1st MENA Regulatory Conference on Bioequivalence, Biowaivers, Bioanalysis and Dissolution

Jordan – September 23-24, 2013

EMA Perspectives on BE regulations

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EMA – European Medicines Agency

Outline

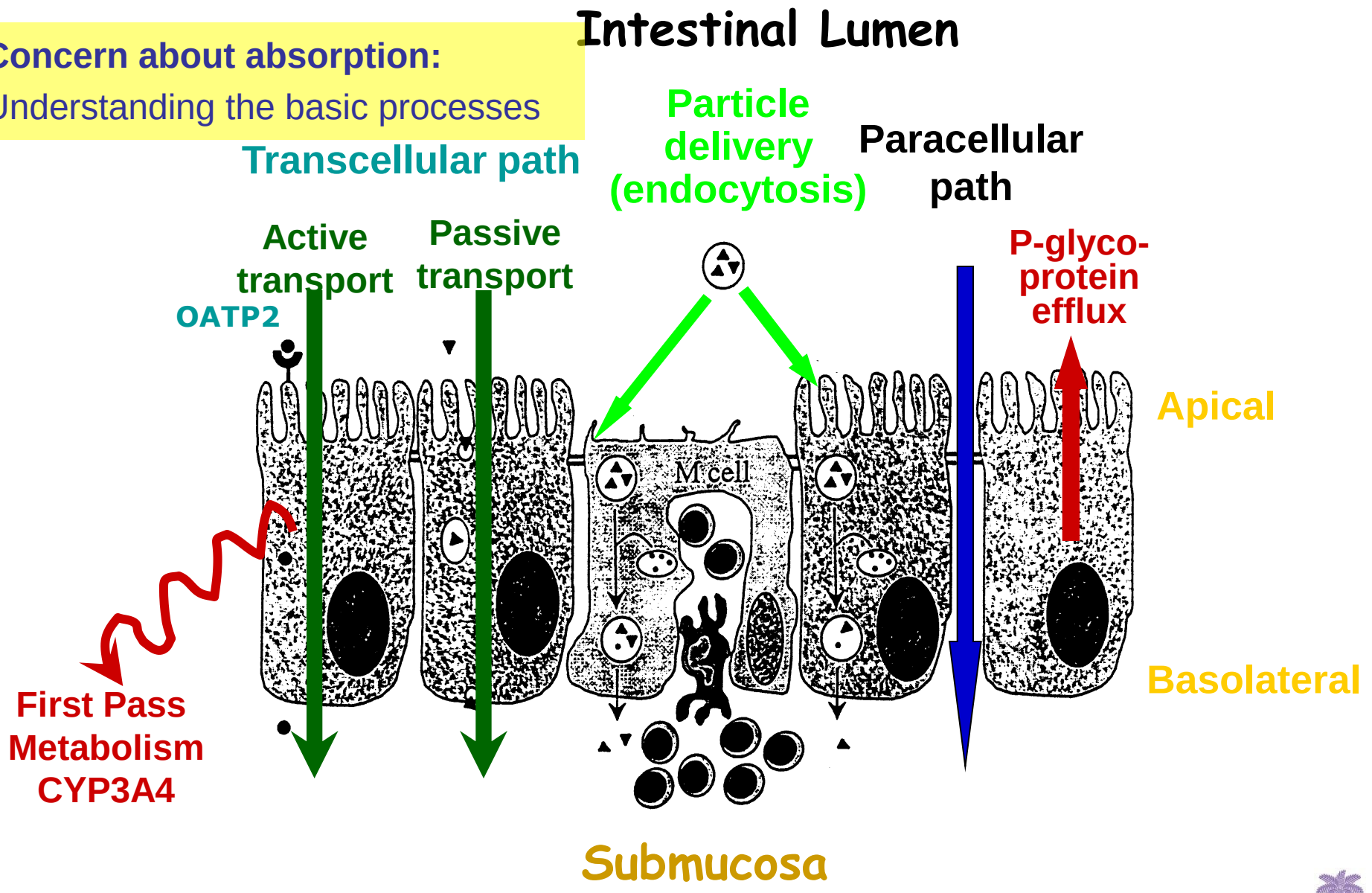
- Mechanisms, concepts and measures of drug absorption – bioavailability (BA)
- The role of quality and Bioequivalence (BE) in drug development
- Issues in BE Study Design and Conduct Covered in the BE Guideline
  - New definition of generic medicinal product
  - Design, conduct and evaluation of BE studies
  - Fasting vs. Fed studies
  - Parent compound vs. Metabolites
  - Strength to be investigated
  - Narrow Therapeutic Index Drugs (NTI) and Highly Variable Drugs (HVD)
  - Biowaiver based on the Biopharmaceutics Classification System (App. III)
  - Appendix II – different dosage forms
- New features and conclusions

Science and regulation issue

- We are dealing with a complex pattern concerning drug absorption that we have
  - to study and understand, as well as
  - to simplify in order to achieve our goal of obtaining the simplest way to ensure bioequivalence between multisource medicinal products
- Exceptions or unexpected behaviour can unravel new mechanisms to be understood

Concern about absorption:

