Selection of the most suitable dissolution technique for development and link to QC

J-M. Cardot

Biopharmaceutical department, University of Auvergne

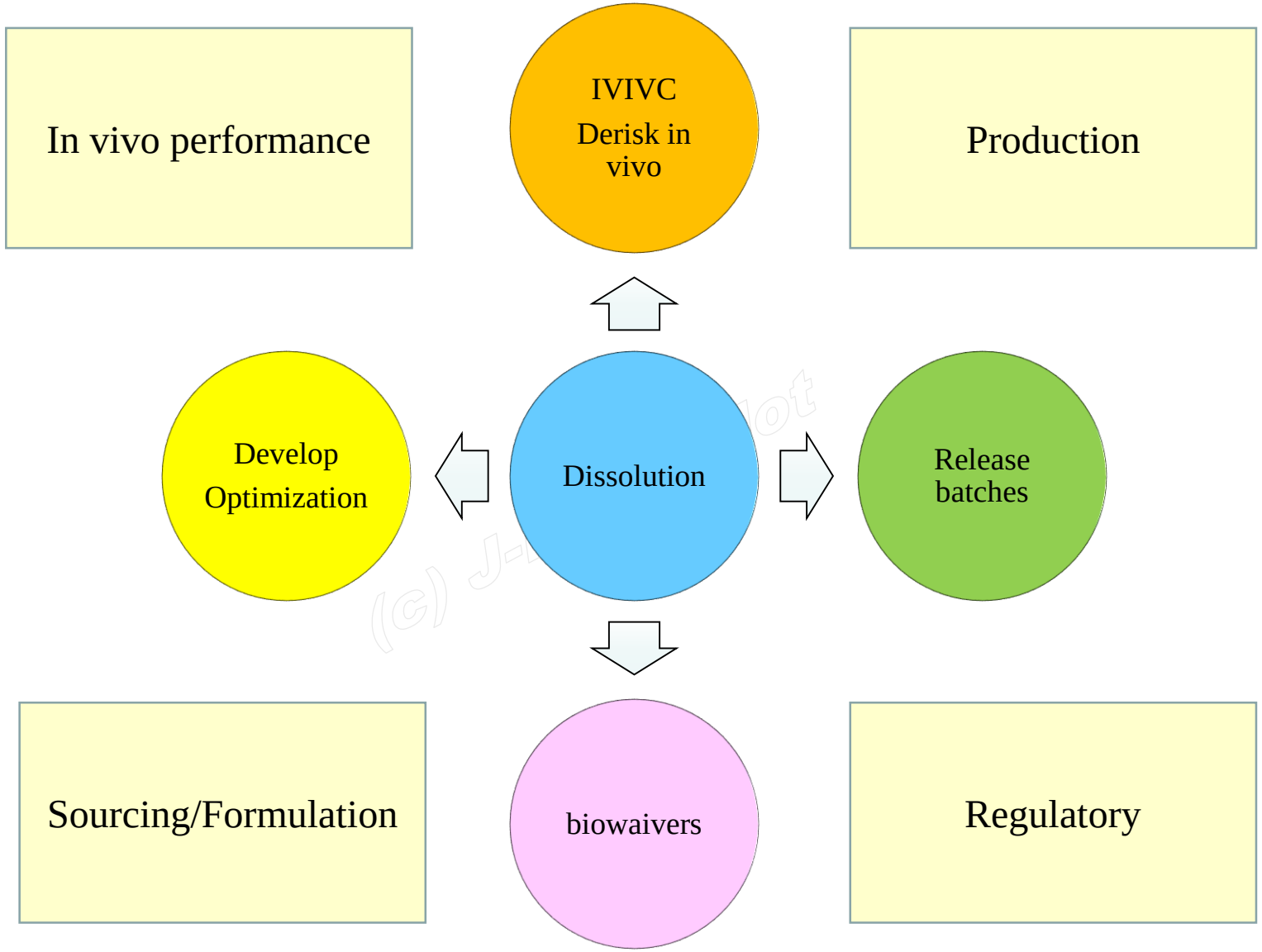
28 Place H. Dunant, BP 38, 63001 Clermont-Ferrand

