Η Συμβολή της ερευνητικής μας ομάδας στην ανάπτυξη-έρευνα/έγκριση των φαρμάκων

Παναγιώτης Μαχαίρας

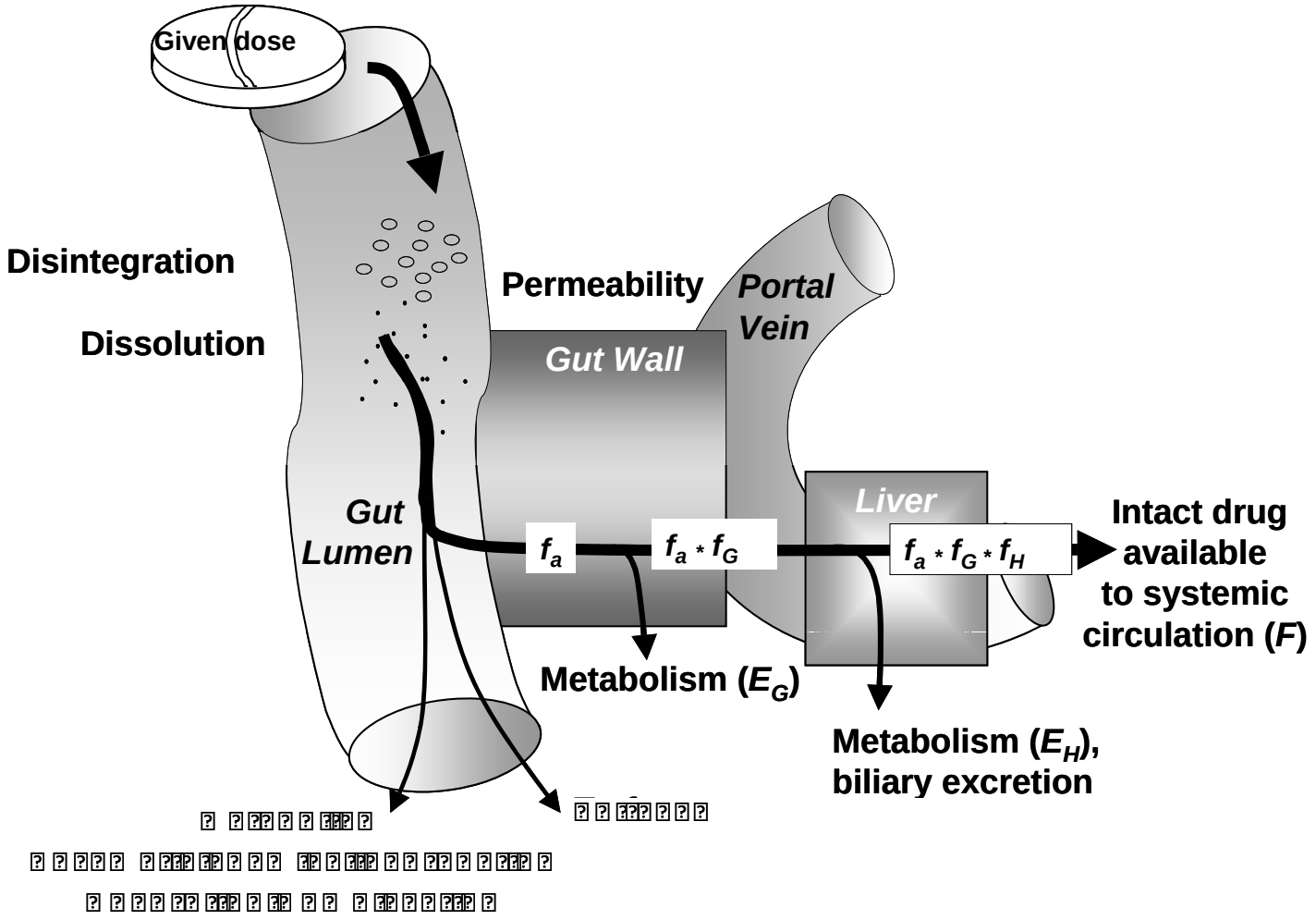
Εργαστήριο Βιοφαρμακευτικής – Φαρμακοκινητικής
Τμήμα Φαρμακευτικής, ΕΚΠΑ

REVIEW JOURNAL OF PHARMACEUTICAL SCIENCES, VOL. 102, NO. 9, P. 3018–3036, SEPTEMBER 2013

Keeping a Critical Eye on the Science and the Regulation of Oral Drug Absorption: A Review

PANOS MACHERAS, VANGELIS KARALIS, GEORGIA VALSAMI

Laboratory of Biopharmaceutics–Pharmacokinetics, Faculty of Pharmacy, National and Kapodistrian University of Athens, Athens 15771, Greece


Given dose
Disintegration
Dissolution
Permeability
Portal Vein
Gut Wall
Liver
Gut Lumen
f_a
$f_a * f_G$
$f_a * f_G * f_H$
Intact drug available to systemic circulation (F)
Metabolism (E_G)
Metabolism (E_H), biliary excretion

THE DRUG (FORMULATION) SPACE

ORIGINAL (Small molecule or biotechnological product)

Proprietary drug, with data and market exclusivities

Generics

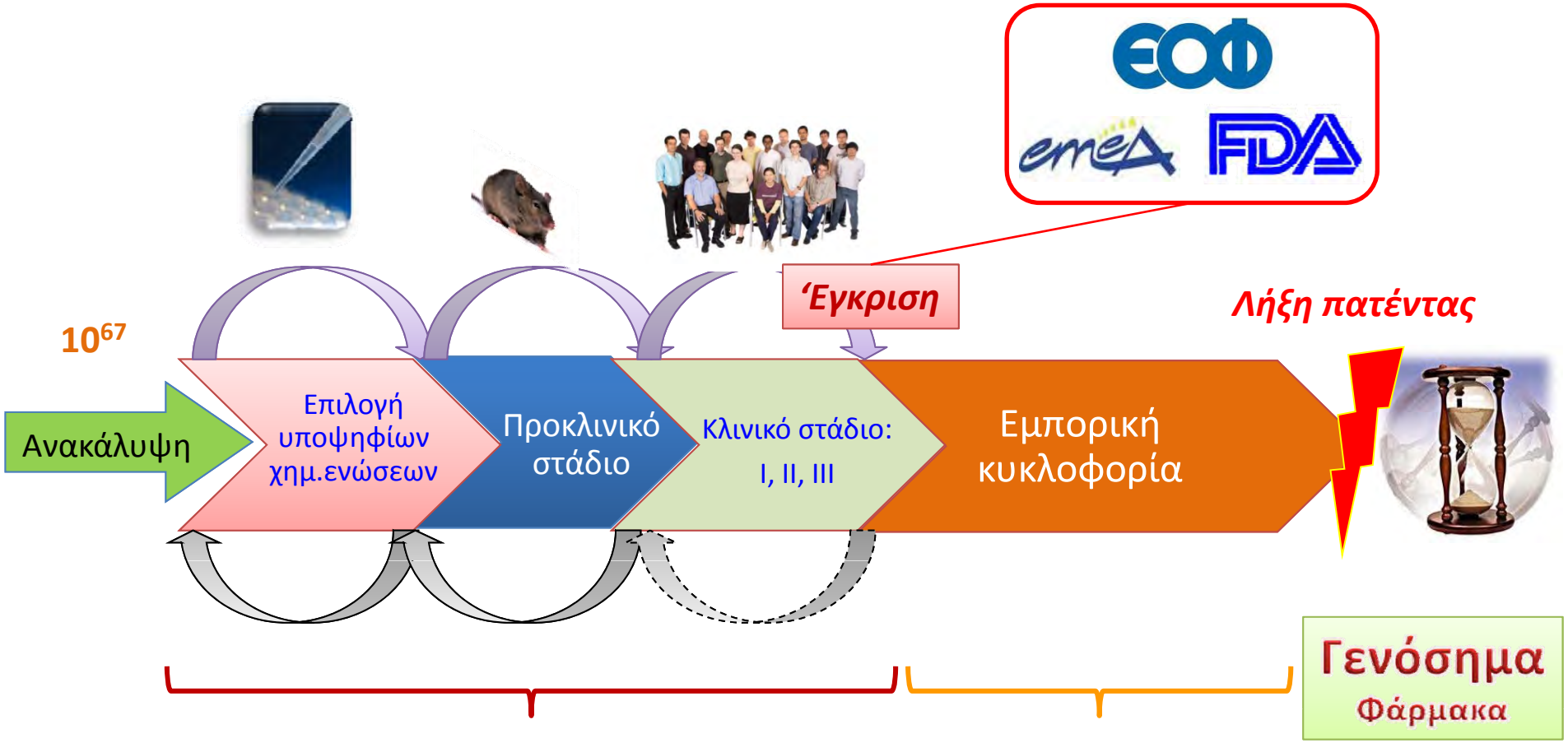
(Copy drugs, only licensed after drug's basic patent has expired)

- **Supergenerics**
  - no official definition
  - one of the many: improved therapeutic entities
- **Complex Drugs** or Non biological complex drugs (NBCDs)
  - no official definition
  - not fully characterized large molecules

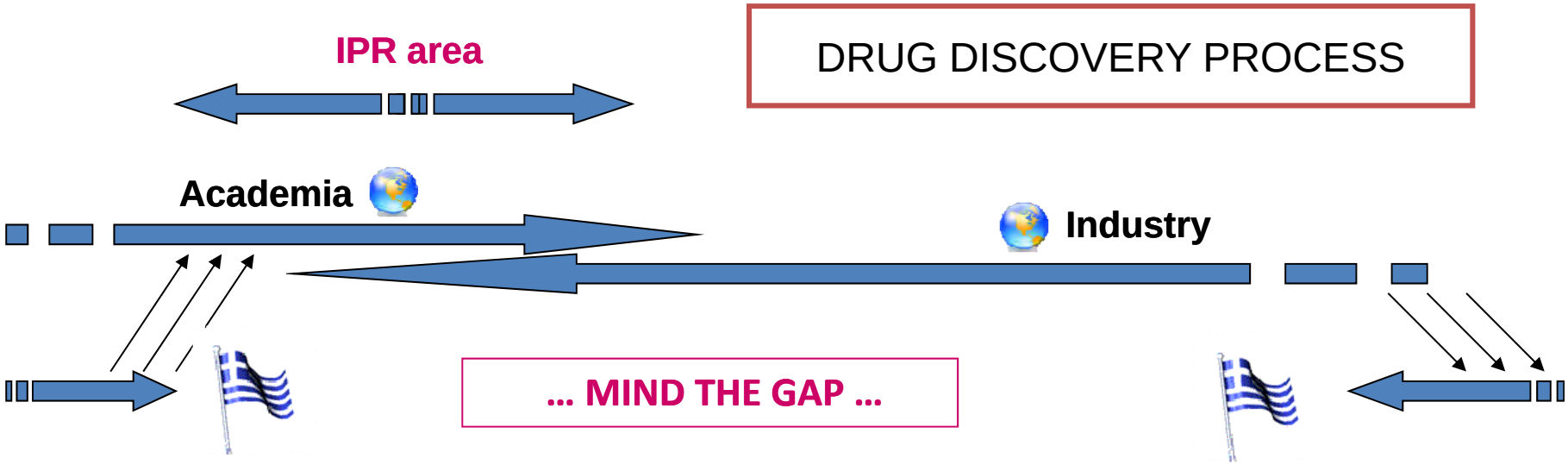
Biosimilars

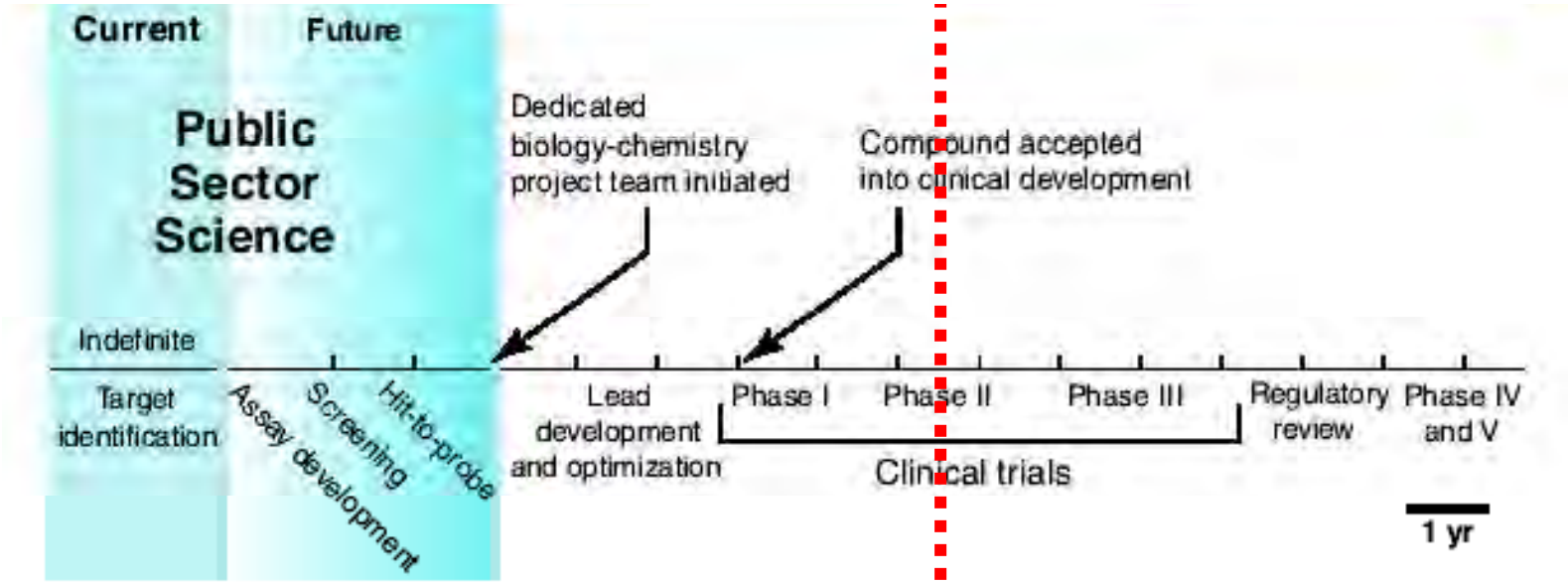
also known as *Similar biotechnological (biological) medicinal products.* Biologic products that are intended copies of an already licensed reference Biologic Product.

