RDC nº53/2015: challenges on impurities qualification

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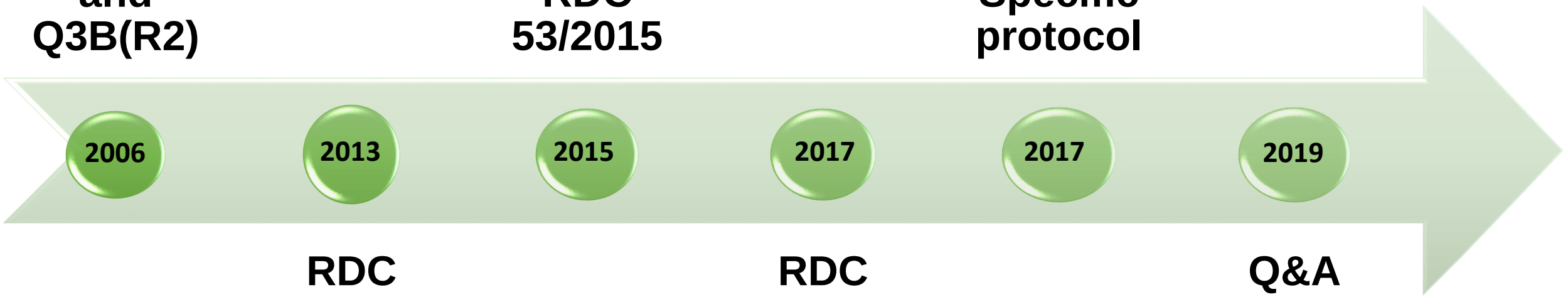
Regulatory marks

When qualify according to RDC nº53/2015?

How to qualify?

- Metabolites
- Literature
- Toxicity assessment
  - **Genotoxicity**
  - **General toxicity**

Regulatory marks



When qualify?

Art. 9°: Reporting, identification, and qualification thresholds

Qualification thresholds for drug product according to RDC nº 53/2015 and Q3B(R2)

Maximum Daily Dose	Threshold
<10 mg	1.0% or 50 µg TDI
10 mg-100 mg	0.5% or 200 µg TDI
>100 mg - 2 g	0.2% or 3 mg TDI
>2 g	0.15%

Qualification thresholds for drug substance according to Q3A(R2)*

Maximum Daily Dose	Threshold
≤ 2 g	0.15% or 1.0 mg TDI
> 2 g	0.05%

*Out of scope of RDC nº53/2015

➢ **If controlled only on API it affects product safety**

When qualify?

Art. 9°: Reporting, identification, and qualification thresholds

§ 5º O(s) produto(s) de degradação com percentual ou valor correspondente acima dos limites de identificação e abaixo dos limites de qualificação que apresentem na sua estrutura química características que conduzam à classificação de produto potencialmente tóxico deverá(ão) ter seu perfil de segurança estabelecido através da avaliação da segurança biológica.

- **Degradation products or impurities below qualification threshold and classified as potentially toxic require qualification**

How qualify?

Art. 10 O produto de degradação poderá ser considerado qualificado quando atender ao menos uma das seguintes condições:

I - o produto de degradação for um metabólito significativo encontrado durante estudos em humanos ou animais;

II - a quantidade observada e o limite de aceitação proposto de um produto de degradação estiverem adequadamente justificados em literatura científica ou compêndios oficiais; ou

III - a quantidade observada e o limite de aceitação proposto para um produto de degradação não exceder o limite adequado observado em estudos de toxicidade.

Parágrafo único. A empresa não será dispensada de identificar o(s) produto(s) de degradação.

- **Metabolite**
- **Literature**
- **Toxicity studies**

How qualify?

➢ Metabolites

➢ **M3(R2)**

"*Nonclinical characterization of a human metabolite(s) is only warranted when that metabolite(s) is observed at exposures greater than 10% of total drug-related exposure and at significantly greater levels in humans than the maximum exposure seen in the toxicity studies*."