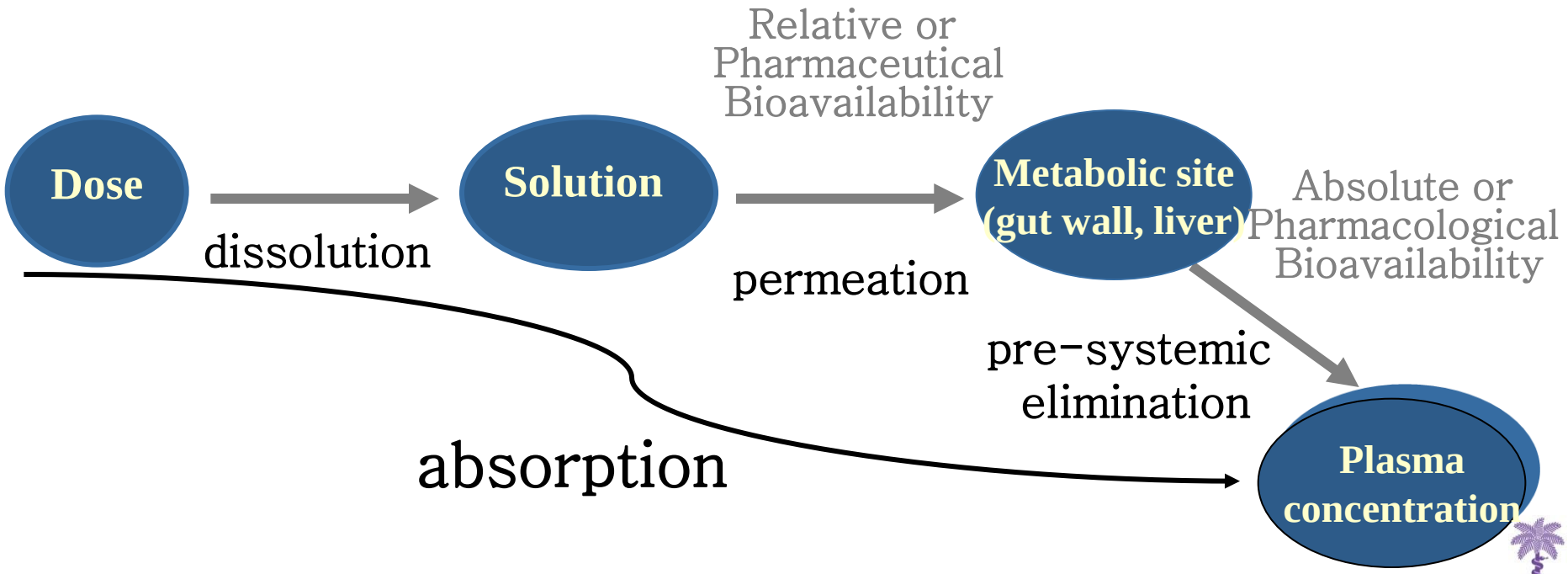
Understanding the basic processes



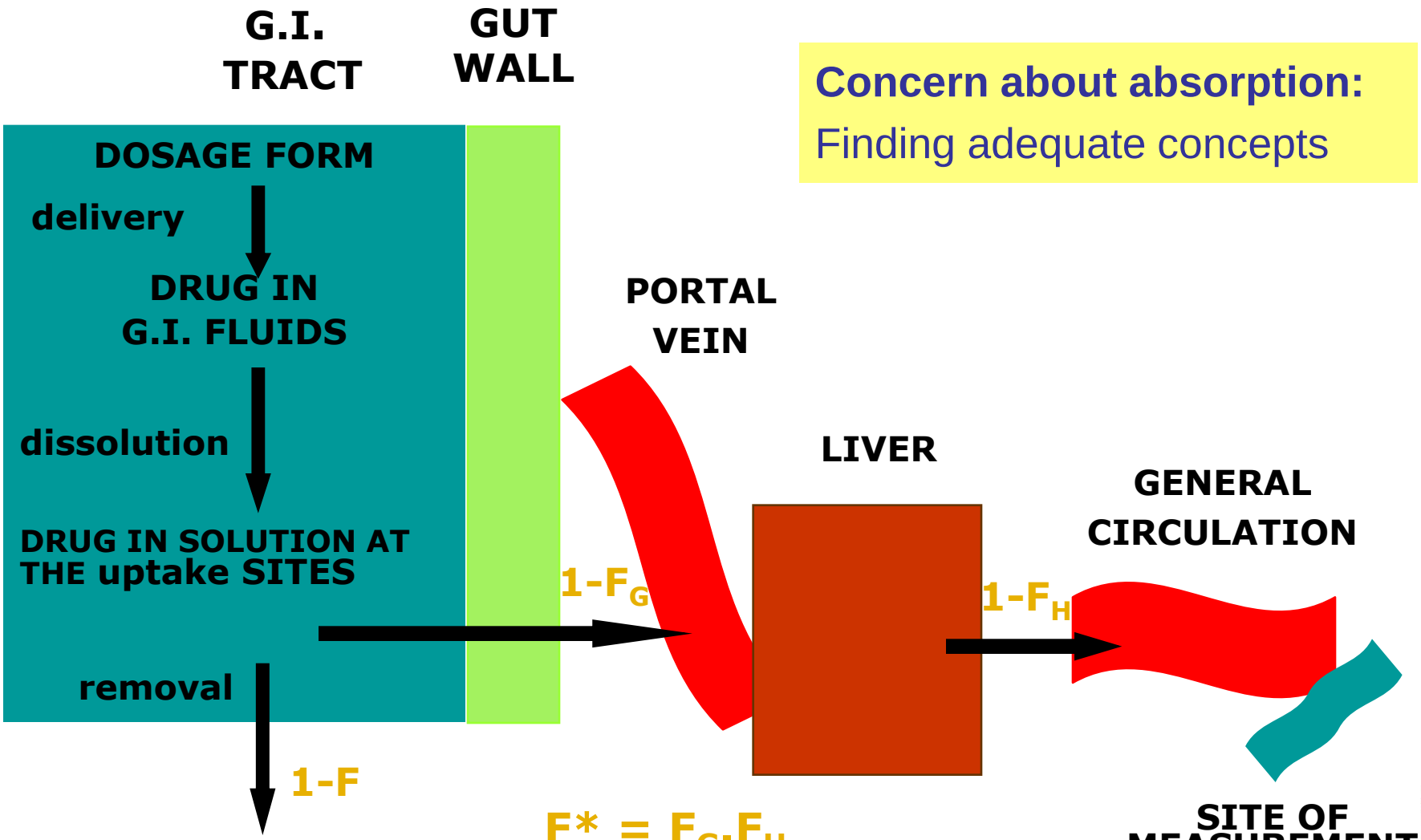
Dissolution, intestinal absorption and pre-systemic elimination processes for orally administered solid dosage forms

Concern about absorption:

Finding adequate concepts



ABSOLUTE, RELATIVE BIOAVAILABILITY ACCORDING TO SITES OR PROCESSES OF LOSS



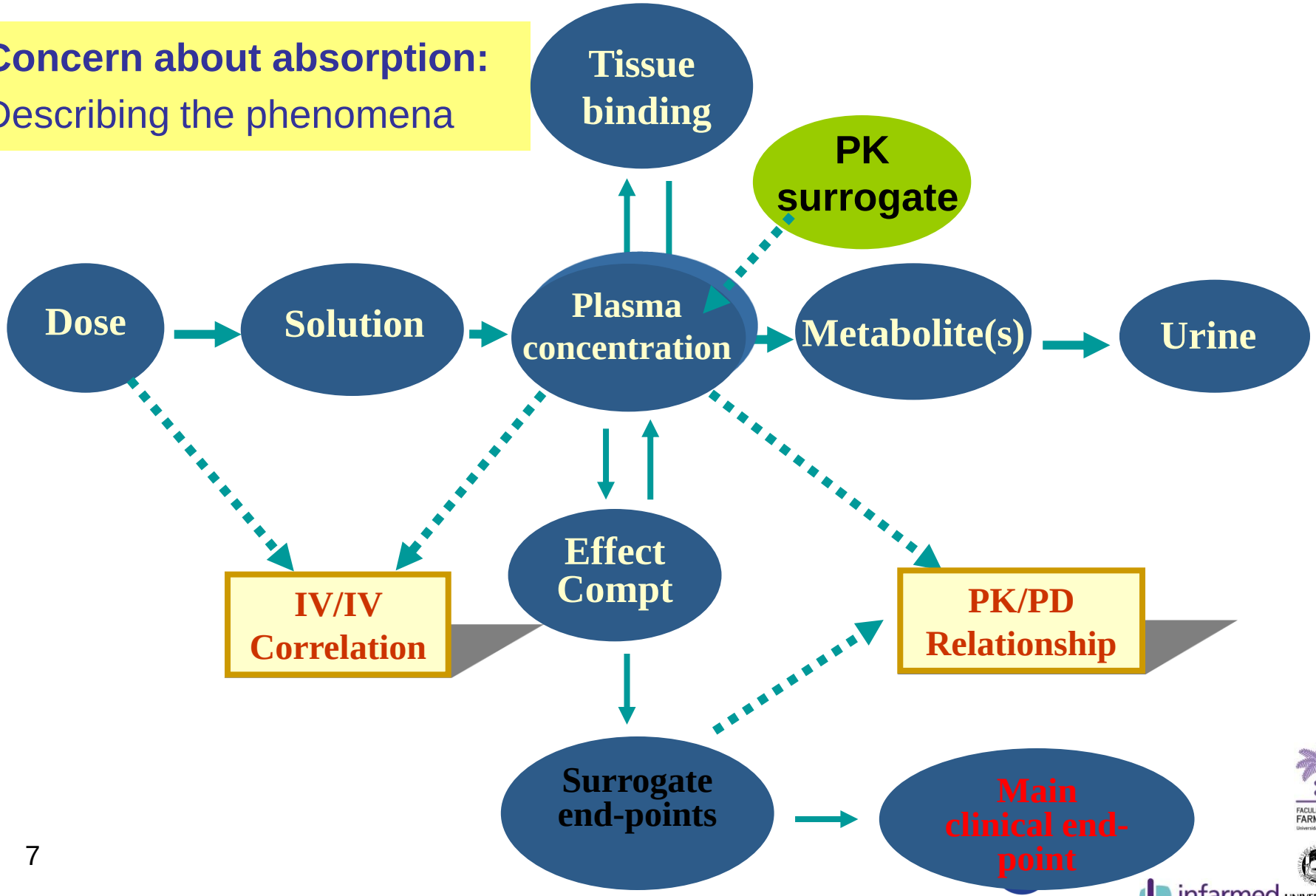
Concern about absorption:

Finding adequate concepts

BIOAVAILABLE DOSE: F.F*.D

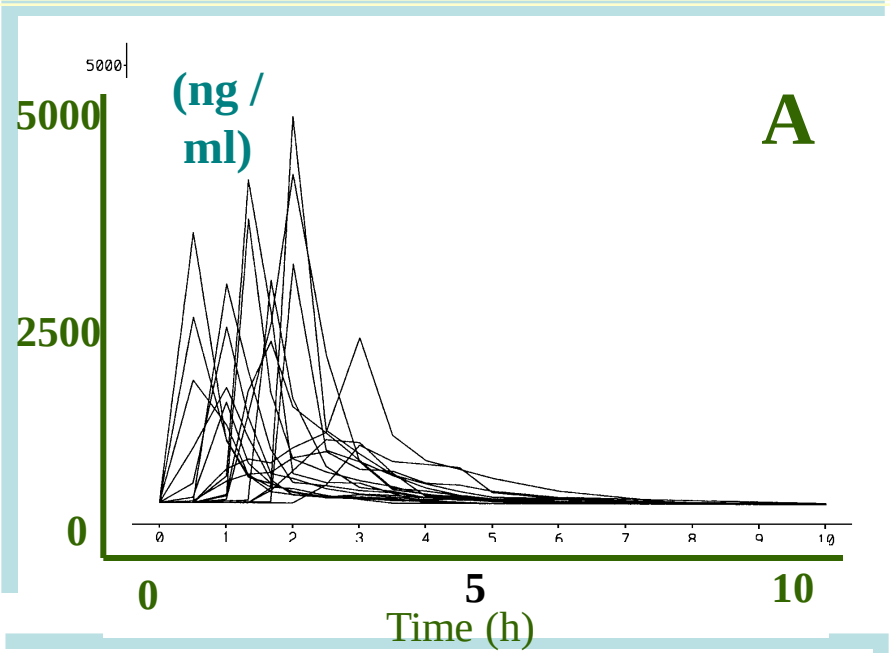
CATENARY CHAIN TYPE OF MODEL FOR IV/IV and PK/PD

Concern about absorption:
Describing the phenomena



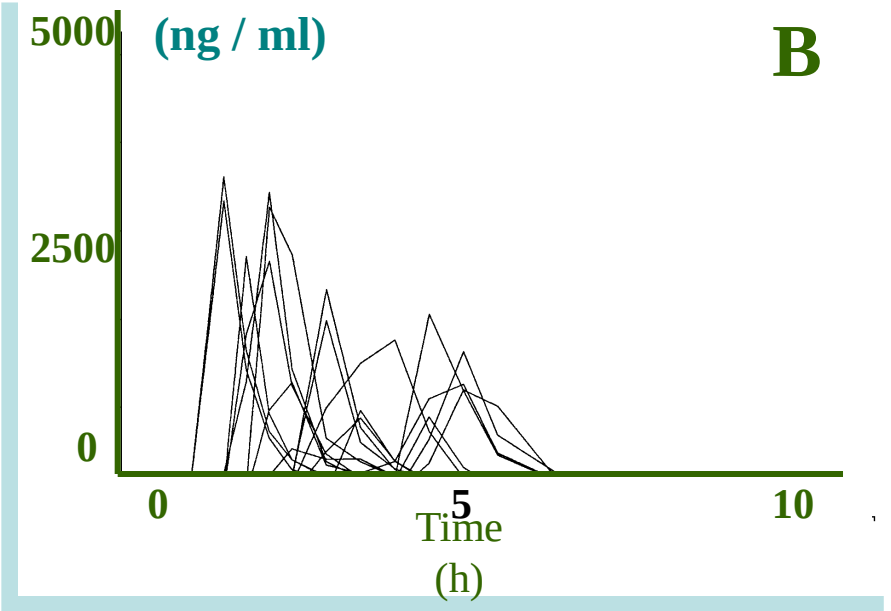
PK is a universally accepted surrogate for efficacy of medicinal products with favourable benefit/risk balance and well established clinical use, thereby validating the use of the Bioavailability concept.

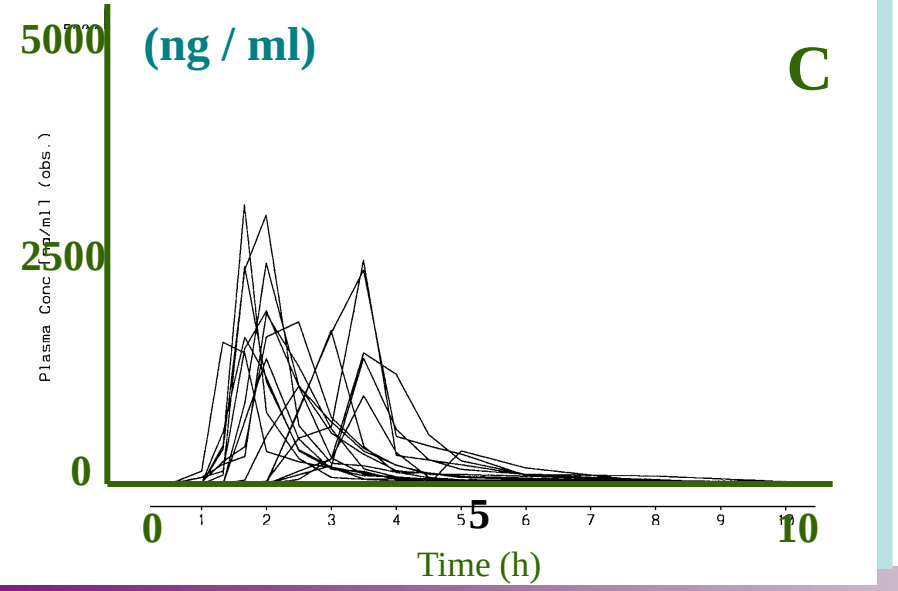
CONCENTRATION VS TIME DATA FOR ALL SUBJECTS



Concern about absorption:

Describing the phenomena

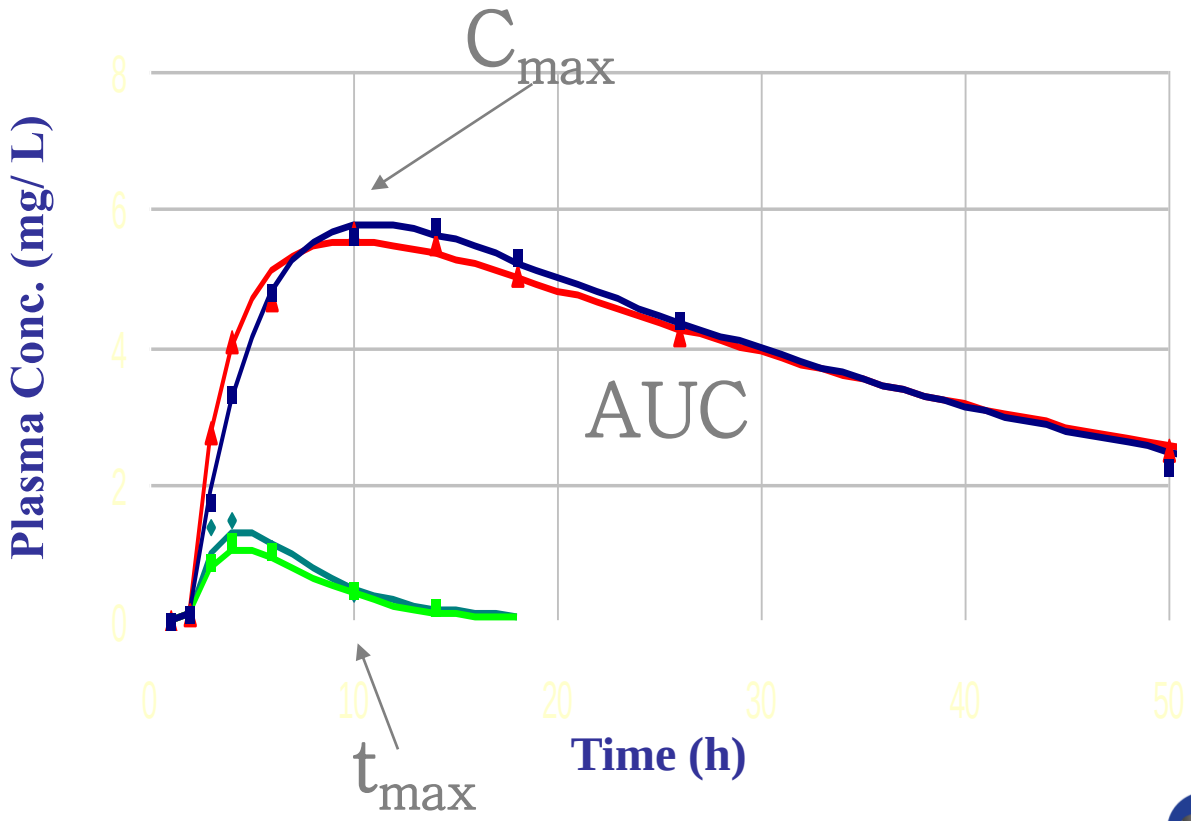




FITTED CURVES TO MEAN ALLOPURINOL AND OXYPURINOL PLASMA CONCENTRATIONS:

Concern about absorption:

Describing the phenomena



Allopurinol

Oxypurinol

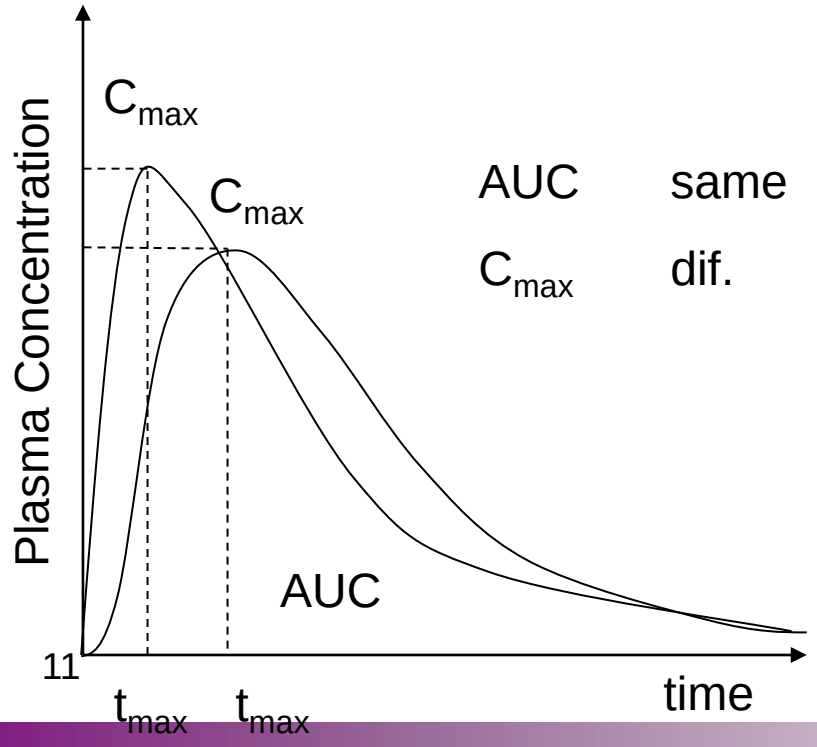
Bioavailability/Bioequivalence Study

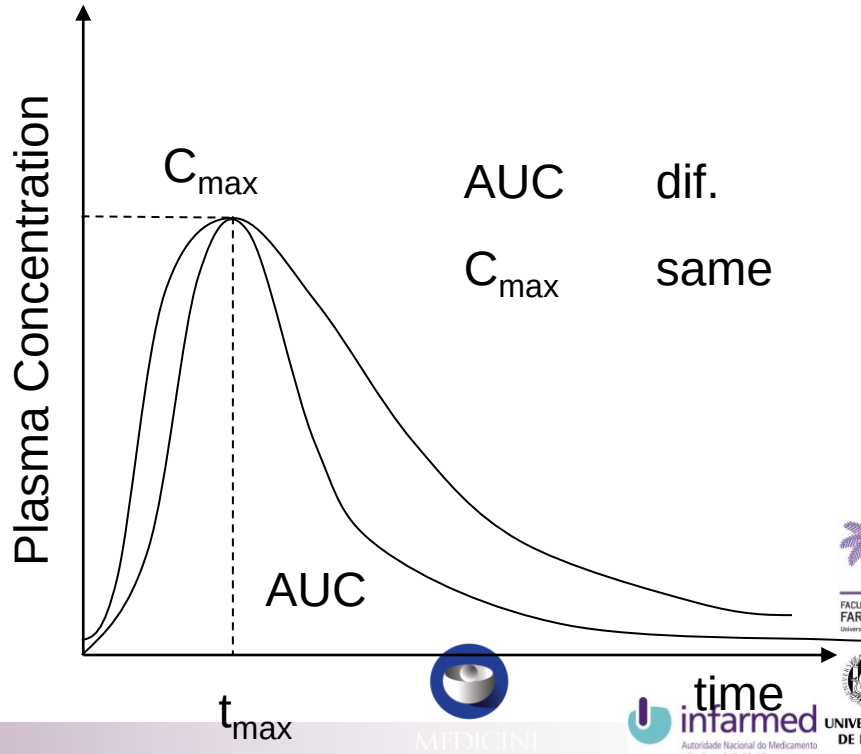
Concern about absorption:

Measuring the parameters

Extent of absorption: **AUC** **C_{max}**

Rate of absorption: **C_{max}** **t_{max}**

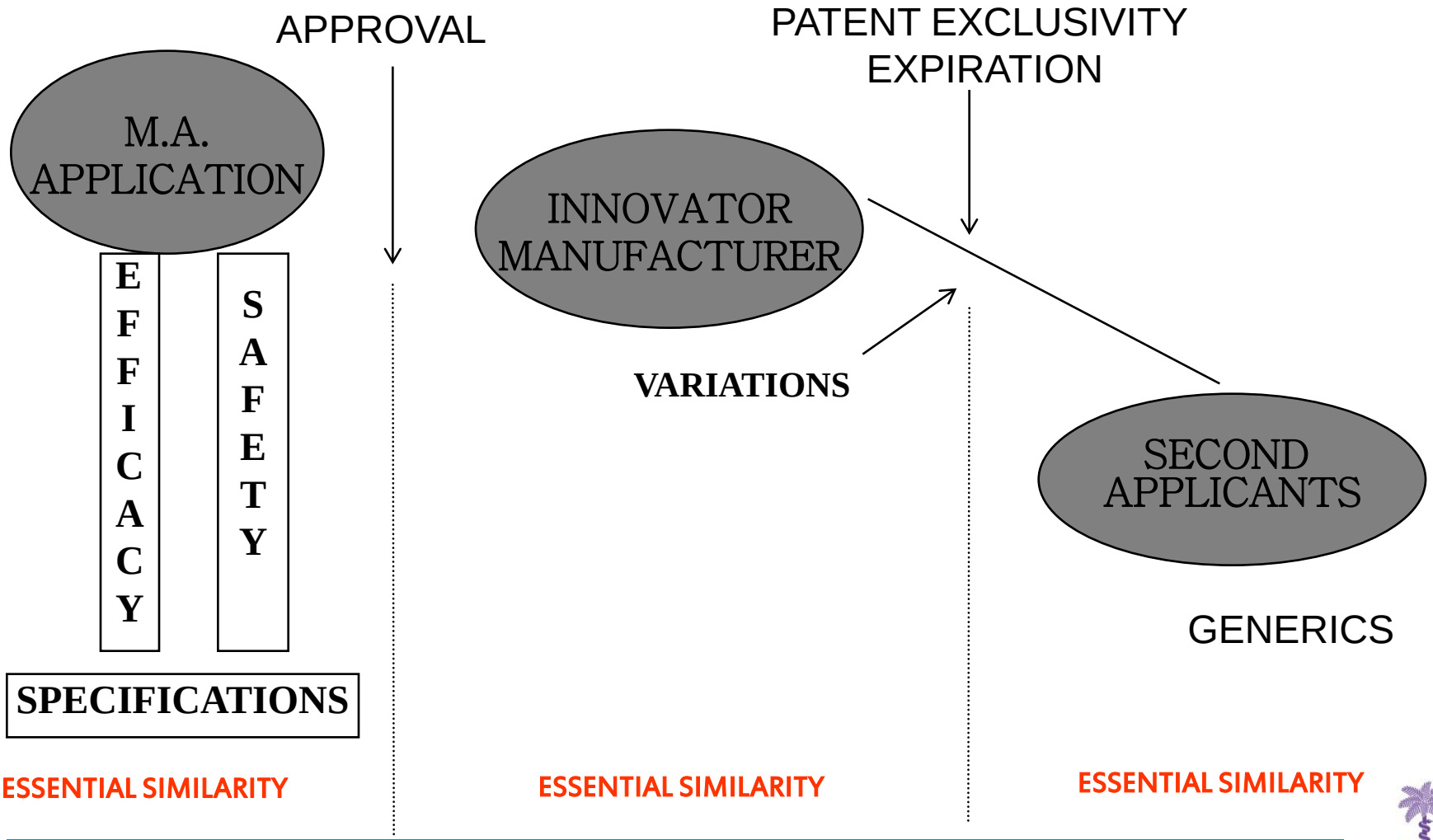




Bioequivalence based on the comparison of Bioavailability under strict criteria has proved to be the gold standard for the approval of generic medicinal products with ca. 40 years of experience without major incidents.