ORIGINAL (Small molecule or biotechnological product)


ΕΟΦ
emea
FDA
'Εγκριση
Λήξη πατέντας
10^{67}
Ανακάλυψη
Επιλογή υποψηφίων χημ.ενώσεων
Προκλινικό στάδιο
Κλινικό στάδιο: I, II, III
Εμπορική κυκλοφορία
Γενόσημα
Φάρμακα
> 10 χρόνια
"10" χρόνια

DRUG DISCOVERY PROCESS





Interface of the MLI and drug development.

By courtesy of Dr George Kollias, Academician,
Biomedical Sciences Research Center , "Alexander Fleming".

Ανακάλυψη

- ***Κέντρο προκλινικών μελετών (φαρμακολογική, τοξικολογική, βιοφαρμακευτική αξιολόγηση)***

- ***Νομοθετικό πλαίσιο για τα δικαιώματα της πνευματικής ιδιοκτησίας ερευνητών και Πανεπιστημίου***

‘Εγκριση

- ***Χώρα αναφοράς***

OUTLINE

A. Generics' R&D/approval:

1. Well-Established Use (WEU)
2. Biowaivers
3. Classical route via Bioequivalence studies
4. Complex drugs
5. SuperGenerics

5a. SuperGenerics: Milk Based Formulations

B. Biosimilars

C. Application of Pharmacokinetics-Pharmacometrics in Clinical Practice: Individualisation of therapy

Generics' R&D/approval:

1. Well-Established Use (USE)

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

Article 10a

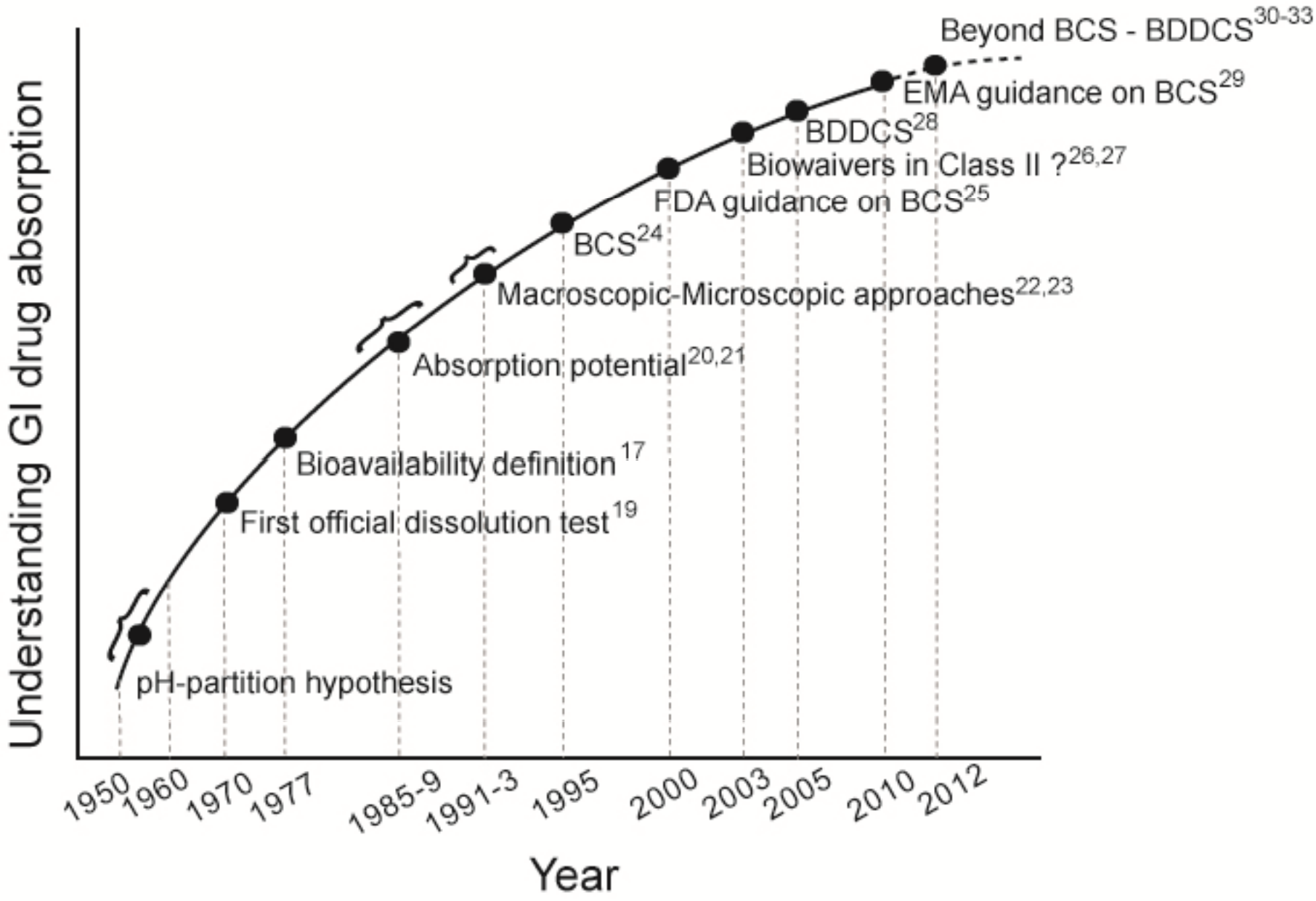
By way of derogation from Article 8(3)(i), and without prejudice to the law relating to the protection of industrial and commercial property, the applicant shall not be required to provide the results of pre-clinical tests or clinical trials if he can demonstrate that the active substances of the medicinal product have been in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in the Annex. In that event, the test and trial results shall be replaced by appropriate scientific literature.

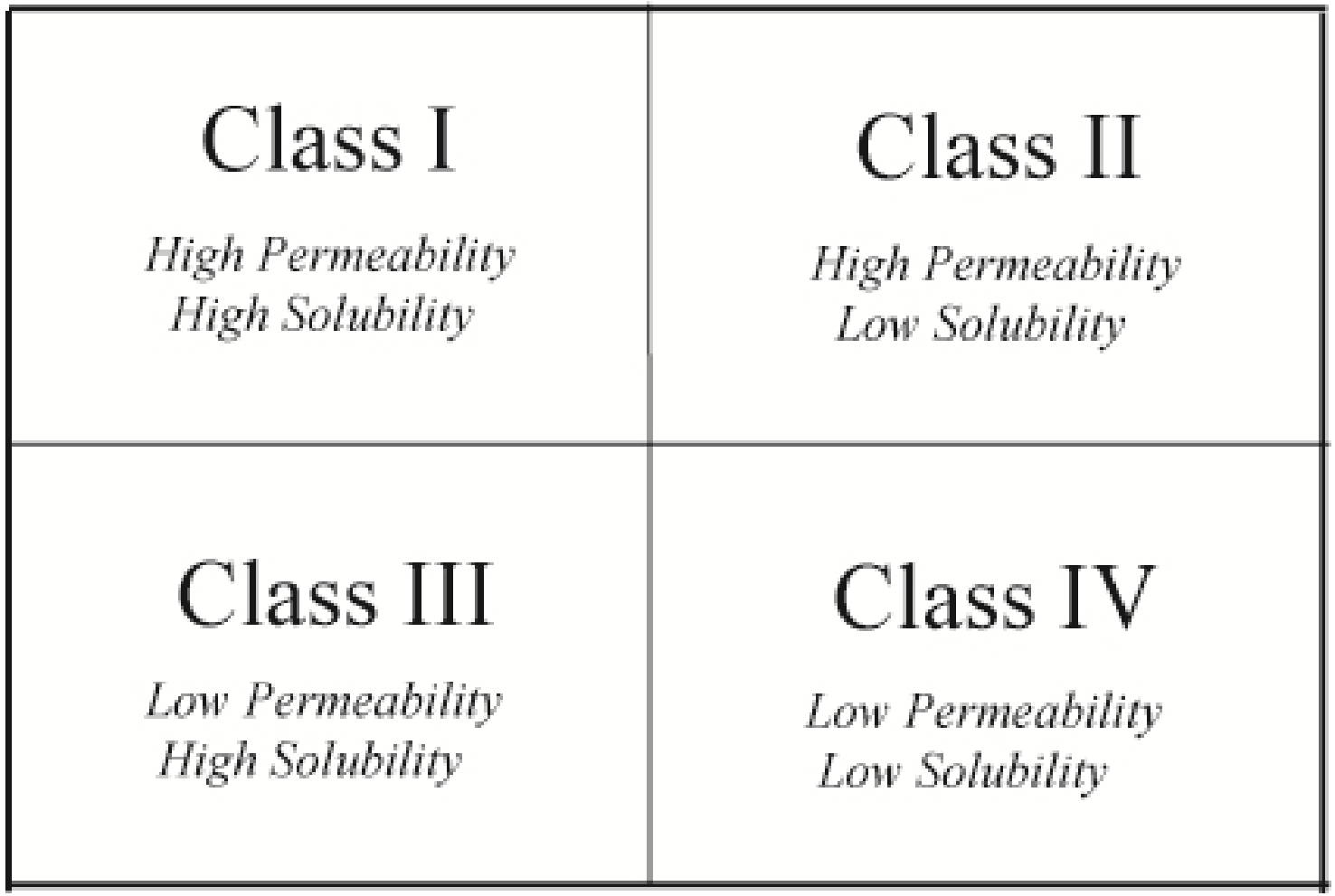
Parameters to focus on:

- Years in the market
- Extent of use / Geographical basis
- Scientific interest
- Active substance (qual./quant)
- The role of excipients (qual./quant)
- Pharmaceutical formulation
- Stability issues
- Pharmacological issues: Safety, efficacy
- Regulatory issues

Generics' R/D/approval:

2. Biowaivers


Understanding GI drug absorption
Year
1950
1960
1970
1977
1985-9
1991-3
1995
2000
2003
2005
2010
2012
pH-partition hypothesis
First official dissolution test[19]
Bioavailability definition[17]
Absorption potential[20,21]
Macroscopic-Microscopic approaches[22,23]
BCS[24]
FDA guidance on BCS[25]
Biowaivers in Class II ?[26,27]
BDDCS[28]
EMA guidance on BCS[29]
Beyond BCS - BDDCS[30-33]



Amidon GL, Lennernas H, Shah VP, Crison JR. *Pharm. Res.* **12**: 413-20 (1995))

Guidance for Industry

Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
August 2000

European Medicines Agency

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

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

APPENDIX III

BCS-based Biowaiver

III.2 Absorption

The demonstration of complete absorption in humans is preferred for BCS-based biowaiver applications. For this purpose complete absorption is considered to be established where measured extent of absorption is ≥ 85 %. Complete absorption is generally related to high permeability.

Complete drug absorption should be justified based on reliable investigations in human. Data from

- absolute bioavailability or
- mass-balance

studies could be used to support this claim.

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. 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. Phase 1 oxidative and Phase 2 conjugative metabolism can only occur after absorption (i.e. cannot occur in the gastric or intestinal fluid). Hence, data from mass balance studies support complete absorption if the sum of urinary recovery of parent compound and urinary and faecal recovery of Phase 1 oxidative and Phase 2 conjugative drug metabolites account for ≥ 85 % of the dose.

Identification of Biowaivers among Class II Drugs: Theoretical Justification and Practical Examples

E. Rinaki, A. Dokoumetzidis, G. Valsami, P. Macheras. *Pharm Res.* 2004 Sep;21(9):1567-72.

QBCS

Quantitative Biopharmaceutics Classification System (QBCS): The Central Role of Dose/Solubility Ratio

E. Rinaki, G. Valsami, P. Macheras.
Pharm. Res. 20: 1917-1925 (2003)

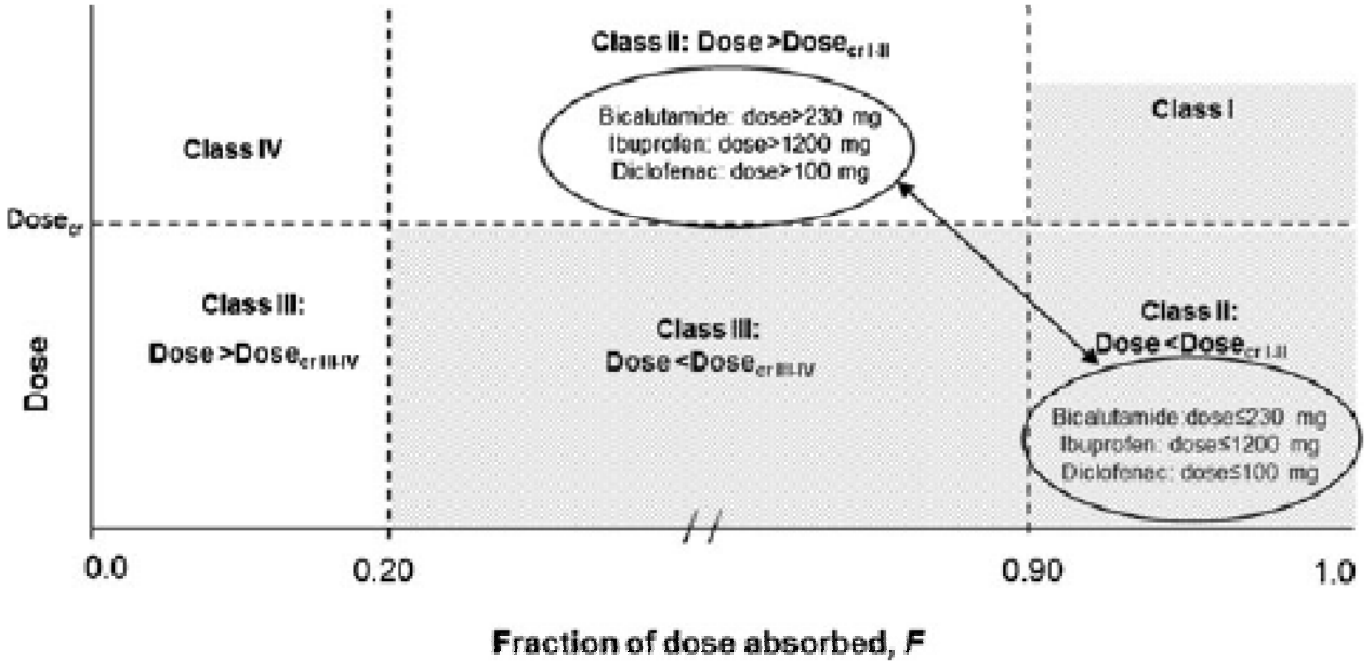
Dose Dependent Biopharmaceutic Classification System (DDBCS)

Pharm Res
DOI 10.1007/s11095-012-0815-4

RESEARCH PAPER

Elucidating the Role of Dose in the Biopharmaceutics Classification of Drugs: The Concepts of Critical Dose, Effective *In Vivo* Solubility, and Dose-Dependent BCS