➢ Other alternatives may be considered on a case-by-case basis

How qualify?

➢ Metabolites

➢ Example: ramipril and ramiprilat (impurity E)

"Ramipril (HOE 498) is a long-acting, angiotensin converting enzyme (ACE) inhibitor that does not contain a sulfhydryl group. It is a pro-drug that is rapidly cleaved by esterases in the liver to its active dicarboxylic acid (ramiprilat)."

"The concentrations of ramipril and its active metabolite in these samples were determined by radioimmunoassay (…)"

Aurell. M., Delin. K., Herlitz. H., Ljungman. S., Witte. P. U., & Irmisch. R. (1987). Pharmacokinetics and pharmacodynamics of ramipril in renal failure. The American Journal of Cardiology, 59(10), D65–D69.

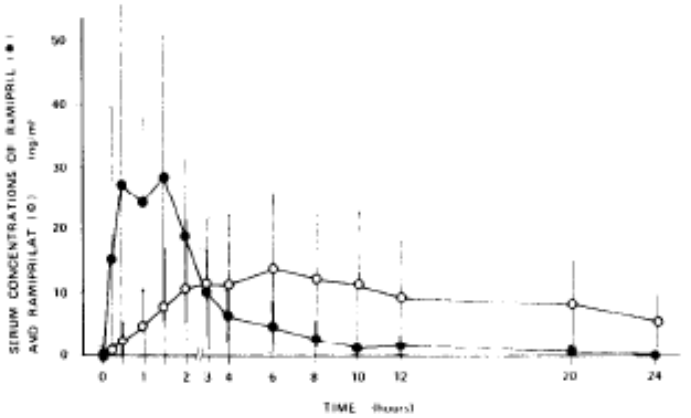


FIGURE 1. Mean (± standard deviation) serum concentrations of ramipril and ramiprilat versus time (n = 6).

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How qualify?

➢ Literature

- **Search strategy**
  - **Database. period**
    - ⊘ only one paper as reference
- **Send full text papers ellected as references**
- **Not necessary to send guidelines as ICH or OECD**

How qualify?

- **Toxicology assessment (safety profile)**

Art. 9°: Reporting, identification, and qualification thresholds

§ 7 º O perfil de segurança expresso no §5º e §6º estará estabelecido para aqueles produtos que atenderem ao disposto no art. 10 e poderá ser determinado por meio de avaliação de genotoxicidade e estudos gerais de toxicidade utilizando metodologia validada e conforme guia específico para a condução de estudos não clínicos de segurança necessários ao desenvolvimento de medicamentos.

- **Genotoxicity + General toxicity**
  - **Validated methodology and specific guidelines**
    - M7(R1), M3(R2), OECD nº408, Guideline non-clinical studies (ANVISA, 2013)

How qualify?

- **Toxicology assessment (safety profile)**
  - **Genotoxicity**

Reference M7(R1)

- ***In silico tools***
  - Employ two complementary (Q)SAR systems (expert rule-based and statistical based)

    →If no alert: Class 5

    → If non-conclusive or out-of domain: apply expert knowledge and *in vitro*/*in vivo* methods

- **Defined endpoint**
- **Unambiguous algorithm**
- **Defined domain of applicability**
- **Appropriate measures of goodness-of–fit, robustness and predictivity**
- **Mechanistic interpretation**

(https://qsardb.jrc.ec.europa.eu/qmrf/)

✓ **Show that softwares are validated - regulatory purpose, OECD**

✓ **Show version**

✓ **Present full reports**

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How qualify?

- **Toxicology assessment (safety profile)**
  - **Genotoxicity**

- **Example: Reports not sent, conclusion based on these tables**

Result from strutural alerts of impurity X using QSAR Toolbox (v. 3.4. 2016)

Structure	Rule 1 : Alert for carcinogenicity ISS/Benigni	Rule 2: Ames. micronucleus and carcinogenicity OASIS V.1.3	Rule 3: mutagenicity in vitro ISS	Experimental data
API	No alert	Alert positive	No alert	Negative
Impurity X	No alert	Alert positive*	No alert	-

*similar to API

Result from different models using statistical software TEST

Structure	Experimental	Hierarquical clustering	FDA	Nearest neighbor	Consensus
API	Negative	0	-	0.8	0.4
Impurity X	Not applicable	0	-	0.17	0.09

How qualify?

