Relevant regulatory aspects and challenges involved with medicines registration in Brazil

Andressa Regina Antunes

Discente de Pós Graduação *Stricto Sensu* em Ciências Farmacêuticas (UNIOESTE)

Analista Pleno de Assuntos Regulatórios - Prati Donaduzzi Medicamentos Genéricos

antunes.andressa@hotmail.com

andressa.antunes@pratidonaduzzi.com.br

- **Rules and their origin**

Agência Nacional
de Vigilância Sanitária

- Regulamentation
- Evaluation

(products, process, documentations)

- Fiscalization

• Goals

- Protection of health secure
- Patient security
- Safe therapy

The register of a new product

- **Steps of process analysis**

1) Pharmacotechnical
2) Efficacy
3) Security

- **Steps of process analysis**

1) Pharmacotechnical (all steps of development)

- Materials acquisition (sources)
- Manufacturing process
- Quality Control, Stability studies
- Release
- Stocking
- Expediction/Dispatch
- And other related control.

- **Steps of process analysis**

1) Pharmacotechnical (all steps of development)

- Stages:

i) Is all necessary documentation present in the process?

ii) Technical report evaluation

- **Steps of process analysis**

1) Pharmacotechnical (all steps of development)

ii) Technical report evaluation

- Clinical studies and Pharmacothecnichal
- Batch manufacturing report
- Package leaflet and Labeling
- **Active Ingredients Technical Information***

- **Steps of process analysis**

ii) Technical report evaluation

- Stability studies:
  - Long term
  - Accelerated
  - Zone Ivb*
  - Forced degradation
  - Photostability
- Pharmacokinetic and Pharmacodynamic
- Manufacturing process and Quality Control

*ANVISA - RDC 45 – August 2012

- **Steps of process analysis**

2) Efficacy
3) Security

Active Pharmaceutical Ingredients Technical Information*

- Drug Master File (DMF)
- CTD format
- Common Technical Document (FDA, EMEA and WHO)
- **Purpose:**

  Propose an adecquate format for documents presentation.

Active Pharmaceutical Ingredients Technical Information*

- Drug Master File (DMF)
- General information about API and their manufacturer,
- Manufacturing process:
  - Fluxogram
  - Synthesis route

Active Pharmaceutical Ingredients Technical Information*

- Drug Master File (DMF)
- Impurities:
  - Synthesis route
  - Organic impurities (Pharmacopoeia)
  - Inorganic impurities
  - Residual solvents
  - Degradation products
  - Genotoxics

Active Pharmaceutical Ingredients Technical Information*

- Drug Master File (DMF)
- Polymorphism, Isomerism,
- Quality Control,
- Packing Material,
- Analythical procedures,
- Validations of analythical procedures,
- Stability Studies

MODULE 3 – QUALITY		
CTD	**EU CTD (NTA, Vol. 2B, Edition 2001)**	**NTA, Vol. 2B (Edition 1998)**
3.1	MODULE 3 TABLE OF CONTENTS	---
3.2	BODY OF DATA	Chemical, Pharmaceutical, Biological Documentation
3.2.S	DRUG SUBSTANCE	
3.2.S.1	General Information	Scientific Data
3.2.S.1.1	Nomenclature	Nomenclature
3.2.S.1.2	Structure	Description: Structural formula
3.2.S.1.3	General Properties	Physico-chemical characterization
3.2.S.2	Manufacture	Manufacture
3.2.S.2.1	Manufacturer(s)	Name(s) address(es) of the manufacturing source(s)
3.2.S.2.2	Description of manufacturing process and process controls	Synthetic or manufacturing route Description of process
3.2.S.2.3	Control of materials	Quality control during manufacture
3.2.S.2.4	Controls of critical steps and intermediates	Quality control during manufacture
3.2.S.2.5	Process validation and/or evaluation	---
3.2.S.2.6	Manufacturing process development	---
3.2.S.3	Characterisation	
3.2.S.3.1	Elucidation of structure and other characteristics	Development chemistry
3.2.S.3.2	Impurities	Impurities
3.2.S.4	Control of drug substance	Specifications and routine tests
3.2.S.4.1	Specification	Specifications and routine tests

CTD	EU CTD (NTA, Vol. 2B, Edition 2001)	NTA, Vol. 2B (Edition 1998)
3.2.S.4.3	Validation of analytical procedures	Development Chemistry: Analytical Validation
3.2.S.4.4	Batch analyses	Batch analysis
3.2.S.4.5	Justification of Specification	Development Chemistry: Comments on the choice of routine tests and standards
3.2.S.5	Reference Standards or Materials	Development chemistry: Full characterization of the primary reference material Batch analysis: Reference material
3.2.S.6	Container Closure System	---
3.2.S.7	Stability	Stability Tests on Active Substance(s)
3.2.P	DRUG PRODUCT	
3.2.P.1	Description and composition of the drug product	Composition and container (brief description)
3.2.P.2	Pharmaceutical Development	Development Pharmaceutics and clinical trial formulae
3.2.P.2.4	Controls and critical steps and intermediates	Manufacturing process (including in-process control and phamraceutical assembly process) Control tests on intermediate products
3.2.P.3	Manufacture	Method of Preparation
3.2.P.3.1	Manufacturer(s)	Administrative Data
3.2.P.3.2	Batch formula	Manufacturing Formula
3.2.P.3.3	Description of Manufacturing Process and Process Controls	Manufacturing Process (including In-process Control and Pharmaceutical Assembly Process)
3.2.P.3.4	Controls of critical steps and intermediates	Manufacturing Process (including In-process Control and Pharmaceutical Assembly Process)
3.2.P.3.5	Process validation and / or evaluation	Validation of the Process
3.2.P.4	Control of excipients	Excipients(s)
3.2.P.4.1	Specifications	Specifications and routine tests