Georgia Charkoftaki • Aristides Dokoumetzidis • Georgia Valsami • Panos Macheras



International Journal of Pharmaceutics 464 (2014) 85–90

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

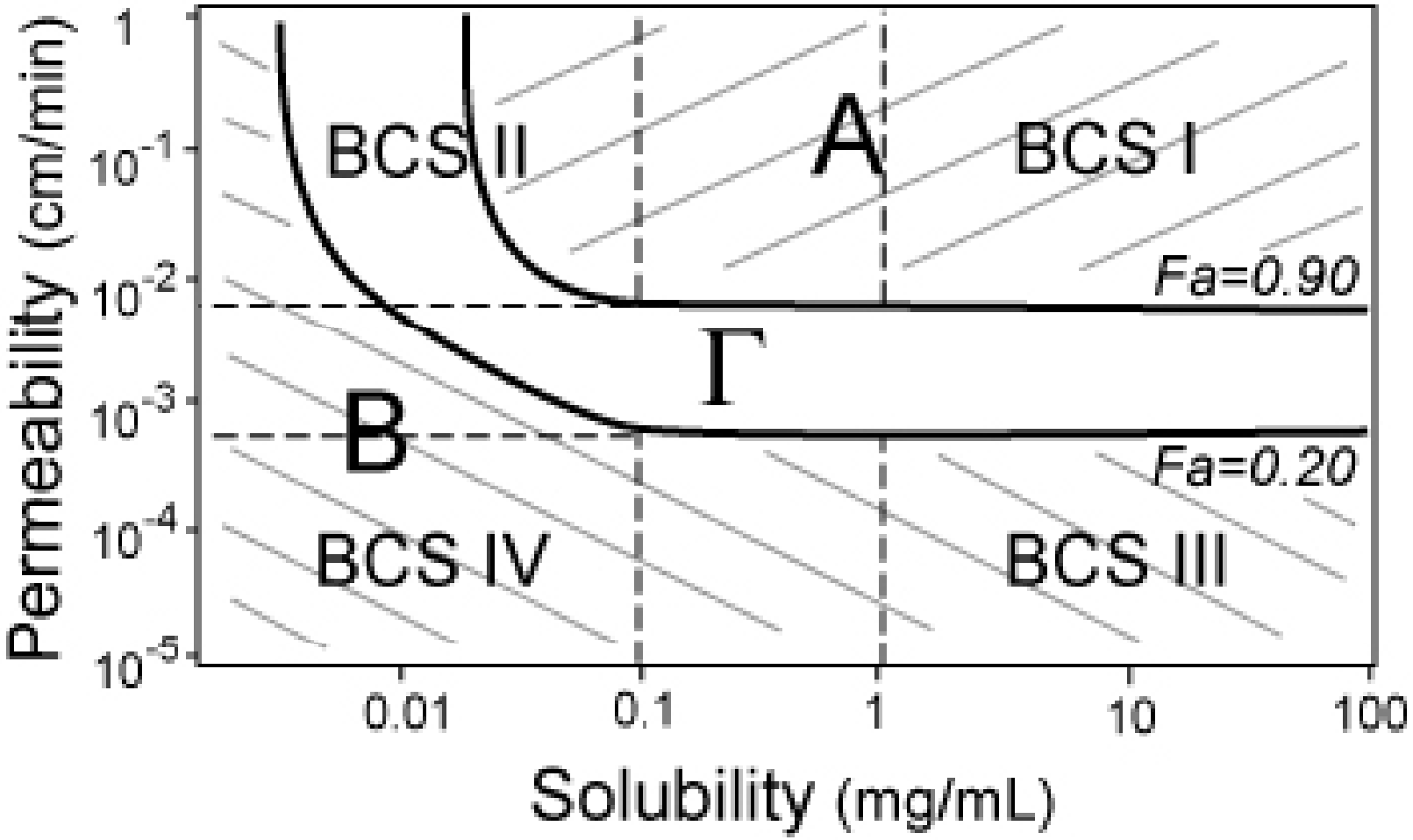
journal homepage: www.elsevier.com/locate/ijpharm

A non-binary biopharmaceutical classification of drugs: The ABΓ system

Panos Macheras*, Vangelis Karalis

Laboratory of Biopharmaceutics – Pharmacokinetics, Faculty of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece

The **ABΓ system** is co-plotted with a continuous version of BCS. The latter was constructed using the cutoff values of high, low solubility and permeability estimates. The dose and particle size values were set equal to 10 mg and 10 µm, respectively.

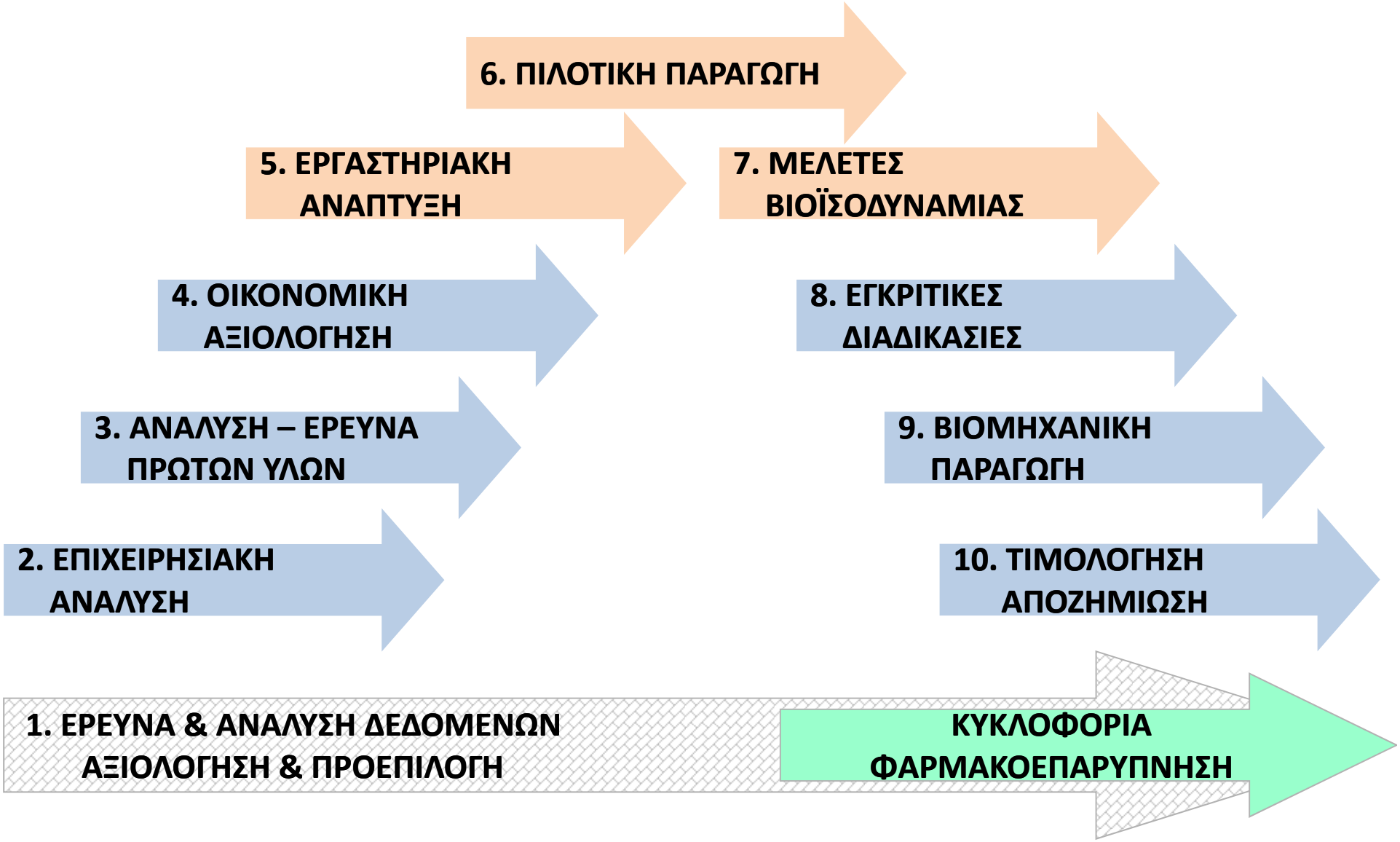


Με βάση biowaiver report από το εργαστηριό μας σήμερα κυκλοφορεί στην Ευρώπη Ελληνικό φαρμακευτικό προϊόν

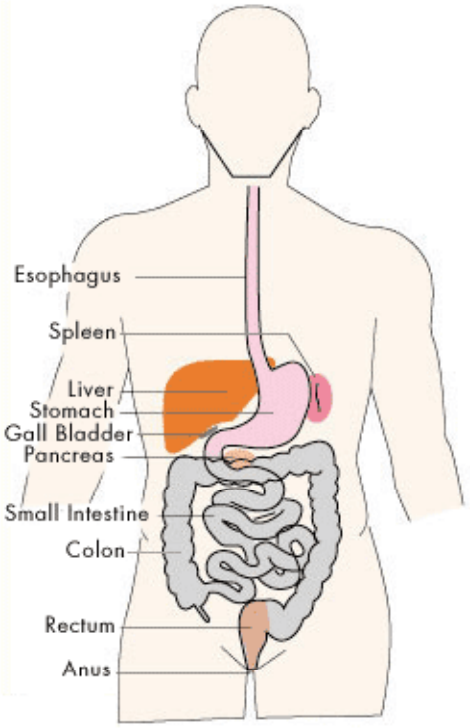
Generics' R&D/approval:

3. Classical route via Bioequivalence studies

ΤΑ ΣΤΑΔΙΑ ΑΝΑΠΤΥΞΗΣ ΕΝΟΣ ΓΕΝΟΣΗΜΟΥ

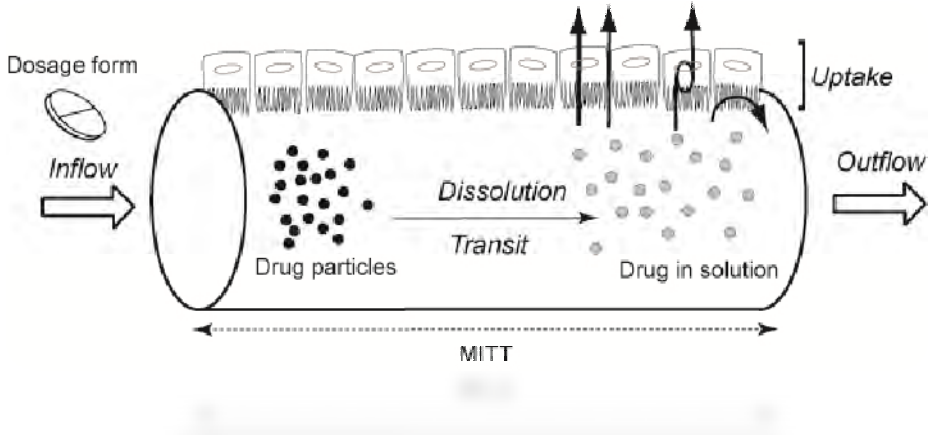


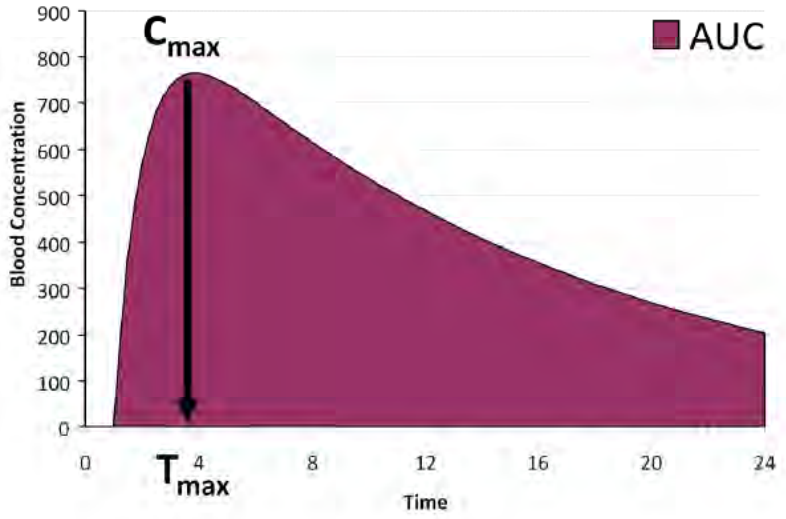
Μελέτες Βιοϊσοδυναμίας



Έκταση και ρυθμός απορρόφησης

" Εκτιμώνται έμμεσα με βάση φαρμακοκινητικές παραμέτρους (metrics) που υπολογίζονται απο δεδομένα C,t, μετά από χορήγηση των σκευασμάτων σε υγιείς εθελοντές "

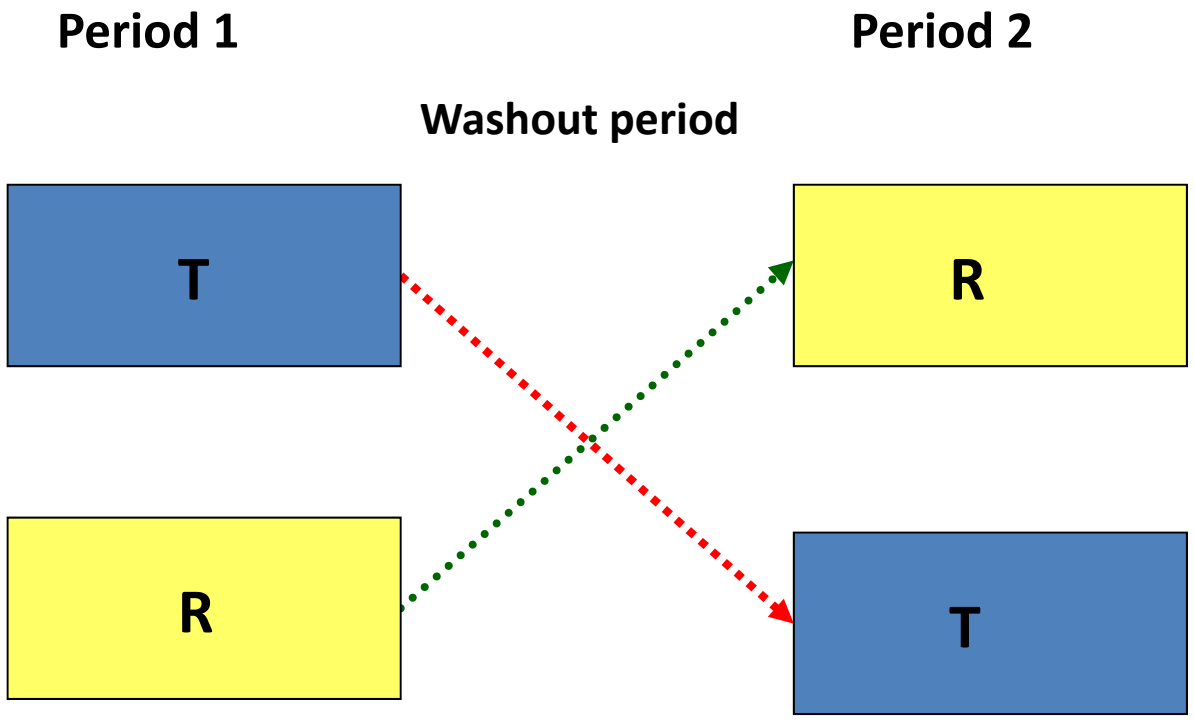




Μελέτες Βιοϊσοδυναμίας

Διασταυρωτός Σχεδιασμός Μελετών Βιοδιαθεσιμότητας-Βιοϊσοδυναμίας

2 x 2 cross-over design



EMA Guideline on Bioequivalence

European Medicines Agency

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

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE INVESTIGATION OF BIOEQUIVALENCE