France

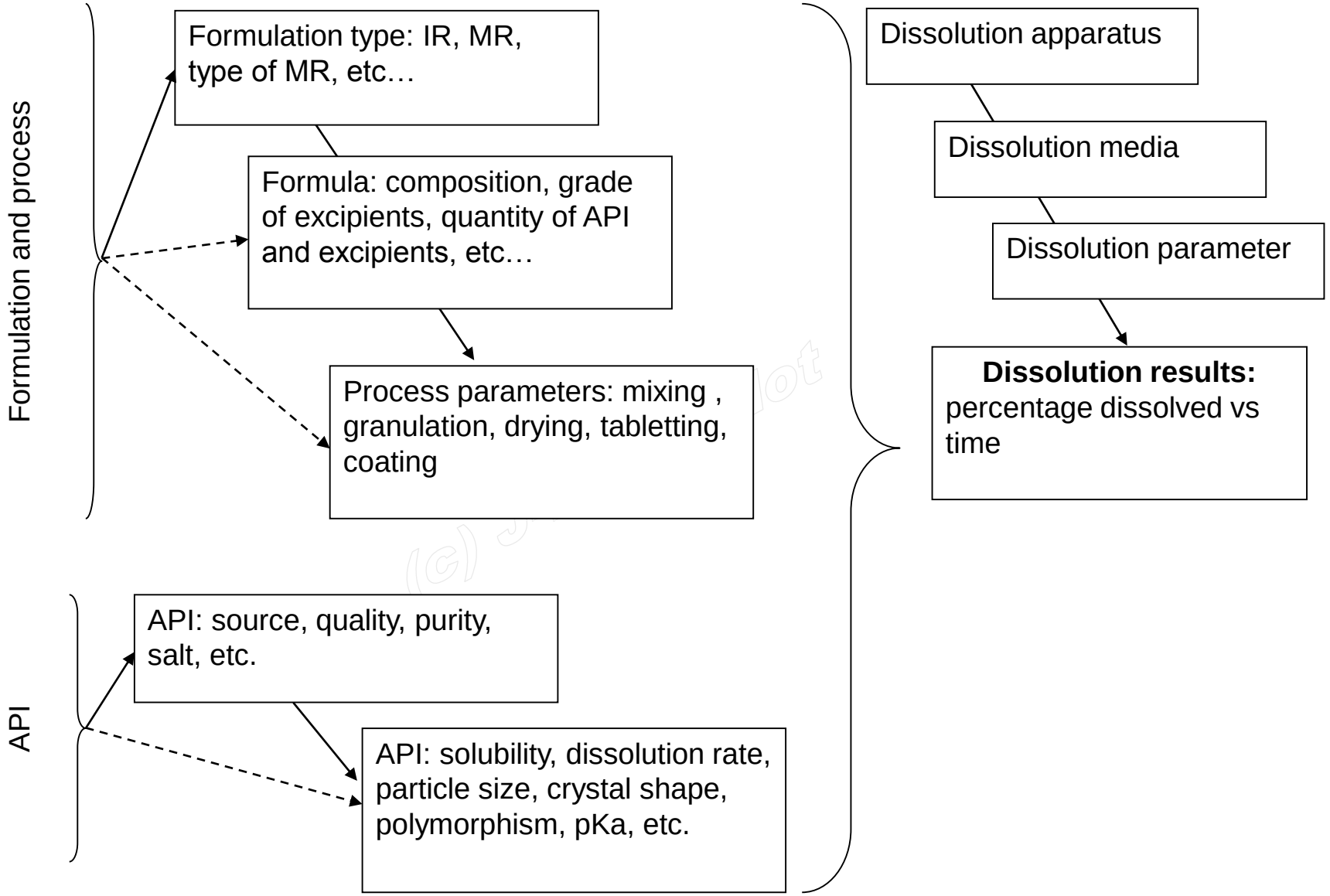
Email: j-michel.CARDOT@udamail.fr

INTRODUCTION

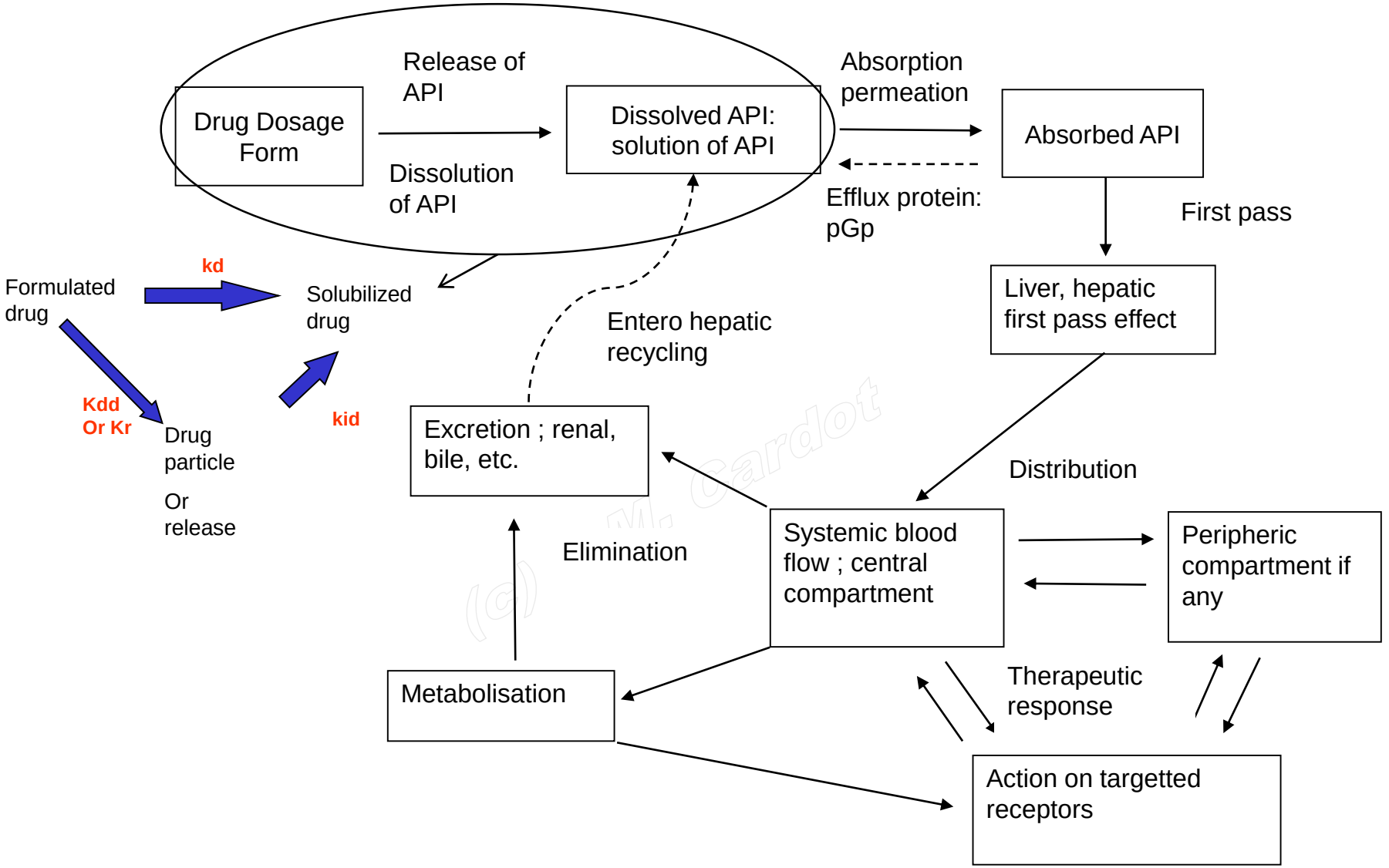
Dissolution



Why dissolution so important



Dissolution and link to in vivo



Dissolution

- During the **development** of a medicinal product a dissolution test is used as a tool to **identify formulation factors** that are influencing and may have a crucial effect on the bioavailability of the drug.
- As soon as **the composition** and the **manufacturing process** are **defined** a dissolution test is used in the **quality control** of scale-up and of production batches to **ensure both batch-to-batch consistency** and that the dissolution profiles remain similar to those of pivotal clinical trial batches.
- Furthermore, in certain instances a dissolution test can be **used to waive a bioequivalence** study.

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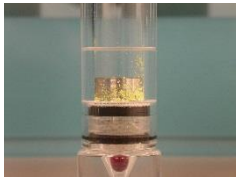
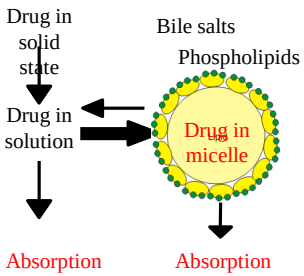
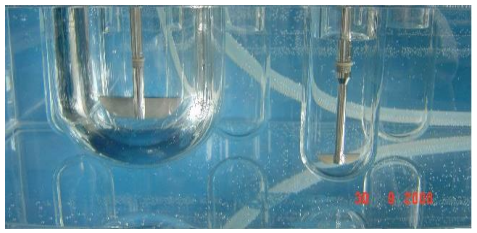
In development => understand and optimize

- API characterization
  - Intrinsic dissolution
  - Apparent dissolution
- Formulation
  - Compendia assessment: apparatus, media
  - Non compendia assessment
  - Food effect: Fassef, Fessif, etc…
- Specific formulation/MD
- Possibly IVIVC