- **Toxicology assessment (safety profile)**
  - **Genotoxicity**

Reference M7(R1)

- ***In vitro/In vivo***
  - Bacterial reverse mutation test (Ames, OECD 471)
  - Micronucleus (OECD 487)
  - Chromossomal aberration test (OECD 473)
  - Others – technical jutification

✓ **Doses choices**

✓ **Certificate of analysis**

How qualify?

- **Toxicology assessment (safety profile)**
  - **General toxicity**

- **Reference Q3B(R2), M3(R2), OECD 408**
  - If necessary to conduct general toxicity study → one species, usually 14 to 90 days
  - **Rastreability** → pivotal studies reference
  - Same impurity named differently
  - Certificate of analysis

- **Administration route**
- **Species choice**
- **Duration**
- **Number of animals/group**
- **Sex**

How qualify?

- Toxicology assessment (safety profile)
  - General toxicity

Example

Material:			Analysis No:
Test	**Results**	**Method**	**Reference**
IMPURITY CONTENT BY HPLC	Total Impurities: 16.1 % 12.89 % 0.39 % RRT 0.14: 0.05 % RRT 0.20: 0.08 % RRT 0.21: 0.62 % RRT 0.32: 0.25 % RRT 0.33: 0.03 % RRT 0.43: 0.04 % RRT 0.44: 0.08 % RRT 0.83: 0.10 % RRT 0.92: 0.08 % RRT 1.08: 0.36 % RRT 1.32: 0.22 % RRT 1.53: 0.19 % RRT 1.63: 0.12 % RRT 1.73: 0.02 % (trace) RRT 1.78: 0.42 % RRT 1.80: 0.11 % RRT 1.91: 0.10 % RRT 1.98: 0.03% (trace)		

How qualify?

- Toxicology assessment (safety profile)
  - General toxicity

Example

Development

Impurity	RRT
Impurity A	0,76
Impurity B	0,60
Impurity RRT 0,81	0,81
Impurity RRT 0,92	0,92
Impurity G	0,97

Registration

Impurity	RRT
Impurity A	0,76
Impurity B1	0,60
Impurity D	0,81
Unknown imp.	0,92
Impurity G	0,97

Between development and registration some years passed and a new method was developed to quantify impurities, some RRT changed and also some impurities were renamed.
Studies were sent with new and old nomenclature → Rastreability ??

How qualify?

- Toxicology assessment (safety profile)
  - General toxicity

Suggestion

Form of qualified impurities

Compound	Sponsor code	IUPAC	Structure	Compendial name	Other synonyms	Specification	Obs
API							
Impurity A				Phr. Eur. USP Far. Bras.			

How qualify?

- Toxicology assessment (safety profile)
  - General toxicity

Conversion to reach qualification level in human

Impurities	A 0001	A 0002	A 0003
Toxicological study	Repeated dose in rats – 4 weeks (TOX 1234A)	Repeated dose in rats – 13 weeks (TOX 2345A)	Repeated dose in rats – 13 weeks (TOX 456B)
Impurity dose at NOAEL (mg/kg/day)	0.06	0.33	0.09
Human exposition qualified (mg/dia)	0.576	3.168	0.864
Specification	≤ 0.40%	≤ 0.25%	≤ 0.20%
Max human exposition at spec level (mg/dia)	0.1	0.075	0.05
Safety margin from transposition of human-animal-dose at spec level	5.7	42.2	17.2

Ratio = 9.6

Considering 60kg for humans and 6.2 from AED (surface area) we have a ratio of 9.67

?

How qualify?