Highly Variable Drugs or Drug Products

European Medicines Agency

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

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

$$*CV(\%) = 100\sqrt{e^{s^2_{WR}} - 1}$$

$$[U, L] = \exp[\pm k \cdot s_{WR}]$$

Pharmaceutical Research, Vol. 23, No. 11, November 2006 (© 2006)
DOI: 10.1007/s11095-006-9107-1

Research Paper

Novel Scaled Bioequivalence Limits with Leveling-off Properties

John Kytariolos,[1] Vangelis Karalis,[1] Panos Macheras,[1] and Mira Symillides[1,2]

European Journal of Pharmaceutical Sciences 44 (2011) 497–505

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

On the leveling-off properties of the new bioequivalence limits for highly variable drugs of the EMA guideline

Vangelis Karalis, Mira Symillides *, Panos Macheras

Laboratory of Biopharmaceutics-Pharmacokinetics, School of Pharmacy, University of Athens, Athens, Greece

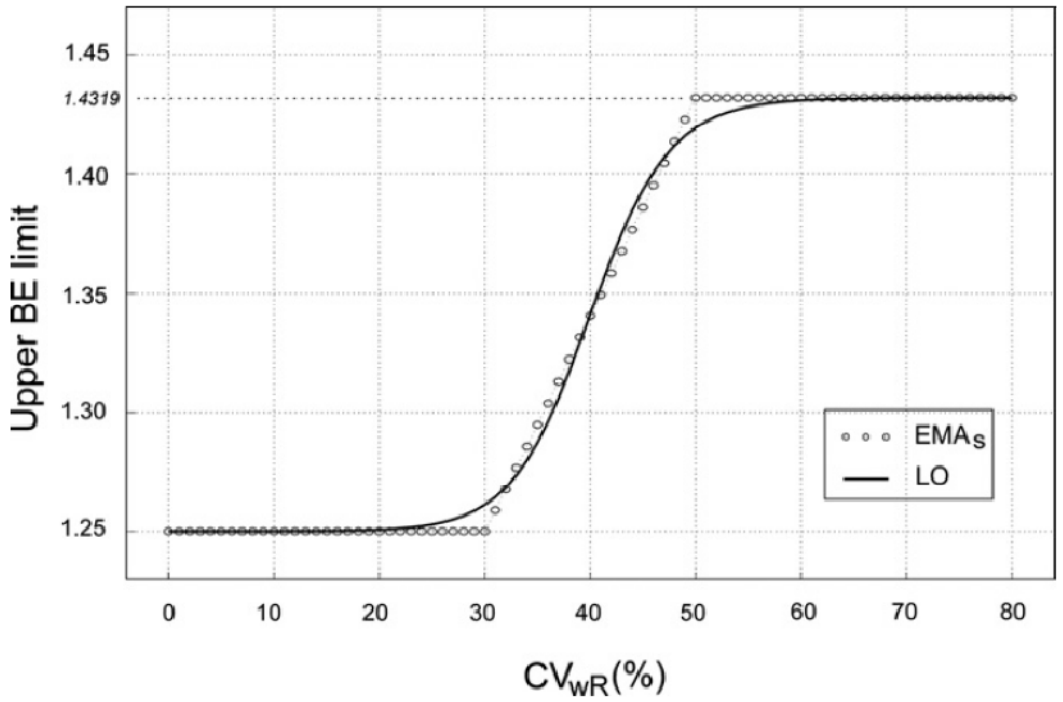


Fig. 2. Fitting of LO limits (Eq. (4)) to the EMA_s approach.

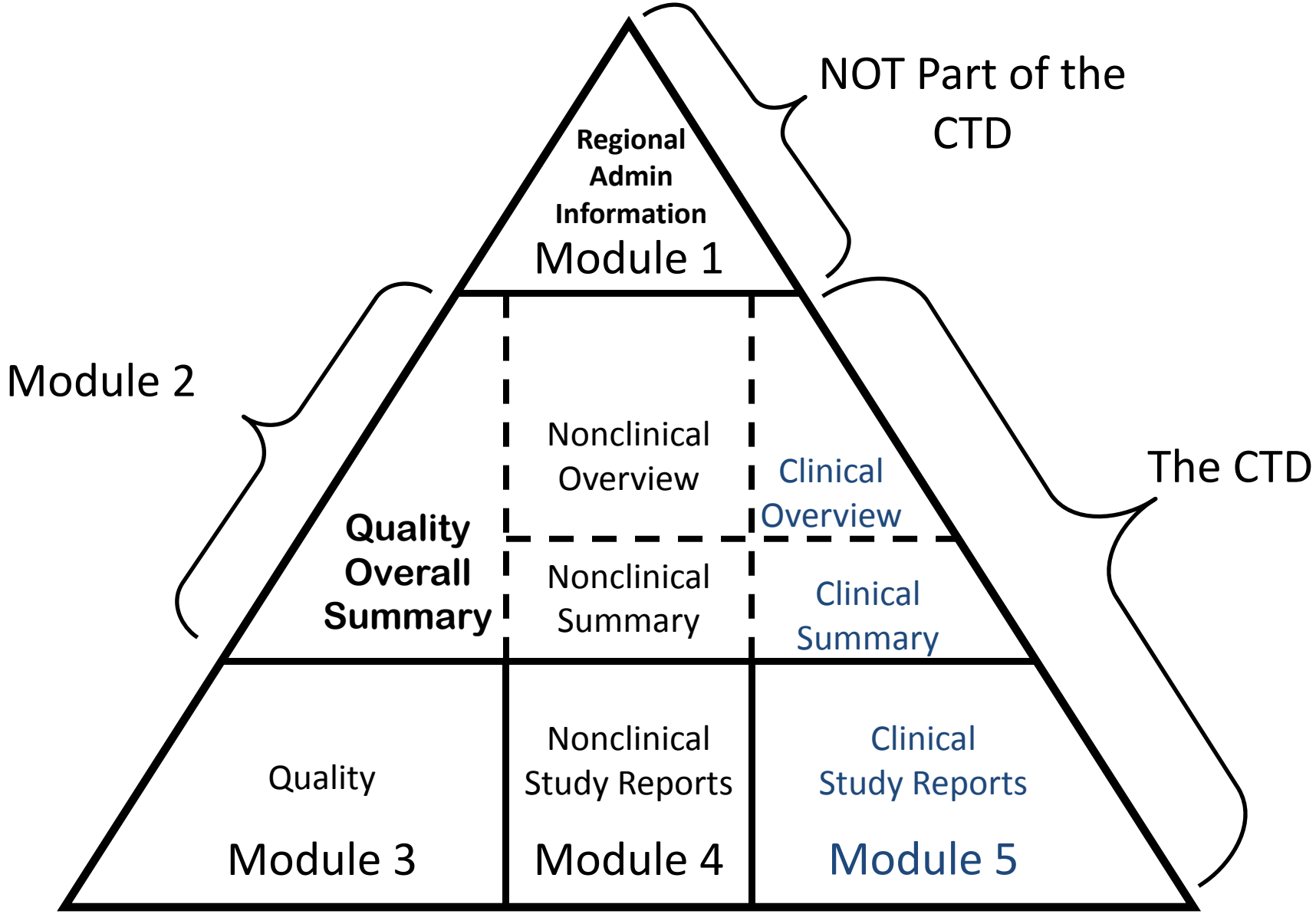
Μελέτες Βιοϊσοδυναμίας στην Ελλάδα ?

ΝΑΙ, αρκεί να μας υποστηρίξετε.
Ήδη δεχόμαστε αιτήματα και προετοιμάζουμε όλα τα κανονιστικά θέματα: GLP, GCP

Ρυθμιστικές Εγκριτικές Διαδικασίες

- Οι εταιρείες ανάπτυξης και παραγωγής γενοσήμων είναι υποχρεωμένες να δημιουργήσουν και να καταθέσουν στον ΕΟΦ φάκελο (**eCTD**) με πλήρη στοιχεία (π.χ. ποιοτική-ποσοτική σύνθεση, ενδείξεις-αντενδείξεις, δοσολογία, κλινικές μελέτες κ.λ.π.)

The CTD Triangle



A. Generics' development/approval:

4. Complex drugs

Complex drugs: Similar but not the same

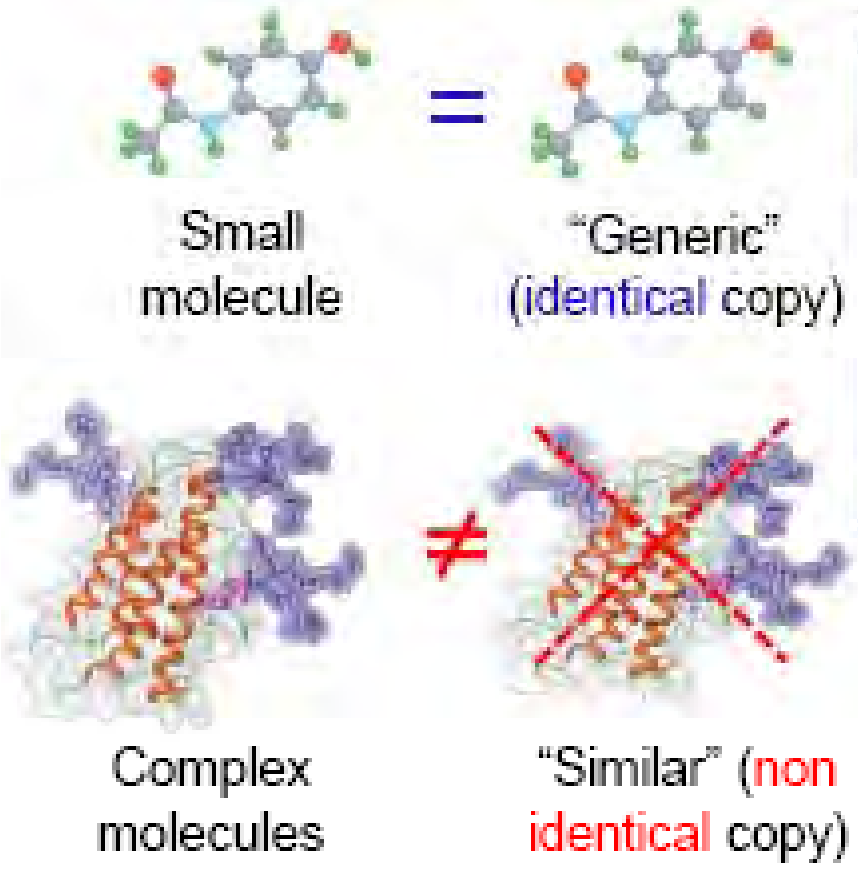


Table 1: Substantial differences between conventional and complex drugs

	Conventional Drugs	Complex Drugs
Size	Small (single molecule)	Large (mix)
Structure	Simple, defined	Complex, defined by the exact manufacturing process
Modification	Well defined	Many options
Manufacturing	Predictable chemical process, identical copy can be made	- Difficult to control from starting material to final API - Impossible to ensure an identical copy
Characterisation	Easy to characterise fully	Cannot be characterised fully because of related molecules

Schellekens et al. Poster AAPS (FIP) 2010:
Non-biological complex drugs:
How to show therapeutic equivalence
http://www.aapsj.org/abstracts/AM_2010/AM341.pdf

Non-biological complex drugs

Liposomal drugs (formulation)

Vesicles composed of phospholipid bilayers that can be formed from a great variety of lipid constituents (EMA reflection paper 2011)

Low molecular weight heparins

(Non-biotechnology biological product)
Mixture of heteropolymers obtained by proprietary depolymerisation processes of unfractionated heparin (EMA guideline on LMWH similars 2009)

Glatiramoids

Synthetic polypeptide mixtures with immunomodulatory activity containing four L-amino acids (glutamic acid, alanine, lysine, tyrosine)

Iron carbohydrates

Colloidal IV iron preparations comprising a polynuclear iron-oxohydroxide core complexed with a carbohydrate to stabilize and prevent iron toxicity and facilitate uptake and processing in macrophages

Regulatory Toxicology and Pharmacology 59 (2011) 176–183

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

The therapeutic equivalence of complex drugs ☆

Huub Schellekens [a,b,*], Ety Klinger [c,1], Stefan Mühlebach [d,2], Jean-Francois Brin [e,3], Gert Storm [f,g], Daan J.A. Crommelin [f,g,h,i]

Εκπονούμε φαρμακοκινητική μελέτη
με ένα complex drug της RAFARM

Generics' development/approval:

5. SuperGenerics

‘Supergenerics’

‘improved therapeutic entities’

‘added value Generics’

‘innovative Generics’

Developing Supergenerics: aspects of an existing drug product that you may alter aiming to create a new slightly different product

- Route of administration
- Dosage form
- Dose strength
- Formulation and release profile
- Improved safety
- Improved Patients compliance
- Improved Bioavailability
- Different pK profile
- Combination product
- Different Indication
- Slight modification to the active moiety
- Different manufacturing process
- Prescription status