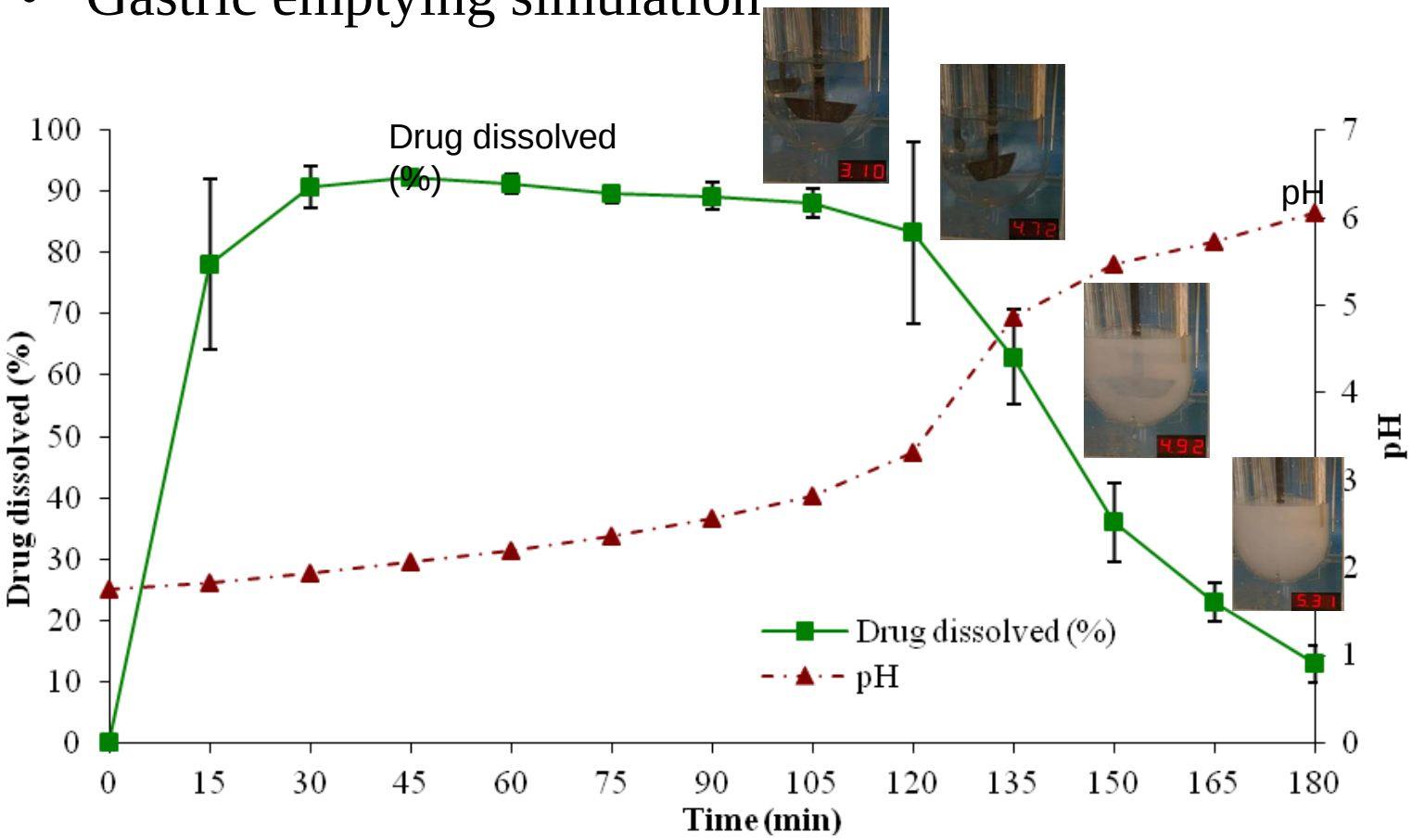






Example repricipitation

- Gastric emptying simulation



- pH has a large influence on dissolution
- Great decrease from 90% to 60% with visible precipitation at pH 5

In QC=> discard bad batches

- Discard bad batches
- Qualified apparatus
- Validated method
- Relatively simple to handle, to use
- If possible compendia
- Fix acceptance limits
- As fast as possible but must respect to discriminative power ….

QC Official devices and media if possible

- Basket method (EP USP JP)
- Paddle method (EP USP JP)
- Reciprocating cylinder (EP USP)
- Flow-through cell (EP USP JP)
- Paddle over disk
- Cylinder
- Chewing apparatus
- Etc…

- Acidic: HCl
- Acetate buffer
- Citric buffer
- Phosphate buffer
- SGF/SIF
- Addition of enzyme
- Addition of surfactants
- Etc…

Biowaiver media and dissolution

- Dissolution apparatus
  - Paddle or basket, classical setting
  - QC method could be different
- Media
  - pH 1.2, no surfactant
  - pH 4.5, no surfactant
  - pH 6.8, no surfactant
  - QC media

Ideal dissolution method … QC ?

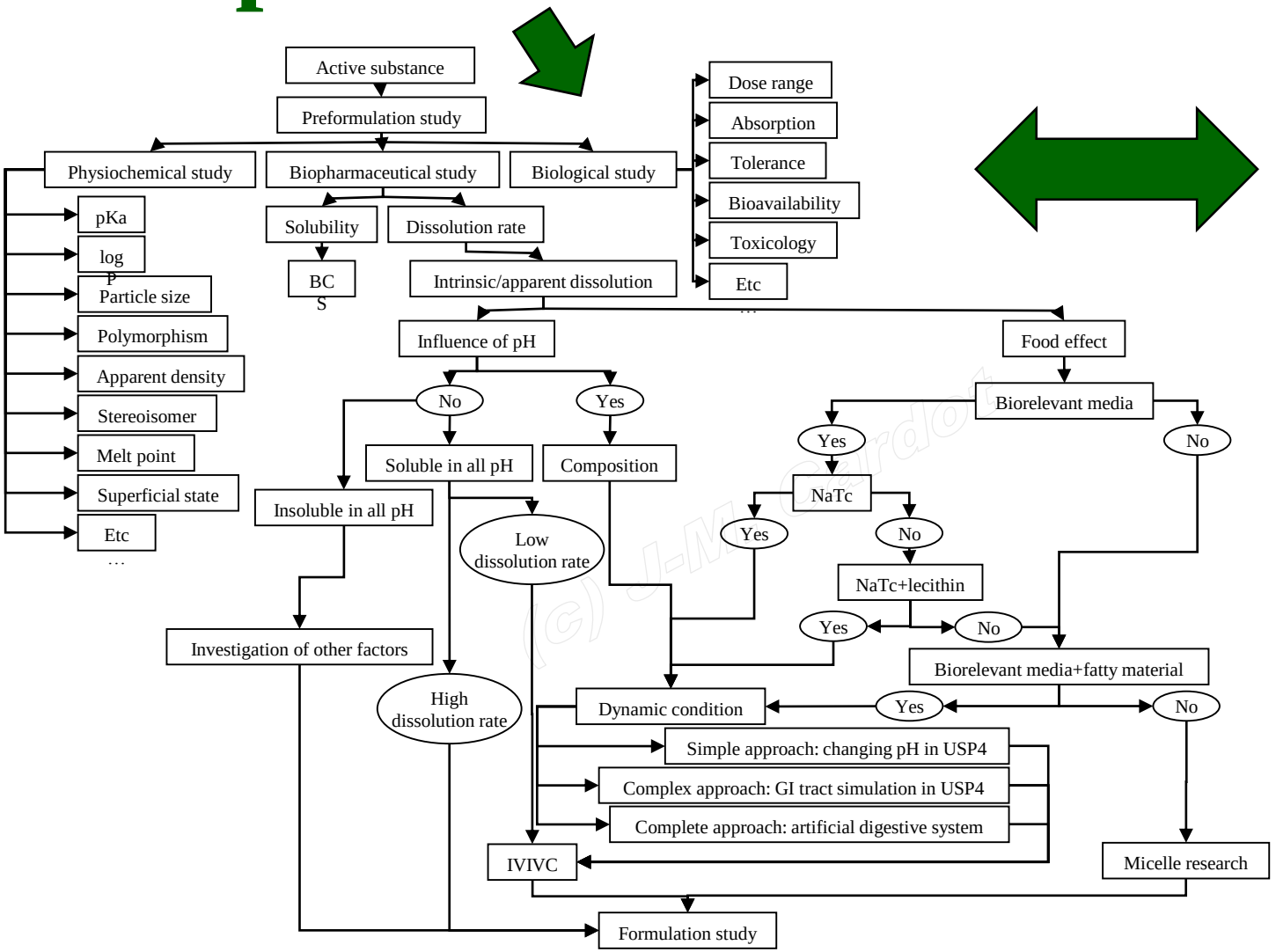
- Goal is to achieve a discriminating method that can predict in vivo performance (or signal possible bio-in-equivalence) and control key manufacturing parameters.
- Purpose of the release method should be to identify problems during the manufacturing process and maintain the dissolution limits for production batches in order to reflect the key quality attributes of the biobatch