- **Toxicology assessment (safety profile)**
  - **General toxicity**

Conversion to reach qualification level in human

- Based on body surface area
- *"Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers"* (FDA. 2005).

- Based on AUC

Table 2: Animal equivalent dose calculation based on body surface area*

Species	Reference body weight (kg)	To convert dose in mg/kg to dose in mg/m², divide by K_m	To convert human dose in mg/kg to AED in mg/kg, either	
			Multiply human dose by	Divide human dose by
Human	60	37		
Mouse	0.02	3	12.3	0.081
Hamster	0.08	5	7.4	0.135
Rat	0.15	6	6.2	0.162
Ferret	0.30	7	5.3	0.189
Guinea pig	0.40	8	4.6	0.216
Rabbit	1.8	12	3.1	0.324
Dog	10	20	1.8	0.541
Monkeys (rhesus)	3	12	3.1	0.324
Marmoset	0.35	6	6.2	0.162
Squirrel monkey	0.60	7	5.3	0.189
Baboon	12	20	1.8	0.541
Micro pig	12	27	1.4	0.730
Mini pig	40	35	1.1	0.946

*Data adapted and modified from FDA draft guidelines.[7] FDA: Food and Drug Administration, AED: Animal equivalent dose

Nair AB. Jacob S. A simple practice guide for dose conversion between animals and human. *J Basic Clin Pharm*. 2016;7(2):27–31.

How qualify?

- Toxicology assessment (safety profile)
  - General toxicity

Example

Impurity	Spec	Tox study	Max dose in Tox study (µg/kg/day) (µg/m²)	Multiple of clinical dose	Batch assay (%)	Batch number	Qualified level(%)
A	0.2%	13 week dog TX123	300	19x	0.02	2016X123	0.38
			6000	10x			0.20
B	0.4%	13 week dog TX 123	300	19x	0.04	2016X123	0.76
			6000	10x			0.4

*Human max dose of 800µg/dia of API. assuming 50kg = 16 µg/kg = 592 µg/m²

** µg/m² conversion using FDA recommended values of x37 for human and x20 for dog

"Although the 100 µg/kg is defined as the NOAEL. since the study showed no adverse effects, at any dose levels, other than those related to the expected pharmacological effects of the product, the highest doses used in the toxicology study can be considered for the qualification of the impurities."

How qualify?

- **Toxicology assessment (safety profile)**
  - **General toxicity**

Example

Requirement 1: The company shall clarify the allometry used for extrapolation of doses from non-clinical studies to clinical results, if the company wishes to use the same rationale for the impurities qualification.

- Impurity level (Batch 2014ABC): is **0.41%**
- Qualifying monkey study NOAEL (Study 000): **20 mg/kg/day**
- Therefore the NOAEL dose of Imp Y administered to the monkey is: **0.082mg/kg/day**

(20 x 0.41% = 0.082mg/kg/day)

- Therefore the human qualified equivalent (for a 60kg human) is: **4.92 mg/day** (0.082 mg/kg/day x 60 kg – 4.92mg/day)
- Therefore % qualified is **1.32%** (4.92mg in one day / daily API dose of 370 mg = 1.32%)

"The approach for toxicologically qualifying the individual impurities was not performed using the allometry used for extrapolation of doses from non-clinical studies to clinical results as the extrapolation from animals to man is complex due the difference in half-life between species. A simpler conventional approach in which the dose of individual impurities on a mg/kg basis was determined…"

How qualify?

- **Toxicology assessment (safety profile)**
  - **General toxicity**

➢ **Example :** Based on AUC

Impurity W of API 1234 exposure in mouse *versus* humans

Species	Study	Dose (mg/kg)	AUC 24h (ng.h/mL)		Multiple of human exposure	
Human	Single dose, oral	60	69.5		-	
Mouse	6 month, oral (gavage)		M	F	M	F
		0.3	28	27	<1	<1
		7.5	772	657	11	9
		15	1827	1546	26	22

Thank you!

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