European Journal of Pharmaceutical Sciences 44 (2011) 447–454

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

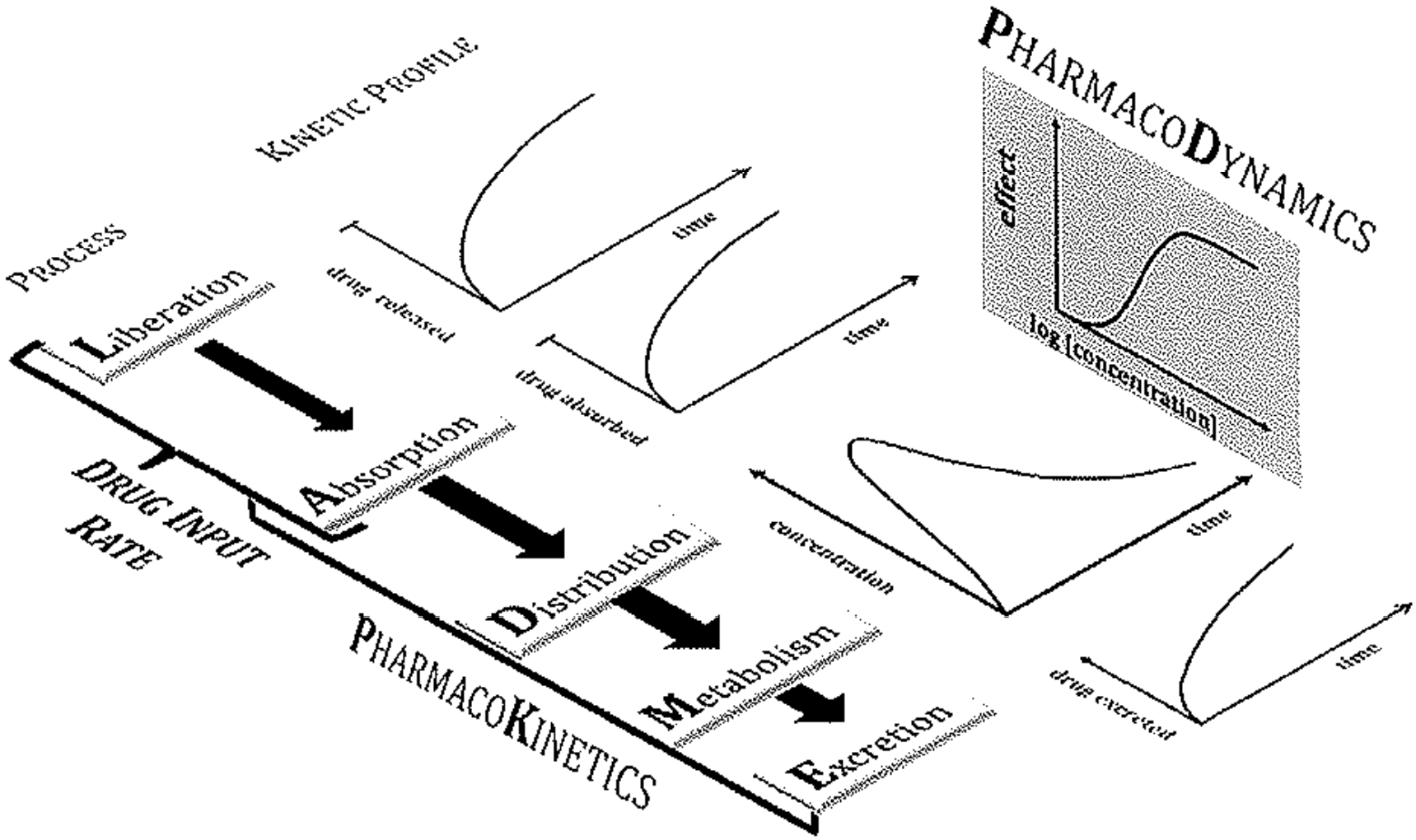
Review

Improved therapeutic entities derived from known generics as an unexplored source of innovative drug products ☆

Sven Stegemann [a,*], Imre Klebovich [b], István Antal [b], Henning H. Blume [c], Kálmán Magyar [d], György Németh [e], Tamás L. Paál [f], Willibald Stumptner [g], György Thaler [e], Armand Van de Putte [a], Vinod P. Shah [h]

Principles of pharmacokinetic optimization.

S. Stegemann et al./European Journal of Pharmaceutical Sciences 44 (2011) 447–454



Από IR σε MR

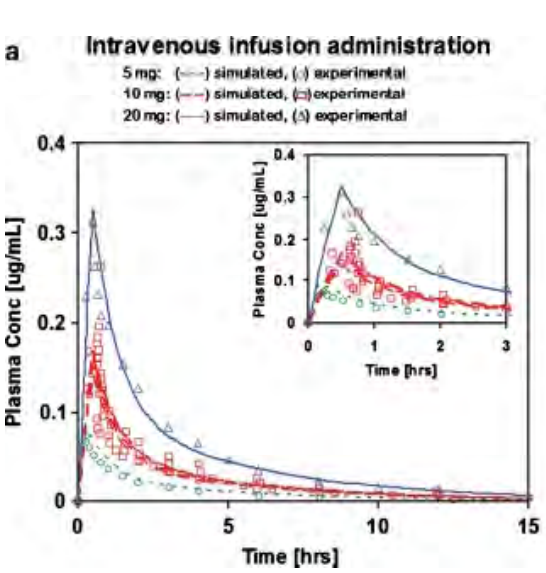
The AAPS Journal, Vol. 11, No. 2, June 2009 (2009)
DOI: 10.1208/s12248-009-9107-2

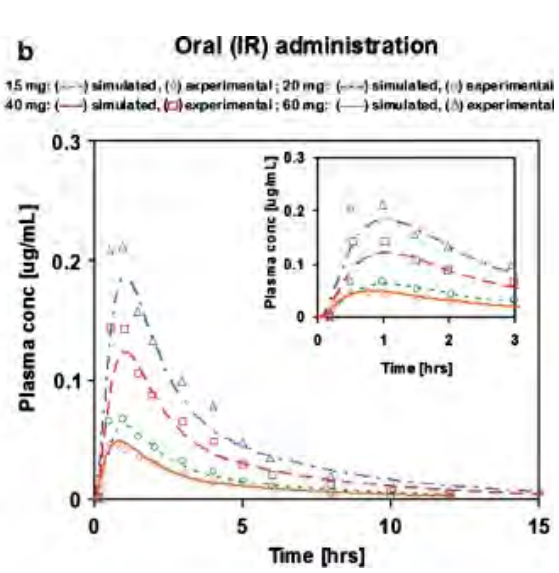
Research Article

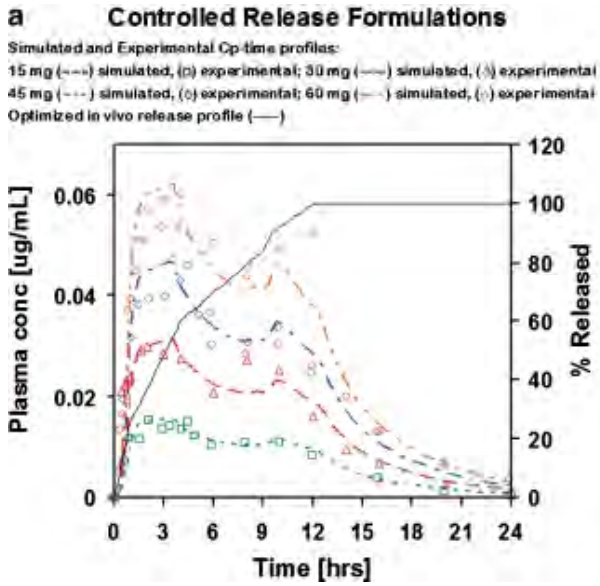
Theme: Towards Integrated ADME Prediction: Past, Present, and Future Directions
Guest Editors: Lawrence X. Yu, Steven C. Sutton, and Michael B. Bolger

Prediction of Modified Release Pharmacokinetics and Pharmacodynamics from *In Vitro*, Immediate Release, and Intravenous Data

Viera Lukacova,[1,2] Walter S. Woltosz,[1] and Michael B. Bolger[1]

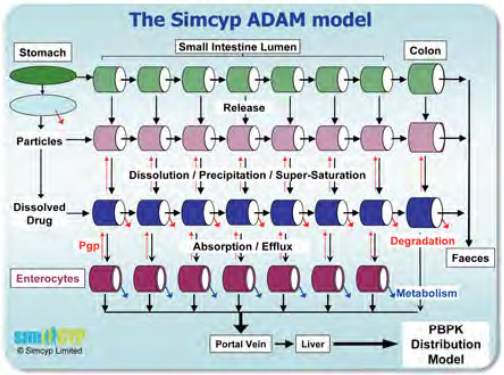






Calibration

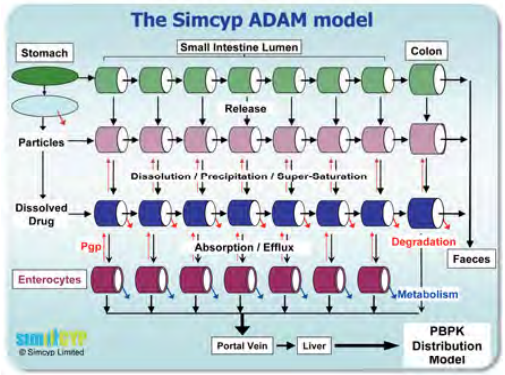
In vitro innovator's formulation



In vivo innovator's formulation

Validation

In vitro new formulation



Failed in vivo new formulation

1.Εφαρμογή MODELING AND SIMULATION για την ανάπτυξη σκευασμάτων:
Υπάρχει πρόγραμμα συνεργασίας με τη PHARMATHEN
2. Εφαρμογή πληθυσμιακών προσεγγίσεων (population approaches) στην ανάλυση δεδομένων μελετών βιοϊσοδυναμίας: Υπάρχει πρόγραμμα συνεργασίας με την ELPEN

A. Generics' development/approval:

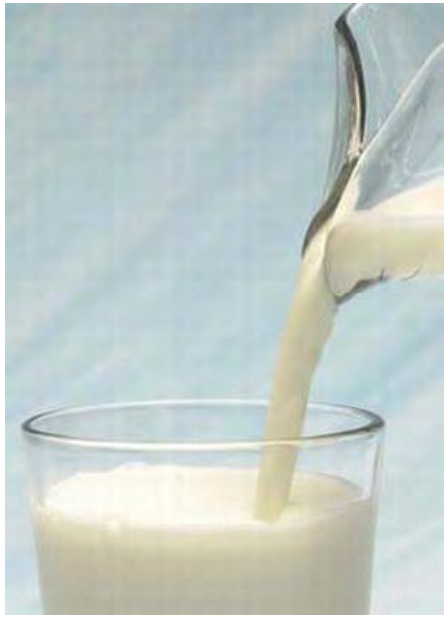
5a. SuperGenerics: Milk Based Formulations

Research in our LAB

- **Drug-milk studies (solubility, dissolution, binding)**
- **Freeze dried drug milk formulations**
- **Simple Milk-based formulations for ionized and un-ionized drugs**
- **Paediatric formulations**

Milk

- A natural, abundant and inexpensive carrier with the desired characteristics for oral drug delivery.
- Oil-in-water natural emulsion
- Fat milk is in separate small globules



Pharmaceutical Research, Vol. 7, No. 5, 1990

Report

Drug Binding and Solubility in Milk

Panayotis E. Macheras,[1,3] Michael A. Koupparis,[2] and Sophia G. Antimisiaris[1]

Received June 12, 1989; accepted December 9, 1989

The binding and solubility of nitrofurantoin, piroxicam, indomethacin, prednisolone, diazepam, dicumarol, and griseofulvin in milk were determined at 15, 25, and 37°C in bovine milk samples with fat contents of 0.75 and 3.50%. Drug binding to milk components was independent of drug concentration over the drug concentration studied, and the fat content of milk strongly affected binding values of most of the listed drugs. Further, drug binding increased with decreasing temperatures for most of the drugs examined. The solubility of all drugs is greatly enhanced in milk compared to their aqueous solubility (pH 6.5 phosphate buffer). The high solubility cannot be accounted for solely on the basis of drug binding to milk components. An attempt is made to correlate the binding and solubility data with physicochemical properties of the drugs (log$P$, pK_a, aqueous solubility). The potential significance of these findings is discussed with regard to preparation and *in vivo* delivery of drugs from drug–milk formulations.

KEY WORDS: binding; solubility; drug; milk.

Studies on Drug–Milk Freeze-Dried Formulations I: Bioavailability of Sulfamethizole and Dicumarol Formulations

PANAYOTIS E. MACHERAS[x] AND CHRISTOS I. REPPAS

Received November 18, 1985, from the *Department of Pharmacy, University of Athens, Athens 10680 Greece.*
14, 1986.

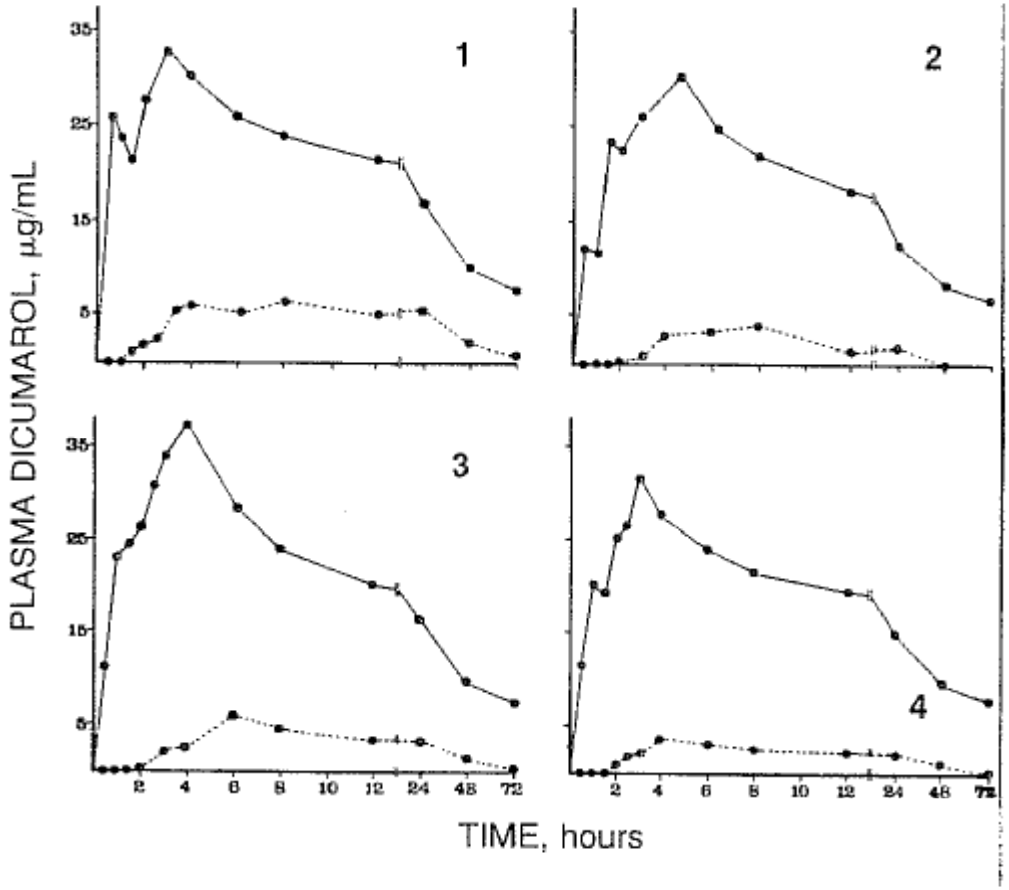


Figure 4—*The individual plasma concentrations of dicumarol in subjects 1–4. Key: (——) formulation A; (– – –) formulation B.*

Studies on Freeze-Dried Drug–Milk Formulations II: Effect of Regenerated Fluid Volume on Nitrofurantoin Bioavailability

PANAYOTIS E. MACHERAS[x] AND CHRISTOS I. REPPAS

Received June 18, 1986, from the *Department of Pharmacy, University of Athens, Athens 10680, Greece.* Accepted October 7, 1986.