Regulatory Aspects in Drug Development

Ensuring quality of medicines across the life time of each active substance



Assumptions and initial considerations

- **Pharmaceutical quality characteristics ensure the maintenance of the established benefit/risk balance of a particular medicinal product.**

- **Throughout the therapeutic life of an active substance differences in formulation undergone by the initially approved medicinal product have to be tested.**

- **In many cases limitations of strictly quality testing require in vivo testing. Dissolution is a valid surrogate for absorption only in limited circumstances (BCS classes I and III)**

Assumptions and initial considerations

- **PK is a universally accepted surrogate for efficacy of medicinal products with favourable benefit/risk balance and well established clinical use.**

- **Bioequivalence based on the comparison of Bioavailability under strict criteria has proved to be the gold standard for the approval of generic medicinal products with ca. 40 years of experience without major incidents.**

- **Regulatory decisions on applications for Marketing Authorisations require that state-of-the-art science is incorporated in guidelines that orient development and assessment, even though it is not always apparent.**

INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

Guideline Title	Investigation of Bioavailability and Bioequivalence
Legislative basis	Directive 65/65/EEC as amended, Directive 75/318/EEC amended
Date of first adoption	December 1991
Date of entry into force	June 1992
Status	Last revised 1991
Previous titles/other references	None/ III/54/89
Additional Notes	This note for guidance concerns the application of Par section E of the Annex to Directive 75/318/EEC amended and Article 4,2 point 8 of Directive 65/65/EEC amended with a view to the granting of a market authorisation for a medicinal product. It defines wl bioavailability or bioequivalence studies are necess for immediate release products with a systemic effect formulates requirements for the design, conduct evaluation of these studies.

CONTENTS

London, 26 July 2001
CPMP/EWP/QWP/1401/98

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

DISCUSSION IN THE JOINT EFFICACY AND QUALITY WORKING GROUP	December 1997 – October 1998
TRANSMISSION TO CPMP	July 1998
RELEASE FOR CONSULTATION	December 1998
DEADLINE FOR COMMENTS	June 1999
DISCUSSION IN THE DRAFTING GROUP	February – May 2000
TRANSMISSION TO CPMP	July – December 2000
RELEASE FOR CONSULTATION	December 2000
DEADLINE FOR COMMENTS	March 2001
DISCUSSION IN THE DRAFTING GROUP	March - May 2001
TRANSMISSION TO CPMP	July 2001
ADOPTION BY CPMP	July 2001
DATE FOR COMING INTO OPERATION	January 2002

Note:

This revised Note for Guidance will replace the previous guideline adopted in December 1991.

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Change in EU medicines registration procedures

- **EU procedures options before 30 October 2005:**
  - **MRP (Mutual Recognition Procedure)**
  - **Centralised : new drugs**

- **EU-procedures options after 30 October 2005:**
  - **MRP (Mutual Recognition Procedure)**
  - **Decentralised Procedure: mostly generics**
  - **Centralised: new drugs and generics (for drugs approved by CP)**

- **Difficulties in the interpretation of the (current) Note for Guidance on BA/BE, prompting**
  - **divergent opinions and**
  - **CMDh and CHMP referrals – time and resources consuming**
    - **Committee for Mutual Recognition and Decentralized Procedures (CMDh)**
    - **Committee for Human Medicinal Products (CHMP)**

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 6 NOVEMBER 2001 ON THE COMMUNITY CODE RELATING TO MEDICINAL PRODUCTS FOR HUMAN USE

Official Journal L – 311, 28/11/2004, p. 67 – 128

as amended

Art. 8(3) (full applications),

Art. 10(1) (2) (generic drug applications),

Art. 10(3) (hybrid applications),

Art. 10(4) (biosimilars),

Art. 10a (well established use),

Art. 10b (fixed combinations),

Art. 10c (informed consent – co-marketing licenses),

Commission Regulations (EC) No 1084/2003 and 1085/2003 for extension and variation.

Main options for the revision

- **Only immediate release oral dosage forms**
- **Only Bioequivalence (not bioavailability)**
- **Simple and clear**
  - **No ambiguity, covering all possible situations**
- **Incorporating previous experience**
- **Quality vs clinically oriented**

European Medicines Agency

London, 20 January 2010
Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE(CH MP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

DISCUSSION IN THE JOINT EFFICACY/QUALITY WORKING GROUP	December 1997 – Oct. 1998
TRANSMISSION TO CPMP	July 1998
RELEASE FOR CONSULTATION	December 1998
DEADLINE FOR COMMENTS	June 1999
DISCUSSION IN THE DRAFTING GROUP	February – May 2000
TRANSMISSION TO CPMP	July – December 2000
RELEASE FOR CONSULTATION	December 2000
DEADLINE FOR COMMENTS	March 2001
DISCUSSION IN THE DRAFTING GROUP	March - May 2001
TRANSMISSION TO CPMP	July 2001
ADOPTION BY CPMP	July 2001
DATE FOR COMING INTO OPERATION	January 2002
DISCUSSION ON REV. 1 IN THE PK-GROUP OF THE EFFICACY WORKING PARTY	May 2007-July 2008
DISCUSSION ON REV. 1 BY THE QUALITY WORKING PARTY	June 2008
DRAFT REV. 1 AGREED BY THE EFFICACY WORKING PARTY	8 July 2008
ADOPTION REV. 1 BY CHMP FOR RELEASE FOR CONSULTATION	24 July 2008
END OF CONSULTATION REV. 1 (DEADLINE FOR COMMENTS)	31 January 2009
REV. 1 AGREED BY THE EFFICACY WORKING PARTY	January 2010
REV. 1 ADOPTION BY CHMP	20 January 2010
REV. 1 DATE FOR COMING INTO EFFECT	1 August 2010

EXECUTIVE SUMMARY

- This guideline specifies the requirements for the design, conduct, and evaluation of bioequivalence studies for **immediate release dosage forms with systemic action.**
  - Limited scope

GENERIC MEDICINAL PRODUCTS

- In applications for generic medicinal products, the purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutic quality between the generic product and an innovator product in order to allow bridging of clinical data associated with the innovator product.

Definitions of Essentially Similar and Generic Products

A proprietary medicinal product will be regarded as essentially similar to another product if it has
(Minutes of Council for 87/22)

- **the same qualitative and quantitative composition in terms of active substances**
- **the pharmaceutical form is the same**
- **and, where necessary, bioequivalence with the first product has been demonstrated by appropriate bioavailability studies carried out**

In general, a generic medicinal product is a product which has
(Directive 2001/83/EC, Article 10(2)(b))

- the same qualitative and quantitative composition in active substances as the reference medicinal product,
- the same pharmaceutical form as the reference medicinal product,
- and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.
- However, bioavailability studies need not be required of the applicant if he can demonstrate that the generic medicinal product meets the relevant criteria as defined in the appropriate detailed guidelines.