LINK DEVELOPMENT AND QC

Development ←→ QC

- In development the method could be over discriminant, long, complex and … could be not the final one as the in vivo behavior of the formulation is not known (especially for generics before BE).
- In QC the method is linked with the FMI and the key parameters of the formulation

Selection of the method a long process … or a short rule



In lab XXXXX only Paddle and pH 1.2

….

Not the best approach

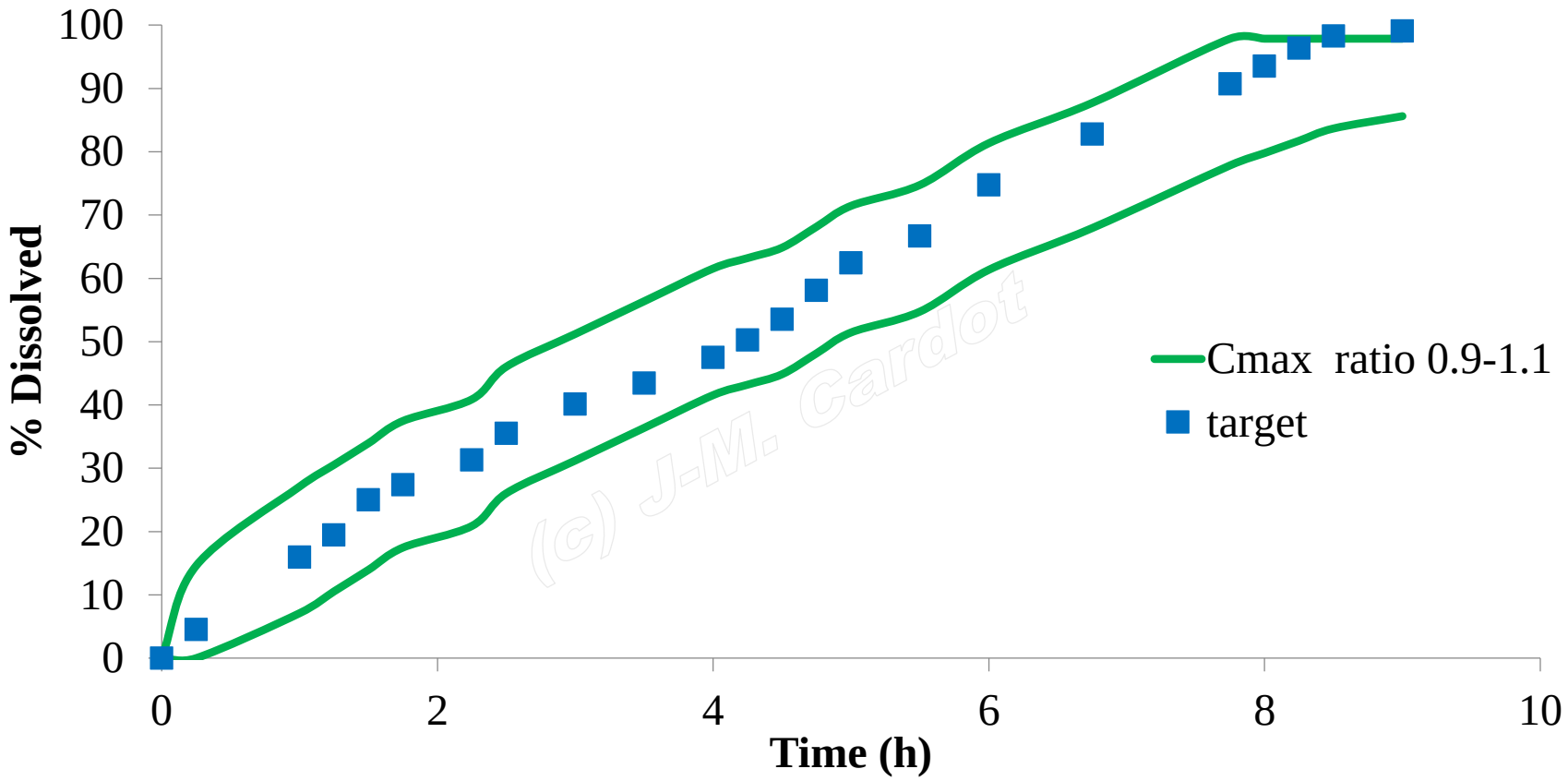
Optimal case: same method

- Same method in development and in control
  - Validation
    - Use all the development part
    - Use critical parameters
  - Fix dissolution limits
    - If IVIVC use it to fix dissolution limits
    - If not use bad batches with in vivo results
    - Otherwise used predefine limits such as ± 10%
    - At least one point for IR
    - At least 3 points for SR

In case of IVIVC

- In presence of level A correlation specifications should be established based on average data. The simulated plasma concentration time profile, based on dissolution limits, result in a maximal difference of 20% in the predicted Cmax and AUC => ± 10% around target.

