification

❖ General principle :

Classification **according to the potential toxicity** for Humans

Classe 1: To avoid absolutely (toxixicity for Humans and for the environment, carcinogenic)
Classe 2: Tolerated use but to avoid (carcinogenic for animals)
Classe 3: To use preferentially (slightly toxic for Humans)

Example of solvents :

Class 1	**Benzene, 1,2-Dichloroethane, 1,1-Dichloroethene …**
Class 2	**Acetonitrile, Chloroforme, Methylene chloride, Hexane, Methanol …**
Class 3	**Acetic acid, Acetone, Ethanol, Formic acid …**

Determination of the authorized limit for the solvents of class 2

Option 1

➡ Daily consumption < 10g

$$Concentration\ (ppm) = \frac{1000 \times PDE}{Dosis}$$

PDE = Permitted Daily Exposure

Option 2

Optional → Option 1 non applicable

Acceptable limits = amount of residual solvents reduced to the maximum

❖ Analytical method :

Gas chromatography: the more used

⇨ **Harmonized method of the European Pharmacopeia**

If not: the manufacturer chooses the most adapted analytical method

If only solvents from class 3 : a simple method is enough (weight loss to the drying...)

The raw material supplier (excipient, drug) must provide to the manufacturer documents attesting of the contents of residual solvents of the proprietary medical products.

❖Limitations to the residual solvents :

Three categories of solvents :

Categories	Characteristics	Permitted Limits	Examples
Class 1	To avoid absolutely : toxic for the environment, carcinogenic	A few ppm/j	Benzene 1,1,1 Trichloroethane Chloroforme
Class 2	Tolerated use but to be avoided	0.6 à 48.4 mg/days (PDE)	Methanol Formamide
Class 3	To be used preferentially Slighly toxic Humans	Pas de limites précises si usage cohérent avec les protocoles	Acetone Ethanol Acetic acid

Note : Fourth class of solvents → any information on the toxicity, then to be avoided (Ether, Trichloroacetic acid…)

❖Method for the determination of the permitted daily exposure (PDE) :

Determination used for the solvents of class 2 :

$$PDE = NOEL \times weight / (F1 \times F2 \times F3 \times F4 \times F5)$$

NOEL : No Observed Effect Level

Weight : Body weight adjusted (50 kg)

F1 à F5 : Factors loadings

- **F1 : Factor of extrapolation enters the animal specie used and the Humans (12 for the mouse, 2 for the dog…)**
- **F2 : Interindividual variance (generally fixed at 10)**
- **F3 : It reflects the study of toxicity for an exposure to short-term.**
- **F4 : is given if generated toxicity is severe (reprotoxicity, neurotoxicity…)**
- **F5 : If NOEL is not determined**

❖**Conclusion :**

✓**Classification of the solvents**

- Toxicity for Humans et for the environment
- To insure the security of the patients during the use

✓**Détermination of the permitted daily limites exposure (PDE)**

✓**Concept of green chemistry :**

- Use of the less toxic solvents

PHARMACEUTICAL DEVELOPMENT

CMPM/QWP/155/96

Goal

❖ To verify that the chosen dosage form and the formulation are satisfying for their application.

Range

❖ Manufacturing production from the laboratory scale: 0.1 to 1% of the size of the industrial batch.

❖ Pilot batches: 10% of the size of the industrial batch.

COMPONENTS OF THE END- PRODUCT

❖ Drugs

- Compatibility studies.
- Studies of the physicochemical characteristics.

❖ Excipients

- Justified choice, due to their functionality and their compatibility.

END-PRODUCT

❖ **Solid dosage forms**

- Homogeneity
- Performance testings
  - ➢ Desagregation
  - ➢ Dissolution

→ Food interaction to be demonstrated.

END-PRODUCT

❖ **Other pharmaceutical dosage forms**

- Transdermal patches:
  - ➢ Physicochemical properties, activity, biocompatibility and clinical goal of the drug.
- Inhalers:
  - ➢ Delivered dosis by the inhaler.
  - ➢ The uniformity of the content of each dosis.
- Dried powders for inhalation:
  - ➢The size, the shape, the roughness and the charge of the particles.
  - ➢ The flow properties of the mixture.

MATERIAL FOR THE CONTAINER

❖ Choice of the material for the primary container.

❖ Integrity of the container and reproducibility of the dosis.

❖ Absorption or adsorption to the primary container.

❖ Reproducibility of the dosis.

MANUFACTURING PROCESSES

❖ Appropriate manufacturing method for the end-product with appropriate raw materials.

❖ Development studies on microbiological, physical and chemical controls.

Guideline on stability testing:

STABILITY TESTING OF EXISTING ACTIVE SUBSTANCES AND RELATED FINISHED PRODUCTS
CPMP/QWP/122/02 Rev 1 corr

Guideline : ICH Q1A(R2) :
« Stability testing of new drug substances and products »

General principles

- To evaluate the variations of the quality for a drug during the time:
  - Relative Humidity (RH)
  - Temperature
  - Light
- In order to determine:
  - the storage conditions
  - the periods for the controls
  - the time for the storage

Storage conditions

General scheme

Study	Storage conditions		Minimal period of time for which the data have to be given
	Temperature (°C)	Relative Humidity (%)	
Long term	25 ± 2 ou 30 ± 2	60 ± 5 ou 65 ± 5	12 months
Intermediate	30 ± 2	65 ± 5	6 months
Accelerated	40 ± 2	75 ± 5	6 months

Selection of batches

- Data from a minimum of 3 batches of end-products (pilot scale batches)
- 1st batch : same formulation
  same container
  same manufacturing
  } than for industrial production

⟹ same quality and specifications

- 2/3 batches : suitable size = 1/10e of a batch for production
- If possible, several different batches of drug in order to obtain a end-product batch.

Trial of Photostability

- Realized on a minimum of one primary end-product
- General conditions described into the guideline Q1B

⟹ To define the sensitivity of the product to the light

⇓

To describe the storage conditions

Container

Stability testings on the container (I et II)

Also, trials : end-product outside of the container I (g^{al} case)

different materials for the container (Eur. Ph. VI ed.)

⟹ Stability data for the trials of forced degradation

- Waterproof container : any test on the humidity or loss of solvent.
- Semi-permeable container: loss of water, physical chemical, biological and microbiological stability.

⟹ Coefficient for permeability of the container I

Specifications

List of trials (analytical, functionnality, preservatives)
Criteria for acceptance (validation of batch + duration) } Q6A/Q6B

Degraded product from end-product } Q3B

Properties from products which can be modified during the storage

⇓

Modification of the quality, the safety and the efficacy

Criteria of acceptance for the duration ⟺ data on the stability

Frequency of trials

Study for a long term ⟹ sufficient to establish the profile for the storage

⇒

Accelerated study minimum 3 additional controls (0, 3, 6 months), 4^{th} control or more samples if changes.

If changes :

⇒

Intermediate study 4 additional controls (0, 3, 6, 12 months)

Storage conditions

• Trials have to define the storage, the sending and the use

• Trials after reconstitution/dilution and after closing by user

⟹ Long term and accelerated studies

Particular cases : storage in a refrigerator
storage in a freezer

Valuation

- Agreement if low degradation and high variability[(1)]:

(1) - Loss of 5% of drug

- Amount of degraded products higher than the specifications

- pH outside of the specified limits

- Dissolution speed lower than the specified limits

- Specifications relative to the appearence and to the non respected physical properties .