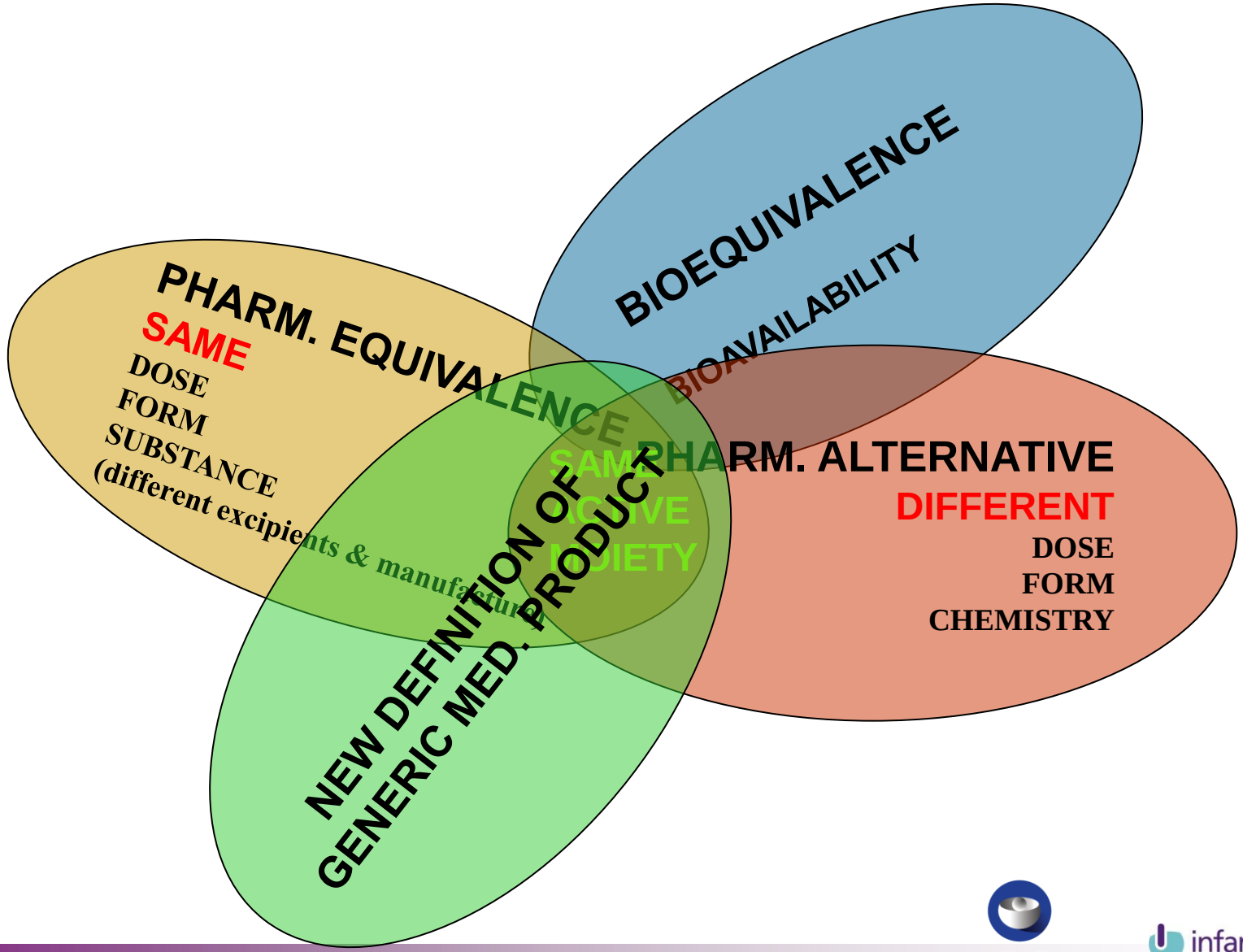
GENERIC MEDICINAL PRODUCTS

Extended scope

- By definition it is considered that different
  - salts,
  - esters,
  - ethers,
  - isomers,
  - mixtures of isomers,
  - complexes
  - or derivatives
- of an active substance are considered to be the same active substance,
  - **unless they differ significantly in properties with regard to safety and/or efficacy**.

- Furthermore, various immediate-release oral pharmaceutical forms can be considered to be one and the same pharmaceutical form
  - Suspensions, capsules, tablets, powders.

Definitions of



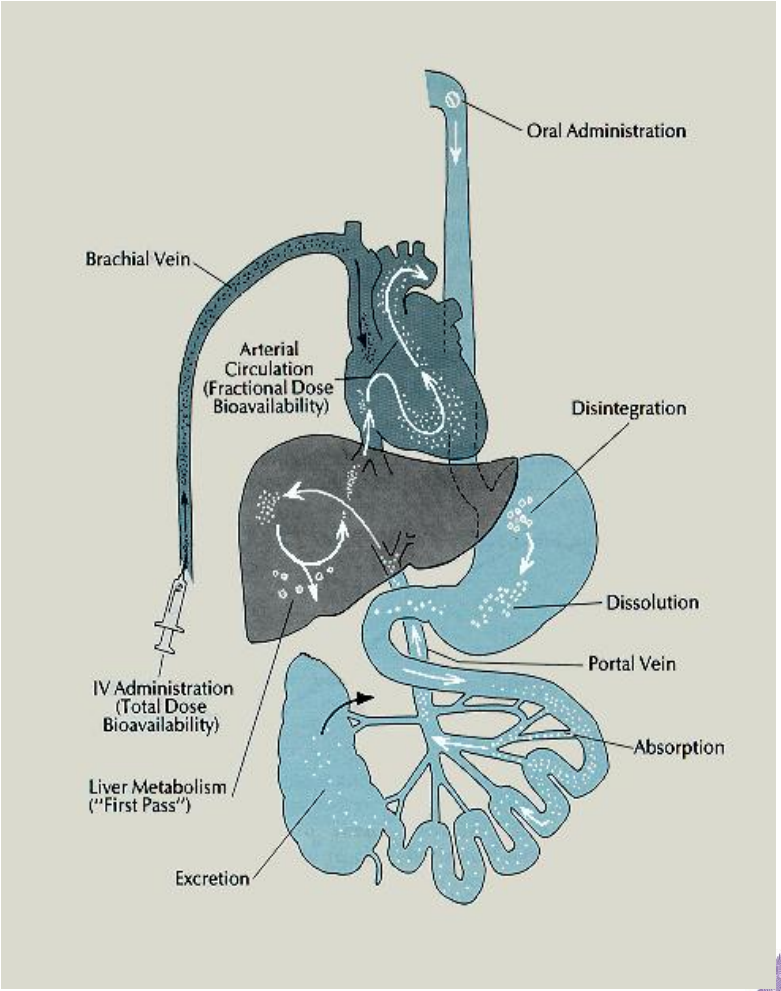
Definition of Bioavailability

- Bioavailability means the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action*

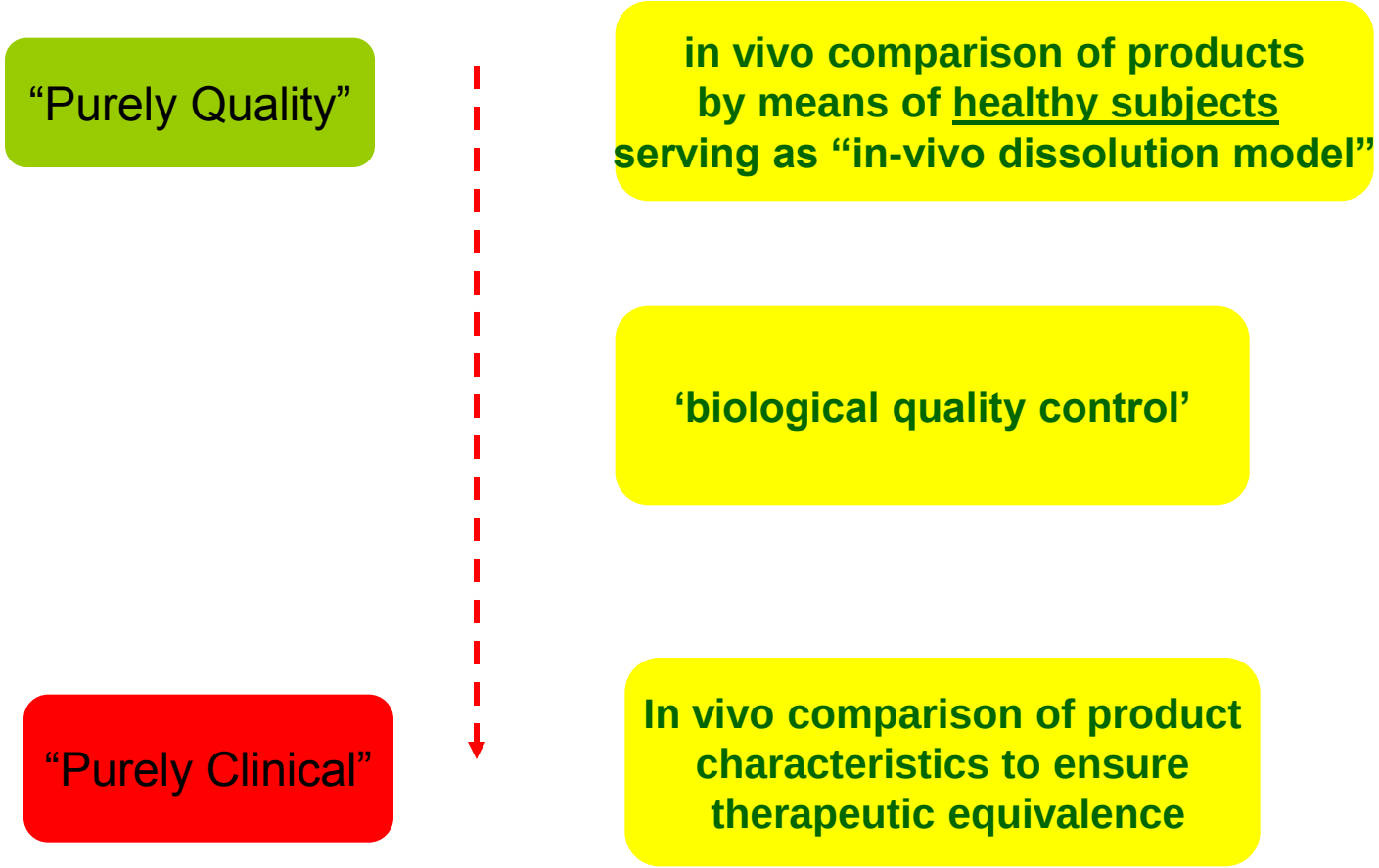
plasma

- Bioavailability is a property which is related to the active substance (absolute) as well as to the formulation (relative) and influenced by food effects, DDI's, intrinsic factors.