3.2.P.4.3	Validation of analytical procedures	Scientific data
3.2.P.4.4	Justification of specifications	Scientific data
3.2.P.4.5	Excipients of human or animal origin	---
3.2.P.4.6	Novel Excipients *(ref to A 3)*	Excipient(s) not described in a pharmacopoeia Scientific data
3.2.P.5	Control of drug product	Control Tests on the Finished Product
3.2.P.5.1	Specification(s)	Product specifications Quality specifications for the proposed shelf life
3.2.P.5.2	Analytical Procedures	Control Methods
3.2.P.5.3	Validation of Analytical Procedures	Analytical validation of methods
3.2.P.5.4	Batch analyses	Batch analysis
3.2.P.5.5	Characterisation of Impurities	---
3.2.P.5.6	Justification of specification(s)	Comments on the choice of routine tests and standards
3.2.P.6	Reference Standards or Materials	Batch analysis: Reference material
3.2.P.7	Container Closure System	Packaging Material (Immediate Packaging)
3.2.P.8	Stability	Stability Tests on the Finished Product
3.2.A	APPENDICES	
3.2.A.1	Facilities and Equipment	---
3.2.A.2	Adventitious Agents Safety Evaluation	---
3.2.A.3	Excipients	---
3.2.R	REGIONAL INFORMATION	Validation of the process
3.3	LITERATURE REFERENCES	OTHER INFORMATION

Regulamentations

- RDC 899, 2003 (Validations)
- RDC 57, 2009 (API Register)
- RDC 45, Agosto de 2012 (Stability studies)
- RDC 60, 2014 (Medicines Registration)
- RDC 53, 2015 (Degradation Products)
- RDC 73, 2016 (Medicines Post Registration)
- ICH – Q1B (Photostability)
- ICH – Q3A and Q3D (Impurities)
- ICH – M7 (Mutagenic impurities)

• Challenges

✓ Regulamentations constantly updated

✓ Short deadlines for adequacy

✓ Greater coast in the product development

(people, equipments, new studies, robust documentation, internal documental evaluation….)

• Challenges

✓ Maintenance of Agility and Quality on analysis

✓ **Nowadays:**

Deadline for process evaluation is between 3 - 6 years.

✓ **Main problem:**

When the process is evaluated, the regulamentation may already have been changed/updated.

• Challenges

✓ **ANVISA** x **FDA** x **ICH** x **EMEA**

- Some specific requirements are made just by ANVISA

Ex: Stability study at Zone IVb (30 +/- 2ºC, 75 +/- 5%).

- **Updated news**

9th November, 2016

Anvisa é novo membro do ICH

Agência foi aceita como membro do International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). O grupo reúne autoridades reguladoras e associações de indústrias farmacêuticas para discutir registro de medicamentos.

• Industry Advantages

- Manufacturing facilities
- Products
- Employees
- Professional growth

• Negative points

- New regulations can to destructure temporarily a company
- Demissions
- Spents with documental, anaythical and structural adjustments

- **What happens if…?**

✓ The company have no attention in some item of legislation?

• Some penalities

- Collection of products,
- Suspension of production,
- Loss of product registration,
- Some unforeseen expenses (milions/bilions)

11th November, 2016

SAÚDE

Anvisa suspende produção de amoxilina em 6 laboratórios

Fiscalização

Processo de síntese do insumo farmacêutico foi alterado sem a aprovação da agência

• Final considerations

✓ To follow the updated information about medicines regulamentation constantly,

✓ Time for process evaluation,

✓ **Alternative:**

To work with better quality in order to send to ANVISA the most complete and robust documentation.

CISDEM
CÁTEDRA IBEROAMERICANA-SUIZA
DE DESARROLLO DE MEDICAMENTOS

unioeste
Universidade Estadual do Oeste do Paraná

THANK YOU!

prati
donaduzzi

Bibliografia

- ANVISA (http://portal.anvisa.gov.br/)
- ICH – Q1B - (Photostability)
- ICH – Q1A(RS) & Q1E – (Stability studies)
- ICH – Q3C(R5) – (Residual Solvents)
- ICH – Q2B – (Validation of Analythical Procedures)
- M7 – (Mutagenic impurities)
- RDC 57 – November/2009 (API register)
- RDC 45 – Agosto/2012 (Stability studies)
- RDC 60 – Dezembro/2014 (New Products Registration)
- RDC 73 – Abril/2016 (From january/2017)
- U.S. Food and Drug Administration - FDA eCTD Overview and Submission WBT (2016) http://www.accessdata.fda.gov/scripts/cder/training/eCTD/backgr/backgr/fd_02_01_0040.htm