Dissolution limits vs a new formulation



Different method between development and control

- Must link them …. but ….
- Must show right discriminance of QC
- Must show that similar processes are identified by both methods Example similar release characteristics : diffusion, erosion
- If similar processes then explain the differences between the methods and why it was change
- Explain how to fix the limits
- Use the qualification and validation to show the discriminance of the method
- Could have an impact on stability tests

Usual Way

- Validation use modification of the formulation
  - Hardness
  - Quantity of desintegrant
  - Quantity of lubricant etc…
- Use some formulation used in development (must have kept them and insure their stability)
- Compare the batches test (and reference ?) used in BE
- Be coherent with the in vivo results otherwise justify
- This method will also be used for the stability

LEGAL ASPECTS: QC

Reflection paper EMA

Guideline EU and US

Sandra Suarez-Sharp, Min Li, John Duan, Heta Shah, Paul Seo, Regulatory Experience with In Vivo In Vitro Correlations (IVIVC) in New Drug Applications AAPS Journal

EMA Reflection paper on dissolution

- The draft EMA reflection paper enforces that
  - dissolution release method has to be capable of detecting the in-vivo difference.
  - expectation represents a simplification of in-vitro / in-vivo relationship.
  - dissolution limits assumes a simple linear relationship between the in-vitro data and in-vivo data, here proposed as direct link between dissolution profile and pharmacokinetic metrics based on biobatch results

US

- Either publish USP or alternatively FDA dissolution
- Individual BE guidelines
- Otherwise case by case and could be advisable to contact the relevant department of US-FDA

In case of IVIVC

- Dissolution limits in QC are linked with IVIVC results
  - Implies in theory that the same method is used in development and in QC
  - Otherwise explain the change the link and the predictability
  - Change (if any) must be made as early as possible for example to have chance to use external predictability

Qualification and validation

- Mandatory
- Made as early as possible
- Important for release … but also for stability, biowaivers (if different from pH 1.2, 4.5, or 6.8 and classical setting in rpm) etc…