- Most of these factors except for formulation affect the systemic availability of the active substance to the same extent for both reference or test formulations. In bioequivalence these factors cancel out.



Bioequivalence studies



Design, conduct and evaluation of bioequivalence studies

ISSUE	STANDARD DESIGN	SPECIAL CASES
Parent/metabolite	PARENT ONLY	METABOLITE
Food effect	NO	YES
High variability	NO	YES
Narrow Therapeutic Index	NO	YES
Chirality	NO	YES
Linearity	YES	NO
Different strengths	PROPORTIONAL COMPOSITION	NON PROPORTIONAL COMPOSITION

Study design

- The study should be designed in such a way that the formulation effect can be distinguished from other effects..

  – **Standard design**

    - If two formulations are to be compared, a two-period, two-sequence single dose crossover design is the design of choice. The treatment periods should be separated by an adequate wash out period: generally 5 elimination half-lives.

Standard study design:

- **single dose, two-period, crossover**
- **healthy volunteers**
- **Test (generic) vs. Reference (comparator)**
- **90% CI AUC and Cmax: 80 – 1 25%**

Study conduct – Fasting or fed conditions

- In general, fasting conditions, unless reference SPC recommends only in fed state.
  - If SmPC recommends intake of the reference medicinal product on an empty stomach or irrespective of food intake,
    - **fasting conditions.**
  - If SmPC recommends intake of the reference medicinal product only in fed state,
    - **fed conditions.**
- Medicinal products with special formulations (e.g. microemulsions, solid dispersions),
    - **both fast and fed unless SPC recommends only in fed state**
- In studies performed under fed conditions, the meal should be a high-fat (approximately 50 percent of total caloric content of the meal) and high-calorie (approximately 800 to 1000 calories) meal.
- Approach is different from FDA's: in principle both fed and fasting, unless BCS class I or label (SPC)

Parent compound or metabolites

In principle, evaluation of bioequivalence should be based upon measured concentrations of the parent compound, even if there are active metabolites

- **Cmax of a parent compound is usually more sensitive to differences in formulations**

Inactive pro-drugs: still use parent compound

- **but**
  - **If not reliably measured and very low or no contribution to activity (as measured by PK and PD)**
  - **Then main active metabolite**

Parent compound or metabolites

- **Use of metabolite as surrogate**
  - **Not encouraged even in the case of pro-drugs**
  - **Only exceptional cases**
    - **Only if sensitivity of bioanalytical method is low for parent – state-of-the-art arguments**
    - **If parent exposure reflected by metabolite exposure**
    - **If metabolite formation not saturated at usual doses**
    - **If metabolite is active and exposure much higher than parent**
  - **Mycophenolate mofetil exception because AUC 12000 fold higher for metabolite**
- **Parent + metabolite**
  - **Not needed**

Strength to be investigated

- If conditions below fulfilled, only one strength
  In general highest strength; If HS, any strength

a) the pharmaceutical products are manufactured by the same manufacturing process,

b) linear pharmacokinetics, i.e. proportional increase in AUC with increased dose, over the therapeutic dose range,

c) the qualitative composition of the different strengths is the same,

d) the composition of the strengths are quantitatively proportional, i.e. the ratio between the amount of each excipient to the amount of active substance(s) is the same for all strengths
   (for immediate release products, coating components, capsule shell, colour agents and flavours are not required to follow this rule),

e) appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing

Strength to be investigated

Deviation from proportional composition

- If there is some deviation from quantitatively proportional composition, condition is still considered fulfilled if
  - the amount of the active substance(s) is less than 5 % of the tablet core weight or the weight of the capsule content in conjunction with
  - the amounts of the different core excipients or capsule content are the same for all strengths and only the amount of active substance is changed or
  - the amount of a filler is changed to account for the change in amount of active substance. The amounts of other core excipients or capsule content should be the same for all strengths

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Needed clarifications on strength and linearity

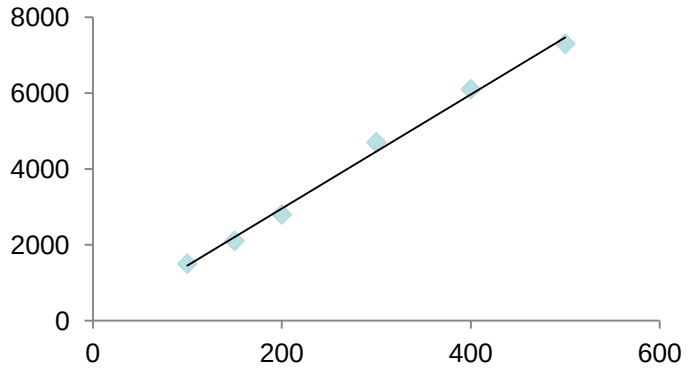
- In case of non-linear pharmacokinetics (i.e. not proportional increase in AUC with increased dose) there may be a difference between different strengths in the sensitivity to detect potential differences between formulations.

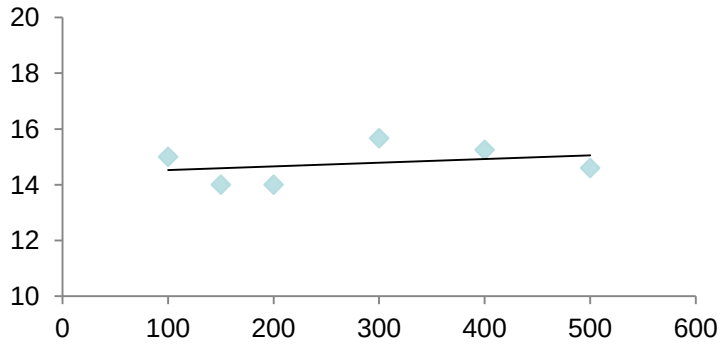
- In the context of this guideline, pharmacokinetics is considered to be linear if the difference in dose-adjusted mean AUCs is no more than 25% when comparing the studied strength (or strength in the planned bioequivalence study) and the strength(s) for which a waiver is considered.

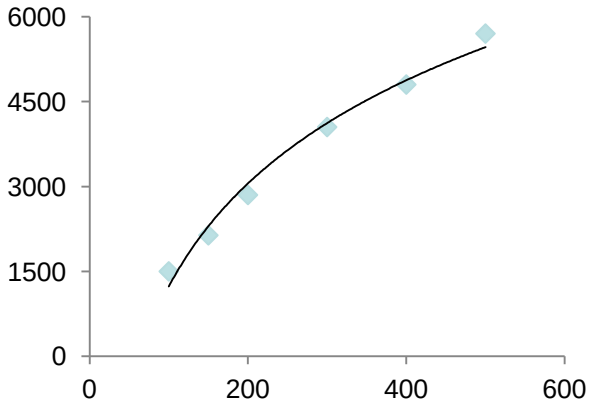
- In order to assess linearity, the applicant should consider all data available in the public domain with regard to the dose proportionality and review the data critically.

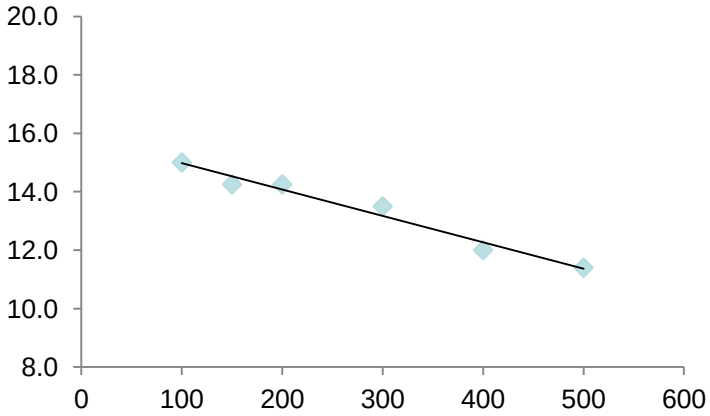
- Assessment of linearity will consider whether differences in dose-adjusted AUC meet a criterion of ± 25%.