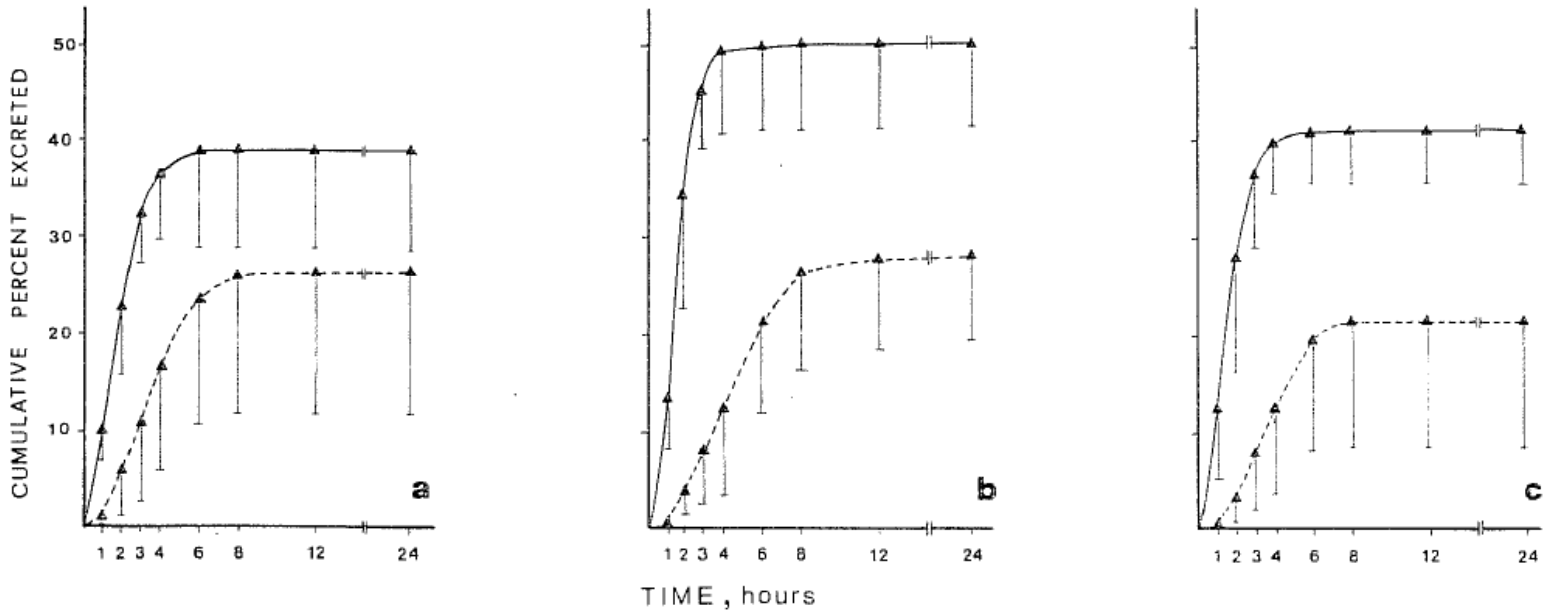


Figure 5—*Mean cumulative percent of nitrofurantoin excreted following the administration of a freeze-dried formulation (——) or a capsule (– – – –). Each point is the mean ± SD of the cumulative percent excreted for all four subjects. Volume of milk used:* (a) *100 mL;* (b) *200 mL;* (c) *400 mL.*

IJP 01210

Dissolution of 4 controlled-release theophylline formulations in milk

P. Macheras [1], M. Koupparis [2] and E. Apostolelli [1]

Departments of [1] Pharmacy and [2] Chemistry, University of Athens, Athens (Greece)

(Received 11 September 1986)
(Accepted 1 November 1986)

Key words: Dissolution study; Dynamic dialysis; Milk; Theophylline; Controlled-release formulation

International Journal of Pharmaceutics, 54 (1989) 123–130
Elsevier

IJP 01825

An in vitro model for exploring CR theophylline–milk fat interactions

P. Macheras [1], M. Koupparis [2] and S. Antimisiaris [1]

Departments of [1] Pharmacy and [2] Chemistry, University of Athens, Athens (Greece)

(Received 14 December 1988)
(Modified version received 14 February 1989)
(Accepted 20 February 1989)

P. Macheras, C. Reppas, and G. Ismailos.

Pharmaceutical Research 11, S-283 (1994), AAPS, Annual Meeting, San Diego, California, USA.

IMPROVEMENT OF THE ORAL ABSORPTION OF CYCLOSPORIN A BY A FREEZE-DRIED CYCLOSPORIN A-MILK FORMULATION IN DOGS

Department of Pharmacy, University of Athens

Numerous attempts have been made to increase oral cyclosporin A (CsA) bioavailability. Based on previous results from our laboratory, a freezed-dried CsA-milk formulation (FDCsA) was prepared and tested *in vivo* using the canine model. Four female mongrel dogs in a four-period randomized crossover design received:

1. 3x100mg CsA as Sandimmune® soft gelatin capsules, and

2, a regenerated FDCsA product whiuch contained 300mg CsA at two different milk volume levels, i.e., 150mL and 350mL (3.5% fat)

The mean SD PK parameters, based on plasma measurements, are summarized as follows:

Treatment	AUC_{0-24}(ng/mL/h)	C_{max}(ng/mL)	T_{max}(h)
Caps/150	6938(1704)	1285(351)	2.7(1.2)
FDCsA/150	10660(4032)	1731(649)	2.2(0.5)
Caps/350	7275(2517)	1365(906)	3.7(1.9)
FDCsA/350	13434(5102)	1977(562)	3.7(0.5)

C_{max} and AUC_{0-24} were significantly higher after the administration of the regenerated CsA-milk product by an average 40% and 70%, respectively.

Int J Pharm. 2010 May 10;390(2):150-9. doi: 10.1016/j.ijpharm.2010.01.038. Epub 2010 Feb 1.

Novel milk-based oral formulations: proof of concept.

Charkoftaki G, Kytariolos J, Macheras P.

Laboratory of Biopharmaceutics-Pharmacokinetics, Faculty of Pharmacy, University of Athens, Panepistimiopolis, 157 71 Athens, Greece.

Int J Pharm. 2013 Feb 28;444(1-2):128-38. doi: 10.1016/j.ijpharm.2013.01.022. Epub 2013 Jan 20.

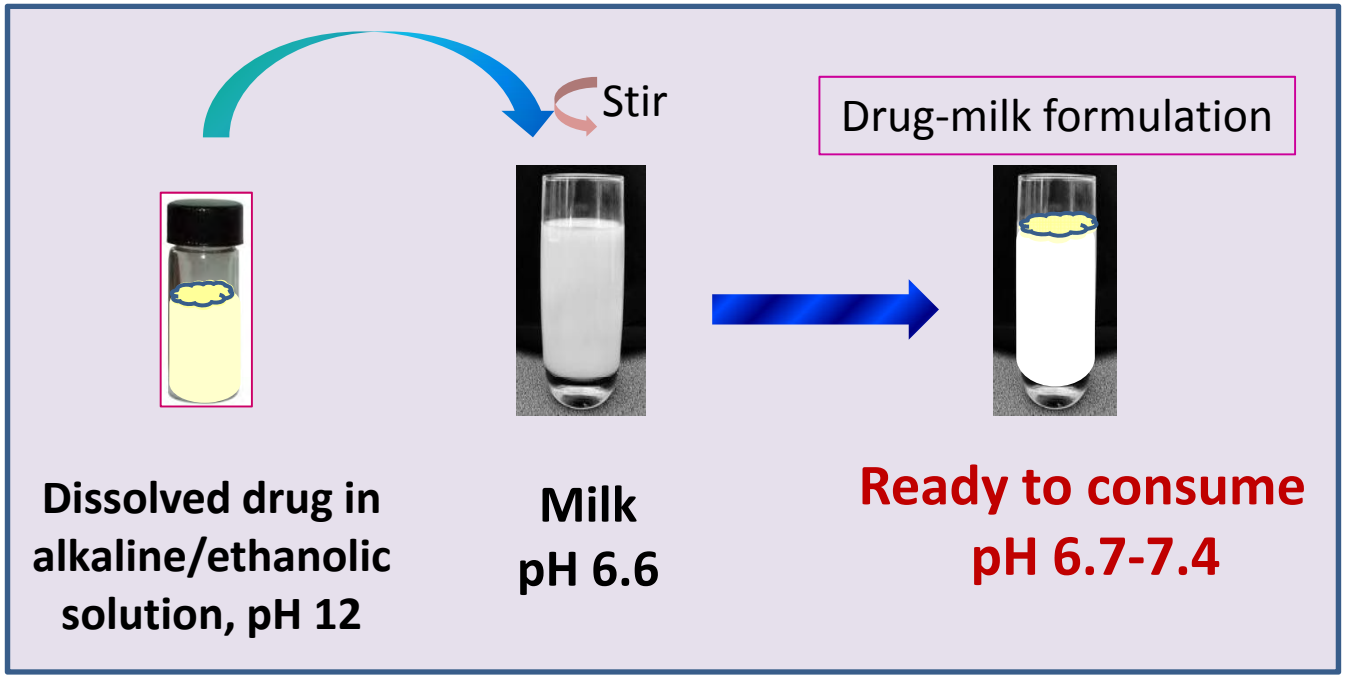
Stability and physicochemical characterization of novel milk-based oral formulations.

Kytariolos J, Charkoftaki G, Smith JR, Voyiatzis G, Chrissanthopoulos A, Yannopoulos SN, Fatouros DG, Macheras P.

Laboratory of Biopharmaceutics-Pharmacokinetics, Faculty of Pharmacy, University of Athens, Panepistimiopolis, GR-15771, Athens, Greece.

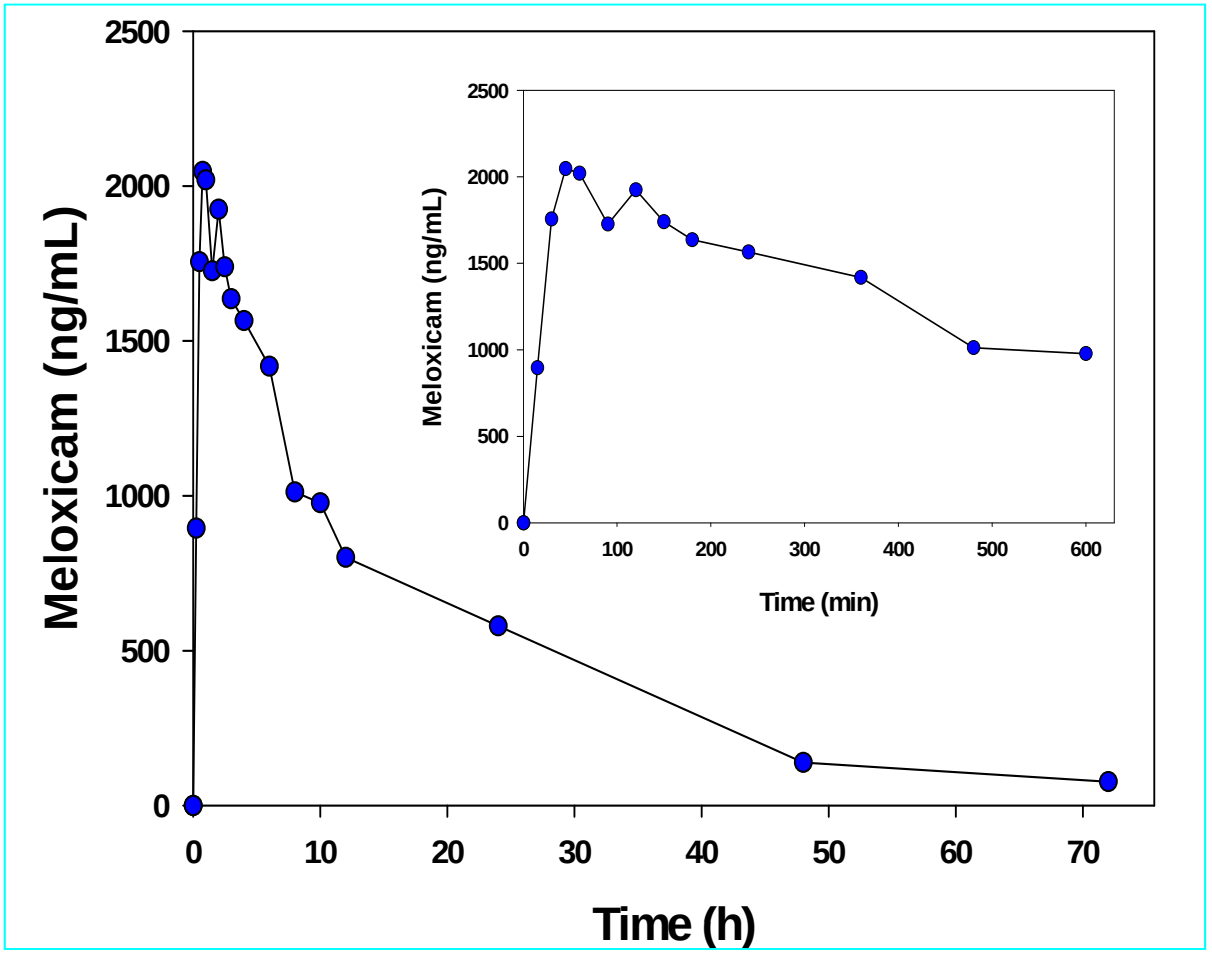
Preparation of the drug–milk formulations

1. Dissolve the compound in the appropriate volume of aqueous alkaline buffer solution pH 12 (2-12.5 mL)/or ethanolic solution.
2. Add the drug-alkaline/ethanolic solution into 150 mL of milk.
3. Stir with a spoon for a few seconds.
4. Ready to consume.



