KONZEPTE IN DER HUMANPHARMAKOLOGIE

L. Lange H. Jaeger W. Seifert I. Klingmann (Hrsg.)

Good Clinical Practice I

Grundlagen
und Strategie

Springer-Verlag

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Good Clinical Practice II

Praxis der
Studiendurchführung

Springer-Verlag

Arbeitsgemeinschaft
für Angewandte
Humanpharmakologie e.V.

AGAH

Association for Applied Human
Pharmacology

Universität Bonn
Abteilung für
Klinische Pharmakologie
Direktor Prof. K. von Bergmann

WORKSHOP

Praktische Erfahrungen mit der 12. AMG-Novelle in der Humanpharmakologie

Ein interaktiver Workshop zum ersten Austausch von Erfahrungen

17. und 18. Januar 2005

Universitätsclub der Universität Bonn
Bonn

Arbeitsgemeinschaft
für Angewandte
Humanpharmakologie e.V.

AGAH

Universität Bonn
Abteilung für
Klinische Pharmakologie

Aufruf zur Teilnahme

Die 12. AMG-Novelle und die dazugehörige GCP-Verordnung sind am 6. August 2004 inkraft getreten. Gravierende Änderungen in der Vorbereitung und Durchführung klinischer Prüfungen sind seither erforderlich geworden. Sowohl Sponsoren im industriellen und akademischen Bereich, als auch die Zulassungsbehörden und Ethik-Kommissionen müssen neue Verantwortungen, Aufgaben und Prozesse einführen, um klinische Prüfungen durchführen beziehungsweise genehmigen zu können. Der Workshop soll allen Teilnehmern Gelegenheit geben, erste Erfahrungen auszutauschen und neue Ideen für eine effizientere Umsetzung der neuen Anforderungen zu entwickeln. Die einzelnen Themen des Programms sollen aus verschiedenen Blickwinkeln präsentiert und dann ausführlich diskutiert werden.

Die Veranstalter möchten alle Kollegen, die erste Erfahrungen mit der Vorbereitung und/oder Durchführung von klinischen Studien bzw. den Aufgaben und Verantwortlichkeiten für Behörden und Ethik-Kommissionen unter der 12. AMG-Novelle gesammelt haben, aufrufen, aktiv an dieser Veranstaltung teilzunehmen.
Je nach Art und Inhalt der Vorschläge und Teilnahmebereitschaft Ihrerseits werden wir die einzelnen Themen gestalten.

Kontaktaufnahme bis zum 15. November 2004 erfolgt am besten per e-mail:

Ingrid Klingmann: iklingmann@skynet.be

Hermann Fuder: hermann.fuder@parexel.com

Applied Human Pharmacology

Definition and implicit Mission Statement about 20 years ago

Ch. de Mey 1992 (translated from German):

Human pharmacology **explores** and **describes** pharmacological processes in man;
i.e. pharmacokinetic and pharmacodynamic interactions between a drug and the organism of healthy human volunteers. In research, these studies are mostly classified as Phase I.

Phase-II-a studies investigate similar questions; however, in symptomatic volunteers.

Pharmaceutical human pharmacology mainly deals with the development of new drugs or further development of known drugs or diagnostics.

Applied Human Pharmacology - Mission Statement in 2010

Claim: Applied Human Pharmacology provides a structured basis of knowledge about PK and PD and their interrelation of new as well as existing drugs

Goals:

- to allow timely decision making during the drug development process and to expedite drug development
- to provide pivotal data for regulatory approval
- to obtain approval based on PD & PK data
- and to redefine the need for therapeutic equivalence trials or even large Phase III trials in patients
- to participate in the ever ongoing process of benefit-risk assessment

The armamentarium:

- to determine the relationship between drug exposure, effect and time
- to predict clinical efficacy based on appropriate surrogate endpoints
- to guide dose-finding and assist in determining the therapeutic index
- to determine the PK and PD drug interaction potential
- to assess and interprete disease conditions with respect to their impact on PK and PD
- to assess and interprete the contribution of genes in PK and PD
- to address special populations (e.g. paediatric population; impact of age, gender, race)
- to provide focussed studies in the safety evaluation of drugs
- to assist in the individualization of medicines

TIMELY DECISION MAKING / EXPEDITED DRUG DEVELOPMENT

European Medicines Agency

June 2009
CPMP/ICH/286/95

ICH Topic M 3 (R2)
Non-Clinical Safety Studies for the Conduct of
Human Clinical Trials and Marketing Authorization for Pharmaceuticals

Step 4

NOTE FOR GUIDANCE ON NON-CLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS
(CPMP/ICH/286/95)

TRANSMISSION TO CHMP	July 2008
TRANSMISSION TO INTERESTED PARTIES	July 2008
DEADLINE FOR COMMENTS	October 2008
APPROVAL BY CHMP	June 2009
DATE FOR COMING INTO OPERATION	December 2009