CONCLUSION

Dissolution

- During the **development** of a medicinal product a dissolution test is used as a tool to **identify formulation factors** that are influencing and may have a crucial effect on the bioavailability of the drug.
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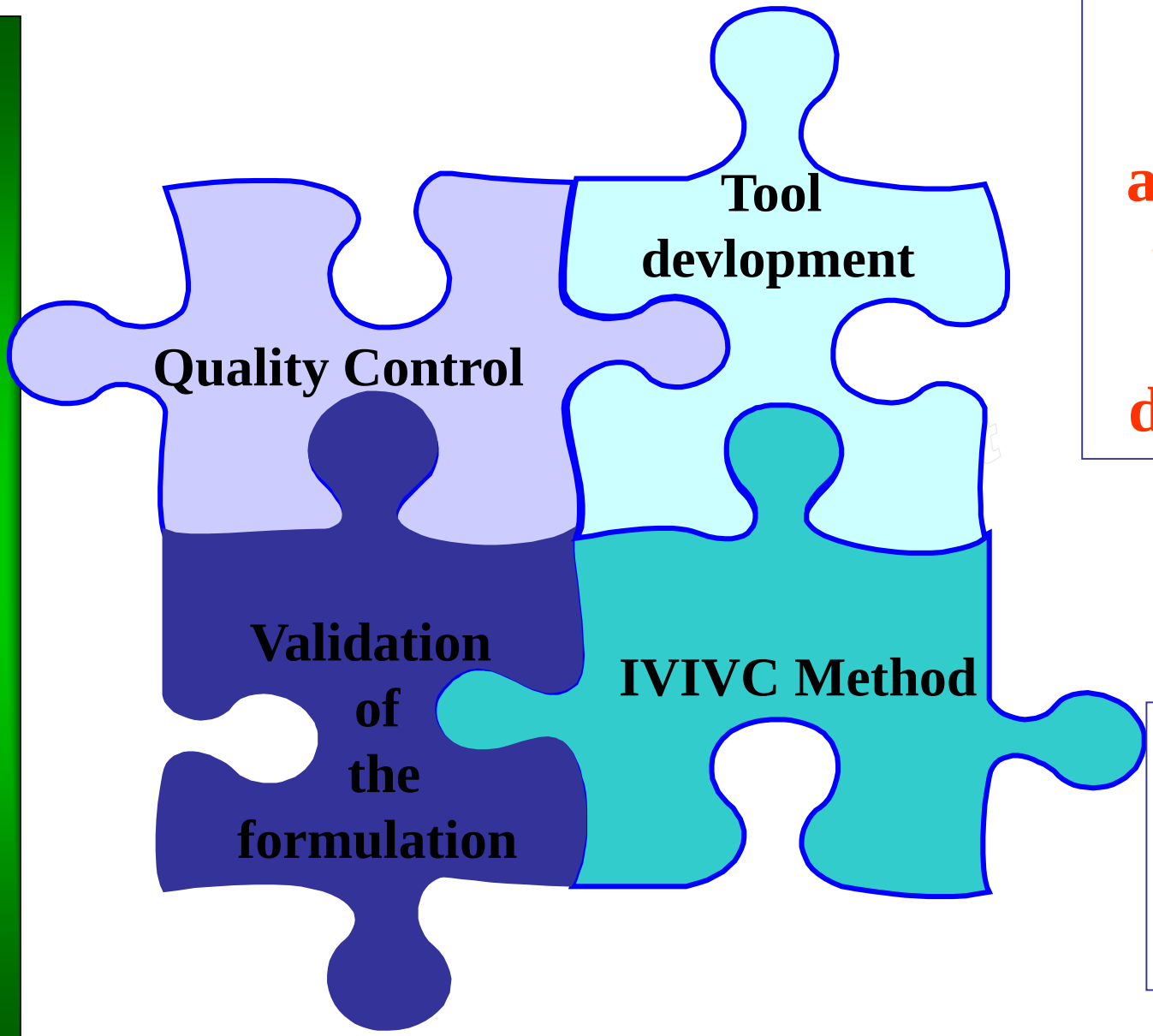
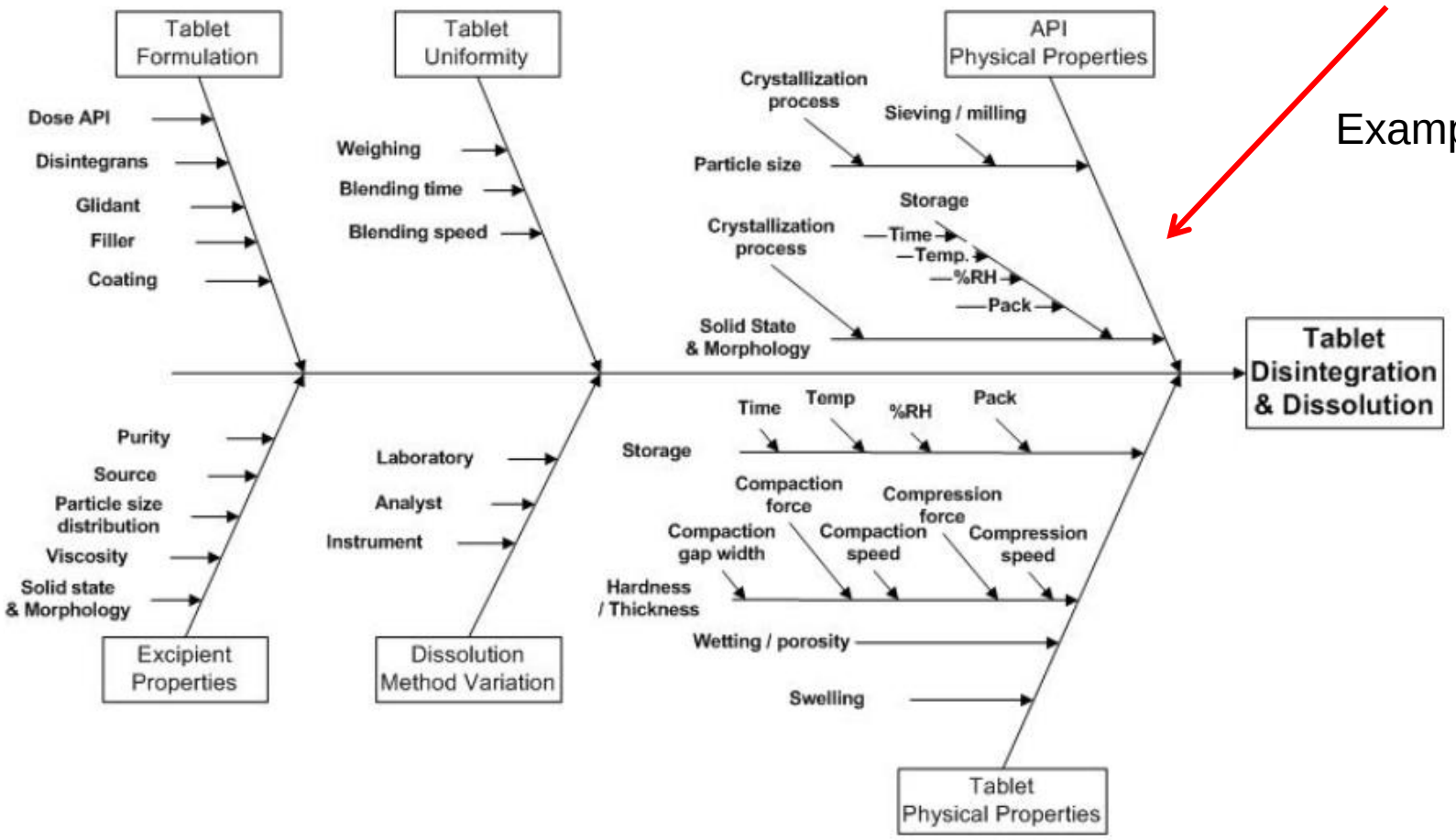