Ionized compounds

In vivo study: Meloxicam/milk formulation



t_{max}=45 min

Non-ionized compounds

In vivo study: Cyclosporine/milk formulation

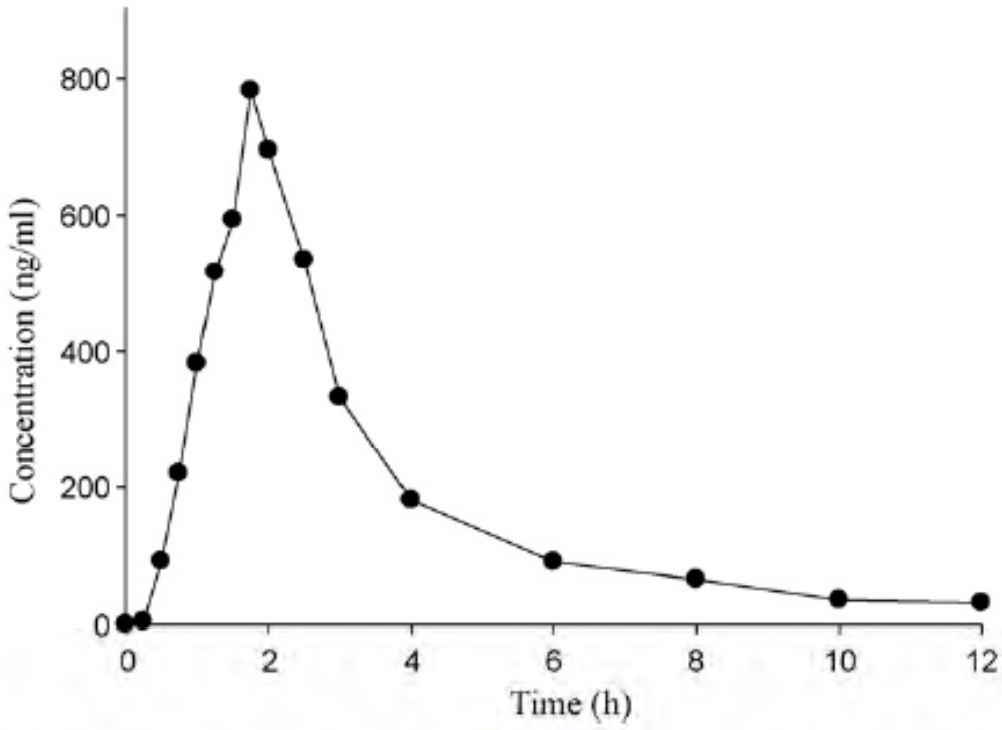


Fig. 7. Plasma concentration–time profile for cyclosporine A after a single oral administration of cyclosporine–milk formulation, containing 100 mg of cyclosporine.

Milk based formulations

- Υπάρχει μία πατέντα στις απλές milk based formulations με τη PHARMATHEN (US 8435982 B1)- granted patent in US καθώς επίσης:

Pending patent application in EPO (EP 2 224 907 A1)

Pending patent application in USPTO (US 2013/0190252 A1)

- Υπάρχει ενδιαφέρον από τη Galenica για ανάπτυξη προϊόντος
- Υπάρχει συνεργασία με τη Vianex στο πεδίο των freeze dried drug-milk formulations αντικαρκινικών
- Ονειρεύομαι και αναζητώ συνεργασία με τη βιομηχανία ΓΓΕΤ-–ογκολόγους-λοιμοξιολόγους για

ι) την αντικατάσταση της ενδοφλέβιας αγωγής με per os χορήγηση freeze dried anticancers-milk formulations

ιι) ανάπτυξη σκευασμάτων αντιρετροϊκών (και για παιδιατρική χρήση -υφίσταται provisional patent)

Potential applications of milk based formulations for Paediatric use

Paediatric formulations

AAPS J. 2013 Aug 2. [Epub ahead of print]

A Report from the Pediatric Formulations Task Force: Perspectives on the State of Child-Friendly Oral Dosage Forms.

Zajicek A, Fossler MJ, Barrett JS, Worthington JH, Ternik R, Charkoftaki G, Lum S, Breitkreutz J, Baltezor M, Macheras P, Khan M, Agharkar S, Maclaren DD.

Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA, zajiceka@mail.nih.gov.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 August 2013
EMA/CHMP/QWP/805880/2012 Rev. 2
Committee for Medicinal Products for Human Use (CHMP)
Paediatric Committee (PDCO)

Guideline on pharmaceutical development of medicines for paediatric use

Draft agreed by QWP	February 2011
Draft agreed by SWP	March 2011
Draft agreed by PDCO	April 2011
Adoption by CHMP for release for consultation	May 2011
End of consultation (deadline for comments)	31 December 2011
Revised version agreed by QWP for release for second consultation	September 2012
Revised version agreed by PDCO for release for second consultation	November 2012
Revised version adopted by CHMP for release for second consultation	November 2012
End of second consultation (deadline for comments)	31 March 2013
Final version agreed by QWP	June 2013
Final version agreed by PDCO	July 2013
Final version adopted by CHMP	July 2013
Date for coming into effect	15 February 2014

Keywords	*child, pharmaceutical development, quality*

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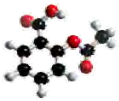
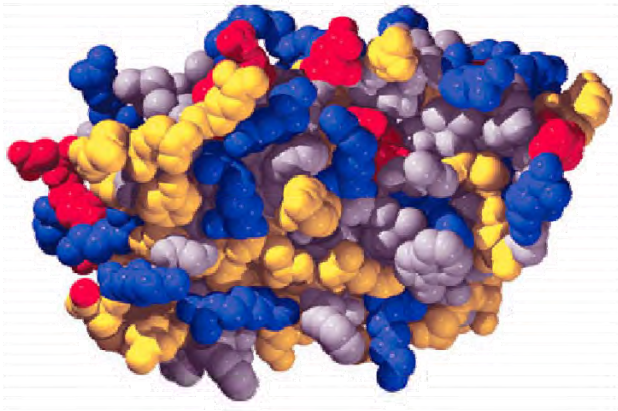
B. Biosimilars

Why biopharmaceuticals are different





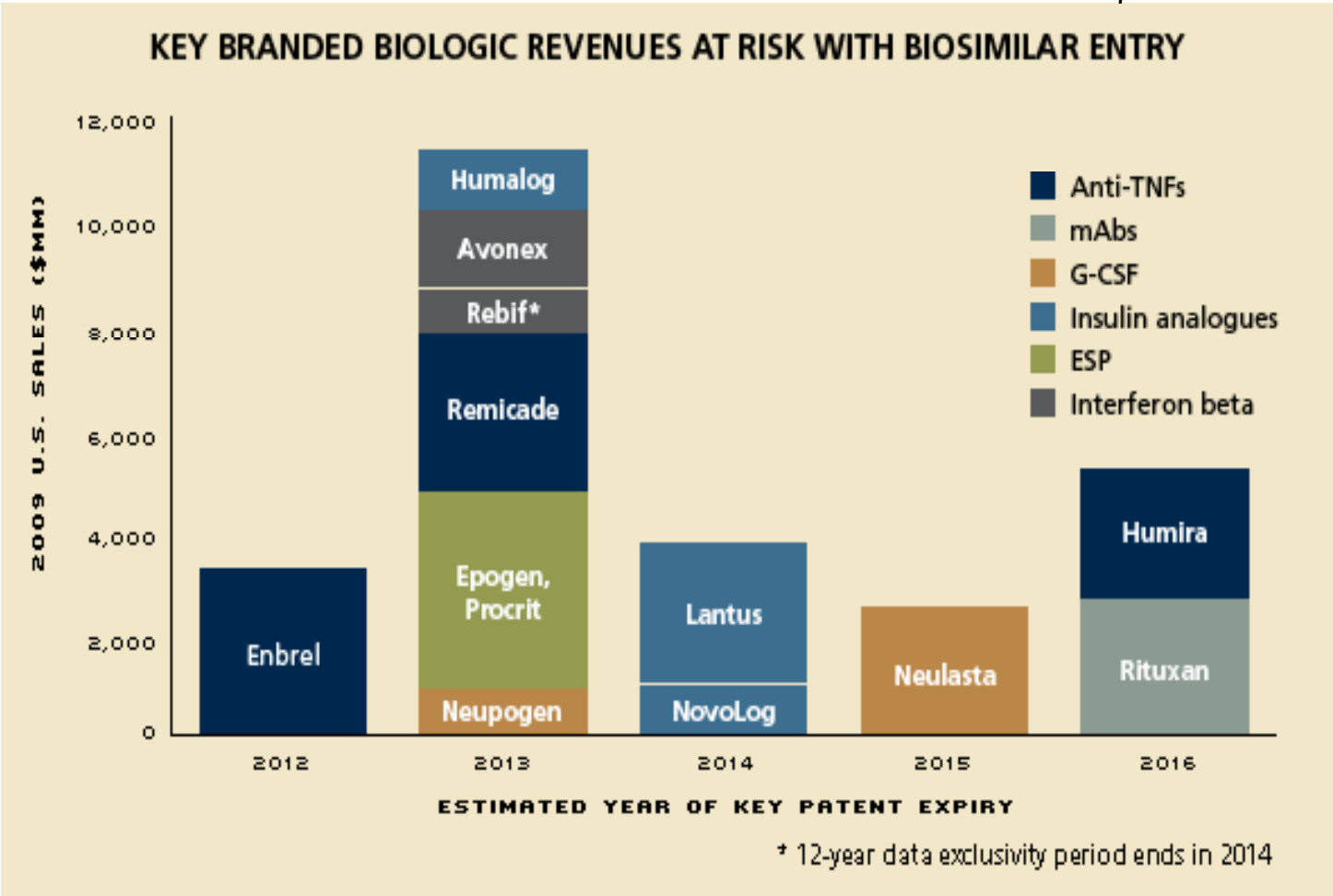
- High MW
- Complex 3D structure
- Difficult to characterize completely by physico-chemical methods
- Produced by living organisms (… often heterogeneous)
- Complex manufacturing process
- Biological activity depends on:
  - reproducibility of the production process
  - in-house standards
  - maintenance of cold-chain integrity
- Inherent risk of immunogenicity

Crommelin DJA, et al. Int J Pharm. 2003;266:3-16.

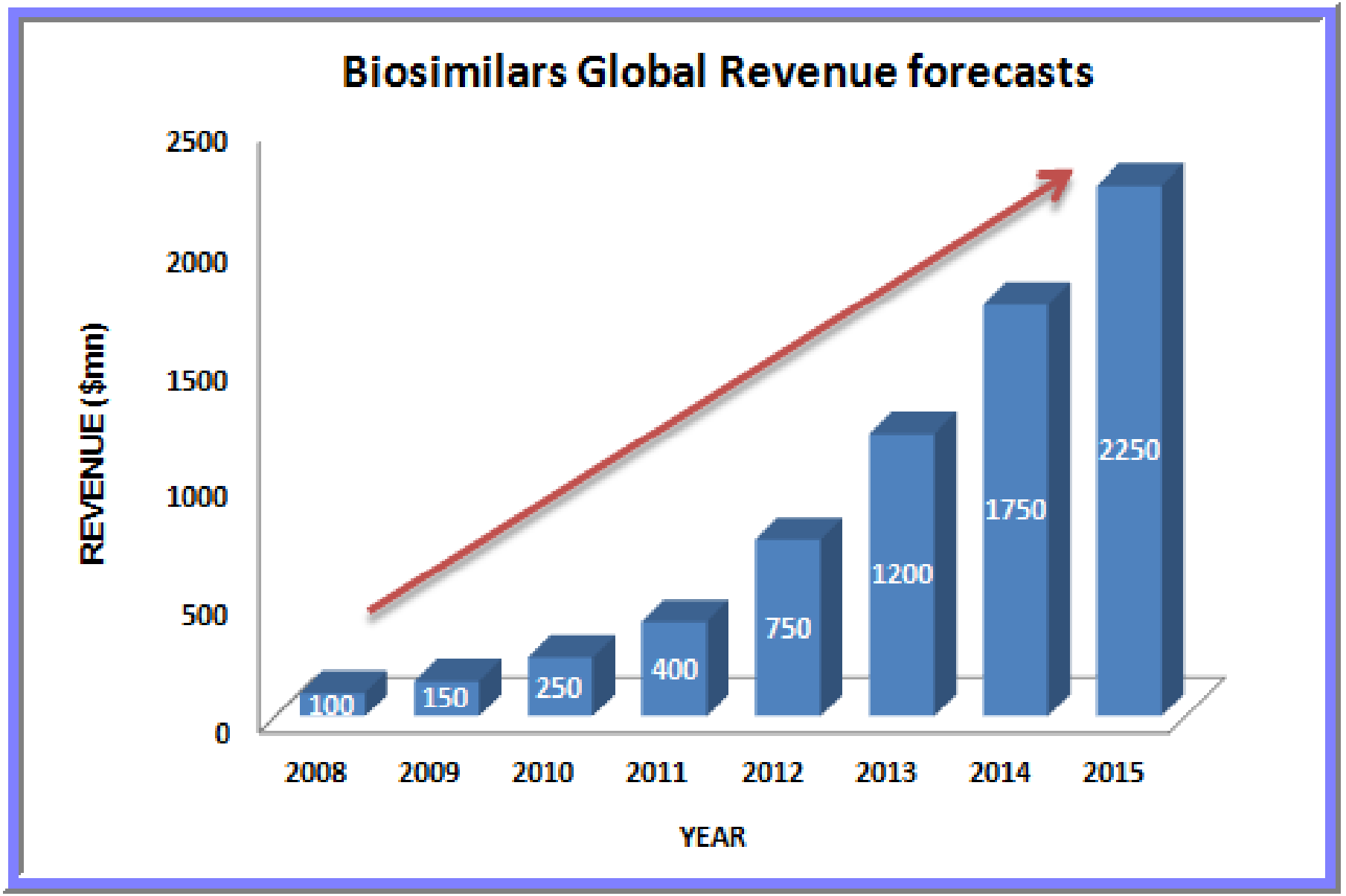
Biotechnological drugs and Biosimilars:
R&D in our country (?)