Needed clarifications on strength and linearity









Max. Diference is 24%

Evaluation

- **Statistical analysis - ANOVA**
  - Sequence, subject, period, formulation effects – not a concern
  - Carry over – exclude subjects with pre-dose > 5% Cmax
- **Acceptance limits** (rounded to 2 decimal places)
  - lower bound ≥ 80.00% and upper bound ≤ 125.00%
- **Two-stage design**
  - At last (pre-specified; type I error-alpha- preserved; interim analysis)
- **Subject accountability (outliers)**
  - Same as Q&A (all data should be included; reasons for exclusion)
- **Presentation of data**
  - All individual concentration data
  - Point estimate + 90% Confidence Interval
  - ANOVA tables
  - Sufficient detail to enable independent PK and statistical analysis

Highly variable drugs or drug products

- Highly variable drug products (HVDP) are those whose intra-subject **variability** for a parameter is larger than 30%.
- Those HVDP in which a difference in Cmax up to 30% is considered **clinically irrelevant** based on a sound clinical justification can be assessed with a widened acceptance range.
- If this is the case the acceptance criteria for Cmax can be widened to a maximum of 69.84 – 143.19%.
- For the acceptance interval to be widened the bioequivalence study must be of a **replicate design** where it has been demonstrated that the within-subject variability for Cmax of the reference compound in the study is >30%.
- The request for widened interval must be prospectively specified in the protocol.

Highly variable drugs or drug products

The extent of the widening is defined based upon the within-subject variability seen in the bioequivalence study using scaled-average-bioequivalence according to [U, L] = exp [±k·sWR],

Within-subject CV (%)*	Lower Limit	Upper Limit
30	80.00	125.00
35	77.23	129.48
40	74.62	134.02
45	72.15	138.59
≥50	69.84	143.19

Narrow therapeutic index drugs (NTIDs)

NTIDs – decided case by case

- In specific cases of products with a narrow therapeutic index, the acceptance interval for AUC should be **narrowed to 90.00-111.11%.**
- Where Cmax is of particular importance for safety, efficacy or drug level monitoring the 90.00-111.11% acceptance interval should also be applied for this parameter.
- If it is not possible to define a set of criteria to categorise drugs as narrow therapeutic index drugs (NTIDs) and it must be decided case by case if an active substance is an NTID based on clinical considerations.

Characteristics to be investigated

- **Enantiomers**
  - **The use of achiral bio-analytical methods is generally acceptable. Measurement of individual enantiomers is recommended only when all the following conditions are met:**
    - **pronounced difference in pharmacokinetics,**
    - **pronounced difference in pharmacodynamics and**
    - **there is a non-linearity in the pharmacokinetics of at least one of the enantiomers, which may result in the concentration ratio of enantiomers to be modified by a difference in the rate of absorption.**

APPENDIX III BCS-based Biowaiver

- The BCS (Biopharmaceutics Classification System)-based biowaiver approach is meant to reduce *in vivo* bioequivalence studies, *i.e.*, it may represent a **surrogate for *in vivo* bioequivalence**.

- *In vivo* bioequivalence studies may be exempted if the equivalence in the *in vivo* performance can be justified by satisfactory *in vitro* data.

- Provided certain prerequisites are fulfilled as outlined in this document comparative *in vitro* dissolution could be even more discriminative than *in vivo* studies.

APPENDIX III BCS-based Biowaiver

BCS-based biowaivers are applicable for an immediate release drug product if

- the drug substance has been proven to exhibit high solubility and complete absorption (**BCS-class I**); and
- either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min or less) *in vitro* dissolution characteristics and
- 'active' excipients are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred.
- If generic is a different salt, BCS biowaiver does not apply
- **Complete absorption means extent of absorption ≥ 85 %**

APPENDIX III BCS-based Biowaiver

Complete absorption

- When data from mass balance studies are used to support complete absorption, it must be ensured that the metabolites taken into account in determination of fraction absorbed are formed after absorption (i.e., Phase 1/ Phase 2 metabolism).

- Hence, when referring to total radioactivity excreted in urine, it should be ensured that there is no degradation or metabolism of the unchanged drug substance in the gastric or intestinal fluid.

APPENDIX III BCS-based Biowaiver

Summary Requirements for BCS-class III drugs

- the drug substance has been proven to exhibit high solubility and limited absorption (**BCS-class III**); and

- very rapid (> 85 % within 15 min) *in vitro* dissolution of the test and reference product has been demonstrated considering specific requirements and

- **excipients are qualitatively the same and quantitatively very similar**

New features

- Bioequivalence only
- New definition of generic medicinal product
- Multiple dose design only exceptionally
- If no reliable bioanalytical method for parent compound
  - Multiple dose
  - Higher dose
  - Metabolite
  - Urinary data
- Clearer guidance on
  - Fed/fasting conditions
  - Use of metabolites
  - Enantiomers
  - Strength to be used

New features

- New bioanalytical guideline
- Reasons for exclusion/inclusion of subjects in statistical analysis
- Two-stage design
- Need to present all the studies performed during development
  - Positive and negative – combined analysis
- HVD
- NTID
- BCS-based biowaiver for class I and class III
- More specific guidance on other dosage forms
- Revision of MR guideline

Problems encountered

- The aim of being very specific and clear was not always achieved.
- Incorporating all the experience and trying to predict every possible situation proved to be impossible.
- About 900 comments received, taken into account and responded to.
- Still there are always new questions

Q&A issues

- **clopidogrel**
  - Metabolite or parent?
    - possible to reliably measure parent
  - Fed and fasting?
    - Only fasting: SmPC; if a food effect is proven-revise
  - Back-conversion of major metabolite
    - Validation of the whole bioanalytical method to avoid back-conversion during extraction, etc.
  - Widening of acceptance for C_{max}
    - it is not definitely proven that widening Cmax acceptance range for clopidogrel is devoid of clinically relevant implications, widening of 90% confidence intervals for Cmax is not recommended.

Q&A issues

- **Losartan**
- Metabolite or parent?
  - angiotensin II antagonist at the AT1-subtype receptor
  - losartan binds competitively to receptor; active metabolite E3174 binds non-competitively
  - AUC of metabolite 4-8 fold higher; activity 20 fold higher
  - However during first hour after administration (single dose)

    AUC x activity of parent equals that of metabolite
  - Metabolite E3174 is secondary, hardly reflecting absorption
  - Parent is preferred for BE assessment with conventional limits

Q&A issues

- **tacrolimus**
  - Narrow therapeutic index based on PD and clinical safety/efficacy considerations
  - The EWP recommends that the bioequivalence acceptance criteria for tacrolimus should be [90-111%] for AUC and [80-125%] for Cmax.

- **mycophenolate**
  - Parent compound inactive and completely converted into the active metabolite yielding a 12000 fold difference in AUC.
  - In addition short tmax and t1/2 of the parent compound which will limit a reliable estimation of Cmax of the parent compound. Metabolite data is acceptable.

Problems encountered

Requirements	Challenge	Comments/Examples
Regulatory issues	Global conference on harmonization for therapeutically equivalent multisource drug products	An international platform for discussion such as ICH, WHO, and others is needed to begin harmonization process
	Regulatory inspection	Foreign inspection and sharing of inspection reports are not harmonized
	Contract research organization (CRO)	Certification of CRO, differences in quality
Bioanalytical methods	Validation	GL in force
In vitro requirements	Pharmaceutical equivalence	Definition (e.g., capsule versus tablet)
	Comparative drug release/dissolution profiles	Use of similarity test to replace in vivo bioequivalence studies
	BCS	Extension of BCS
	Chemistry, manufacturing controls	Different requirements (e.g., stability)

Problems encountered

Requirements	Challenge	Comments/Examples
In vivo requirements	Reference drug product	Reference product is not the same in each domestic marketplace; selection of the dose strength for bioequivalence study is not harmonized
	Design of bioequivalence studies	Special designs for highly variable drugs, long half-life drugs, etc.
	Subject population	Different subject populations and different diets
	Food effect and sprinkle studies	Different requirements globally
	Acceptance criteria for bioequivalence studies	Different criteria for highly variable drugs, critical dose drugs, etc.
	Drugs with an important early time of onset and multiphasic modified release products	Use of partial AUC


THANK YOU!