Different methods according to the type of study and dosage form

Ideal Case

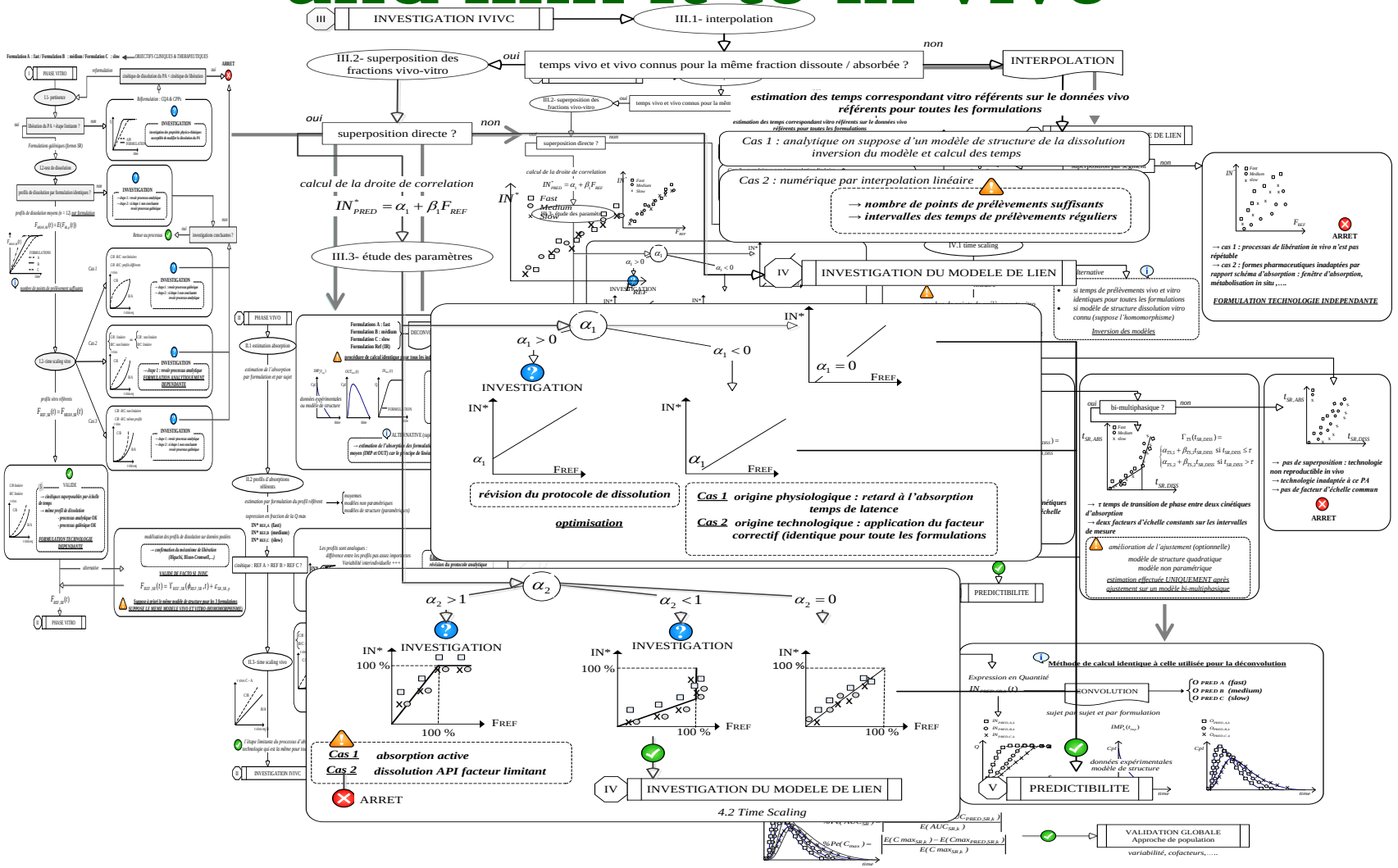
One method for four cases

Need a perfect know how



Roy De Maesschalck
Pharmaceutical Sciences J&J Belgium

Control sources of variations … and link it to in vivo

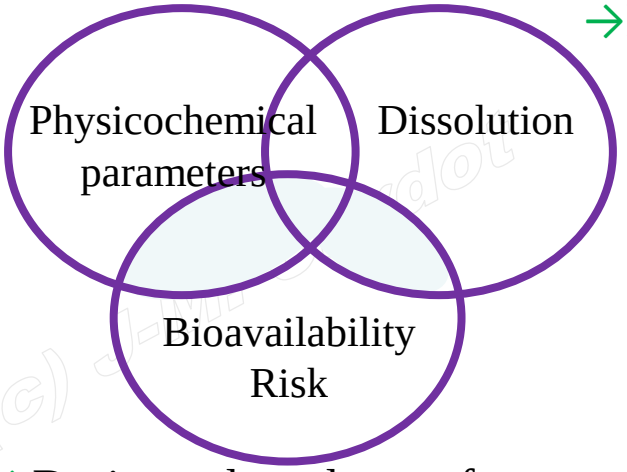


Dissolution a tool to

- Development
  - Understand formulation, process
  - Define key performance parameters early in the development
  - Design products/process to be robust for these parameters

→Determine key factors

→Understand the relations



→Design a drug dosage form

- QC=> Ensure quality and robustness => QC