Loss of Patent Protection

AROUND $25bn Market



Source : *Analysis Group Health Care Consulting Bulletin (Fall/Winter 2010)*


Biosimilars Global Revenue forecasts
REVENUE ($mn)
2500
2000
1500
1000
500
0
100
150
250
400
750
1200
1750
2250
2008
2009
2010
2011
2012
2013
2014
2015
YEAR

Can we succeed?

- New phase in biomedical innovation
- Not alone – EU networking!
- Excellent Greek scientists all over the world (including Greece)
- Small country providing advantages on focus and synergies

Two approaches for success:

1. Create a National Research Platform on functional Genomics and Biotechnology

-build on existing capacities

-invest in infrastructures/human capital/technology transfer

-estimated seed fund: 10^6 euros per year

2. Create a supportive environment for biotech SMEs

-incubate and cluster R&D Innovation and SMEs

-start with a lab focusing on the quality and the assessment of immunological properties of Biotechnological drugs and Biosimilars to attract international interest and investors

Computational-Experimental, Scientific-Regulatory Advances in Drug Discovery, Formulation Strategies, Drug Delivery, ADMET for Small Molecules (Generics) and Biotechnological (Biosimilar) Drugs

The Congress is organized by the *"Controlled Release Society-Greek local chapter",* Athens, Greece, May 31st -June 1st 2015.

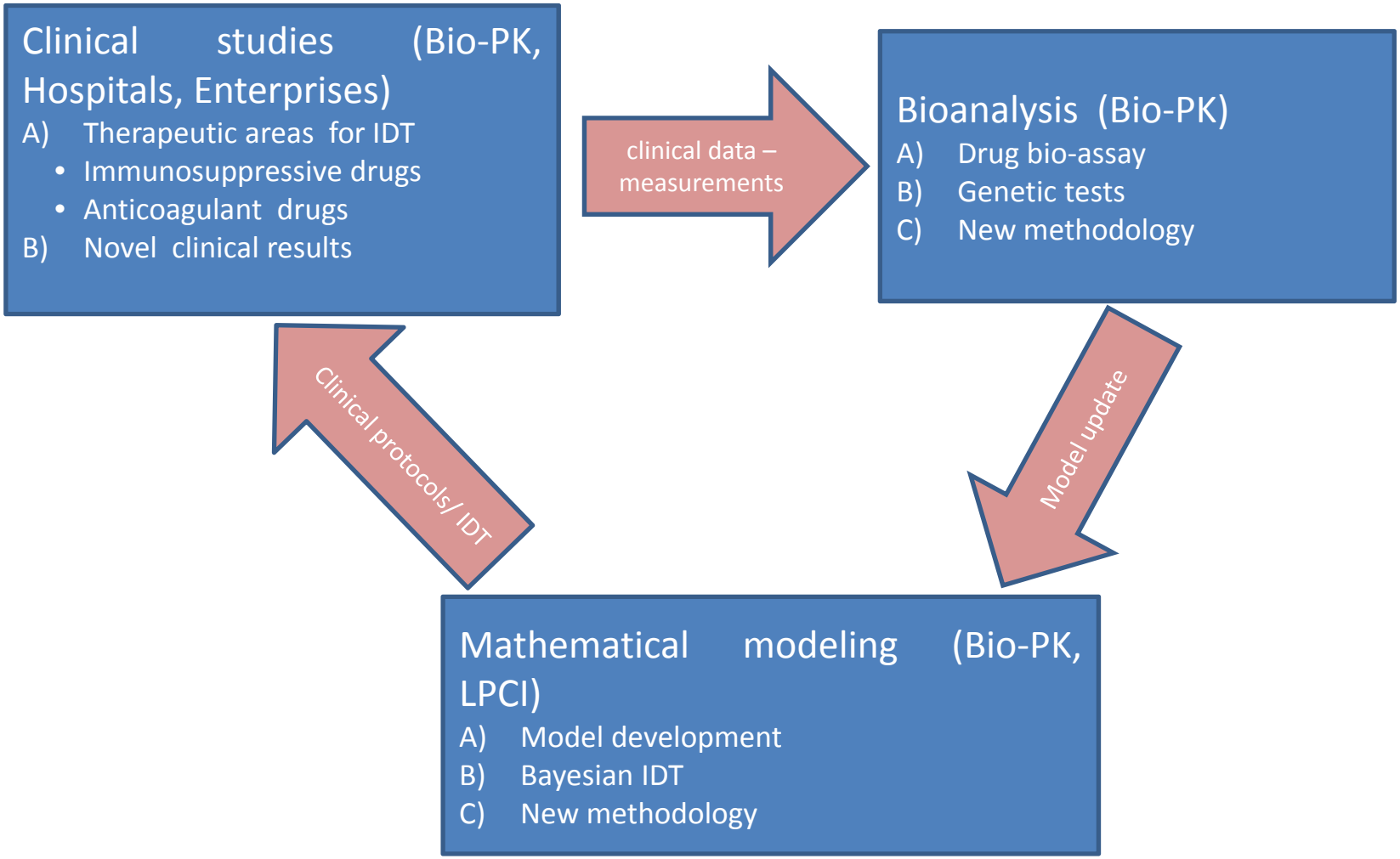
C. Application of Pharmacokinetics-Pharmacometrics in Clinical Practice: Individualisation of therapy

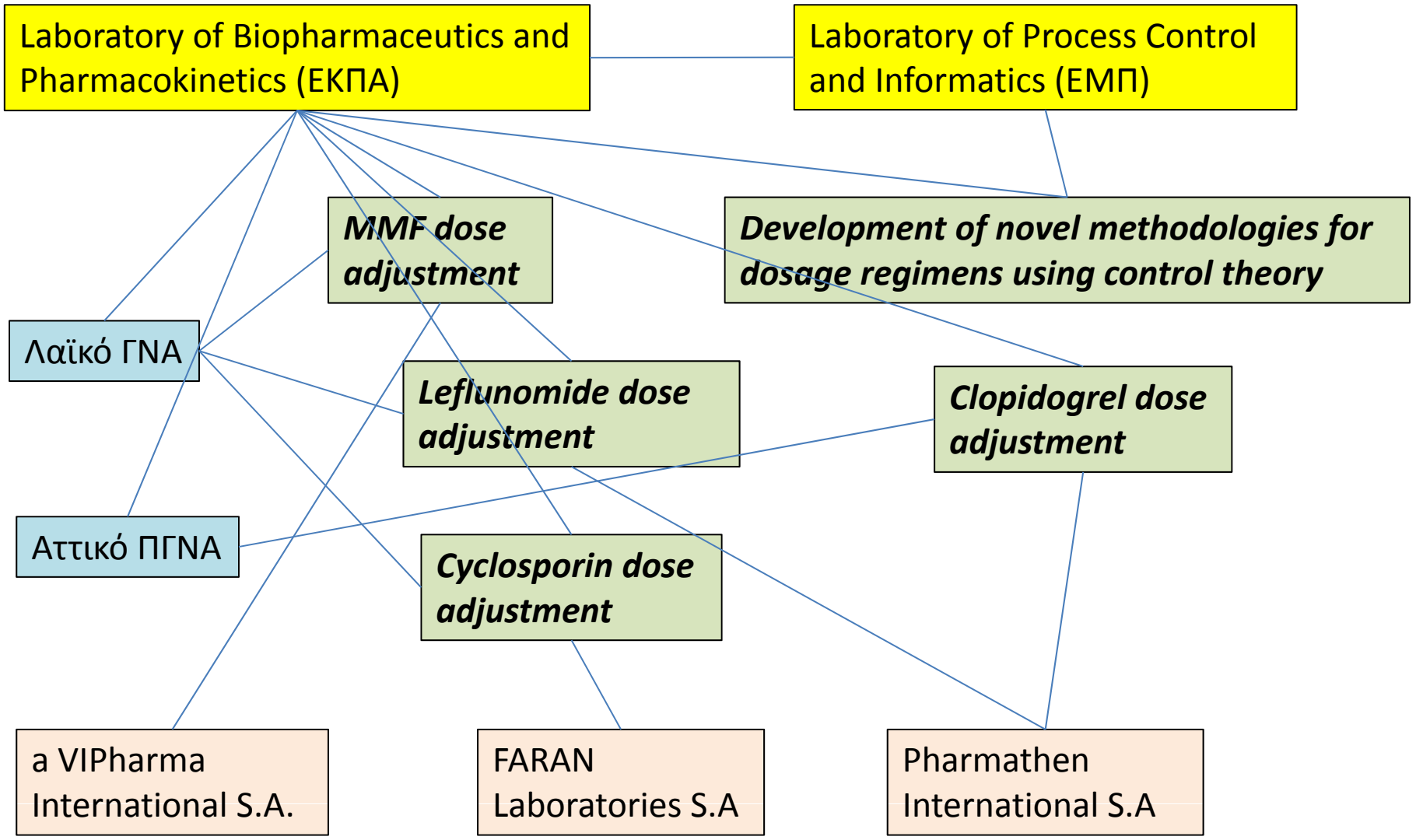
ΕΘΝΙΚΟ ΣΤΡΑΤΗΓΙΚΟ ΠΛΑΙΣΙΟ ΑΝΑΦΟΡΑΣ
ΕΣΠΑ 2007-2013

ΔΡΑΣΗ ΕΘΝΙΚΗΣ ΕΜΒΕΛΕΙΑΣ
«ΣΥΝΕΡΓΑΣΙΑ 2011»
Συμπράξεις Παραγωγικών και Ερευνητικών Φορέων σε Εστιασμένους Ερευνητικούς και Τεχνολογικούς Τομείς

ΕΞΑΤΟΜΙΚΕΥΣΗ ΤΗΣ ΦΑΡΜΑΚΟΘΕΡΑΠΕΙΑΣ ΣΤΑ ΕΛΛΗΝΙΚΑ ΝΟΣΟΚΟΜΕΙΑ ΜΕ ΕΦΑΡΜΟΓΗ ΤΗΣ ΦΑΡΜΑΚΟΚΙΝΗΤΙΚΗΣ ΜΟΝΤΕΛΟΠΟΙΗΣΗΣ: ΕΜΦΑΣΗ ΣΤΑ ΓΕΝΟΣΗΜΑ ΦΑΡΜΑΚΑ

ΕΥΡΩΠΑΪΚΗ ΕΝΩΣΗ
ΑΝΤΑΓΩΝΙΣΤΙΚΟΤΗΤΑ ΕΠΙΧΕΙΡΗΜΑΤΙΚΟΤΗΤΑ ΕΠΑΝ ΙΙ
η περιφέρεια στο επίκεντρο της ανάπτυξης
ΕΣΠΑ 2007-2013 πρόγραμμα για την ανάπτυξη
Υπουργείο Παιδείας και Θρησκευμάτων, Πολιτισμού και Αθλητισμού
ΓΓΕΤ – ΕΥΔΕ.ΕΤΑΚ
Ε. Π. Ανταγωνιστικότητα και Επιχειρηματικότητα (ΕΠΑΝ ΙΙ), ΠΕΠ Μακεδονίας – Θράκης, ΠΕΠ Κρήτης και Νήσων Αιγαίου, ΠΕΠ Θεσσαλίας – Στερεάς Ελλάδας – Ηπείρου, ΠΕΠ Αττικής

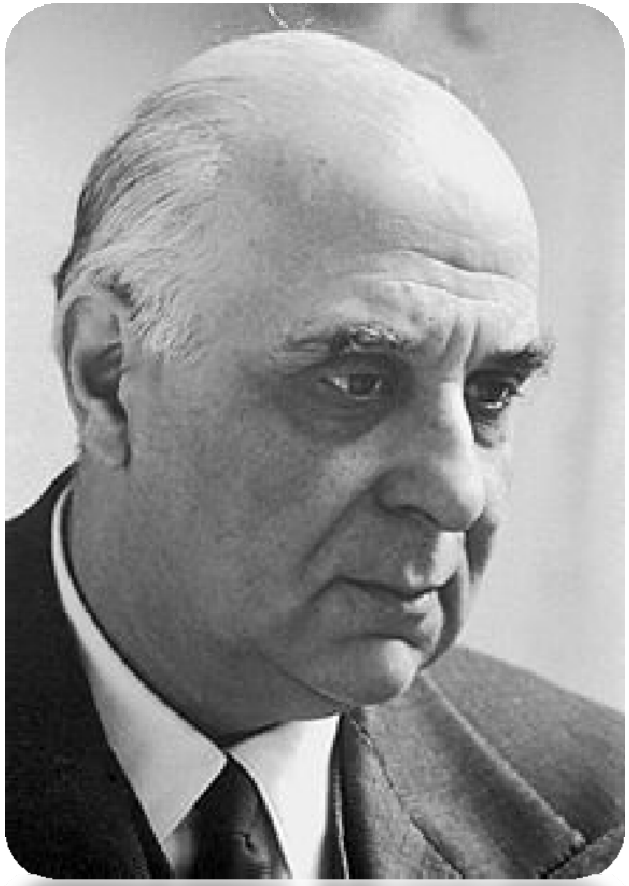

Clinical studies (Bio-PK, Hospitals, Enterprises)
A) Therapeutic areas for IDT
• Immunosuppressive drugs
• Anticoagulant drugs
B) Novel clinical results
clinical data – measurements
Bioanalysis (Bio-PK)
A) Drug bio-assay
B) Genetic tests
C) New methodology
Model update
Clinical protocols/ IDT
Mathematical modeling (Bio-PK, LPCI)
A) Model development
B) Bayesian IDT
C) New methodology


Laboratory of Biopharmaceutics and Pharmacokinetics (ΕΚΠΑ)
Laboratory of Process Control and Informatics (ΕΜΠ)
MMF dose adjustment
Development of novel methodologies for dosage regimens using control theory
Λαϊκό ΓΝΑ
Leflunomide dose adjustment
Clopidogrel dose adjustment
Αττικό ΠΓΝΑ
Cyclosporin dose adjustment
a VIPharma International S.A.
FARAN Laboratories S.A
Pharmathen International S.A

Ονειρεύομαι:
Τη δημιουργία Εθνικού κέντρου εφαρμοσμένης Φαρμακοκινητικής-Φαρμακομετρίας στο Εργαστήριο Βιοφαρμακευτικής-Φαρμακοκινητικής του ΕΚΠΑ για την ορθολογική χρήση των φαρμάκων στα Ελληνικά Νοσοκομεία

Giorgos Seferis

13 March 1900 – 20 September 1971



Nobel Prize in Literature 1963

“Καταλαβαίνει κανείς πως δουλεύει καλά, όταν κάθε περιστατικό, το πιο μικρό και ασήμαντο, της καθημερινής ζωής του και της σκέψης του, έρχεται, σαν μοναχό του, και βάζει ένα πετραδάκι στο πράγμα που φτιάνει.”