7. Exploratory Clinical Trials

7.1 Microdose trials

7.2 Single-dose trials at sub-therapeutic doses or into the anticipated therapeutic range

7.3 Multiple dose trials
(up to 14 days to determine PK and PD in the therapeutic dose range;
no determination of the MTD)

PhRMA Survey on the Conduct of First-in-Human Clinical Trials Under Exploratory Investigational New Drug Applications

Adel H. Karara, PhD, FCP, Timi Edeki, MD, PhD, FCP, James McLeod, MD, Alfred P. Tonelli, PhD, and John A. Wagner, MD, PhD, FCP

The FDA guidance on exploratory IND studies is intended to enable sponsors to move ahead more efficiently with the development of promising candidates. A survey of PhRMA member companies was conducted in 2007 to obtain a cross-sectional industry perspective on the current and future utility of exploratory IND studies. About 56% of survey responders (9 companies of 16 survey responders) conducted or were planning to conduct clinical studies under exploratory INDs. The majority of microdosing studies are performed to characterize human pharmacokinetics or to examine target organ pharmacokinetics using PET imaging techniques. On the other hand, the majority of pharmacological end point studies conducted under exploratory IND are performed to determine whether the compound modulated its pharmacological target or to evaluate the degree of saturation of a target receptor. The present survey suggests that although the merits of exploratory INDs are still being debated, the diversity in the applications cited, the potential for early clinical guidance in decision making and the increasing pressure on containing drug development costs, suggest that the exploratory IND/CTA will be a valuable option with evolving and possibly more specific applications for the future.

Keywords: *Pharmaceutical Research and Manufacturers of America; exploratory investigational new drug applications; screening investigational new drug applications; microdosing studies; pharmacological end point studies; mechanism of action studies; early clinical trials; phase 0 trials*

Journal of Clinical Pharmacology, XXXX;XX:xxx-xxx

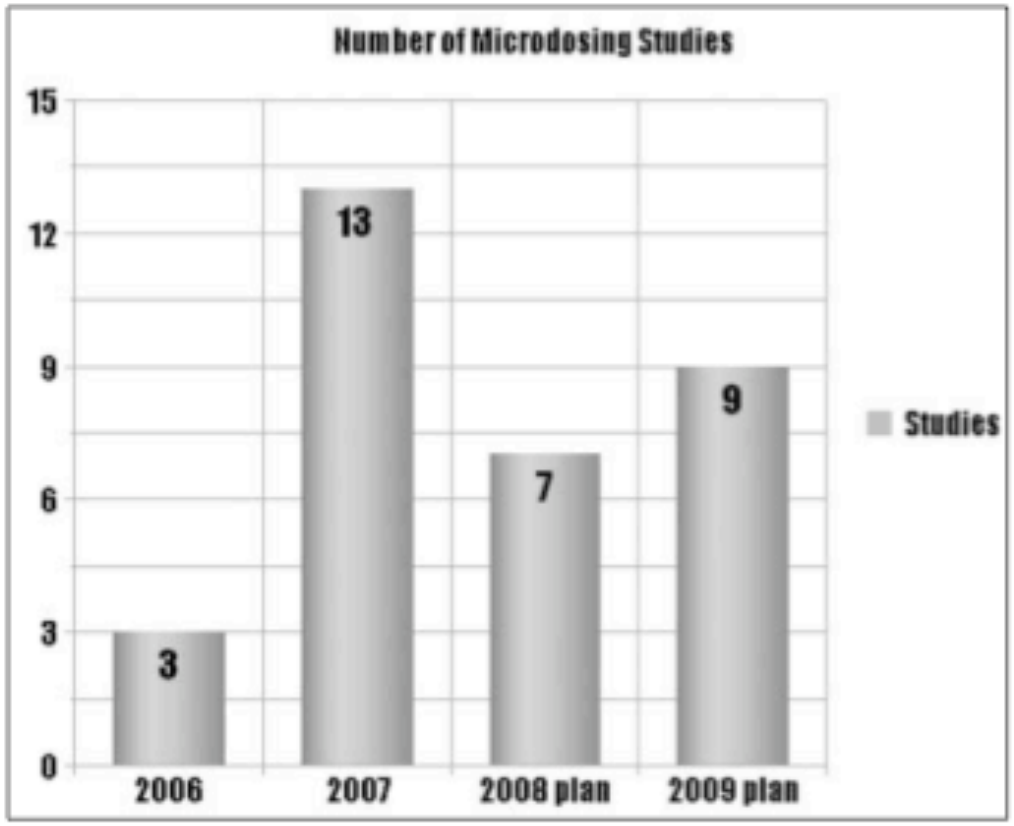


Figure 2. Since the FDA guidance on exploratory IND became available in January 2006, how many microdosing studies were conducted by your company under an exploratory IND? Number of microdosing studies conducted/plan to be conducted by 9 responder companies.

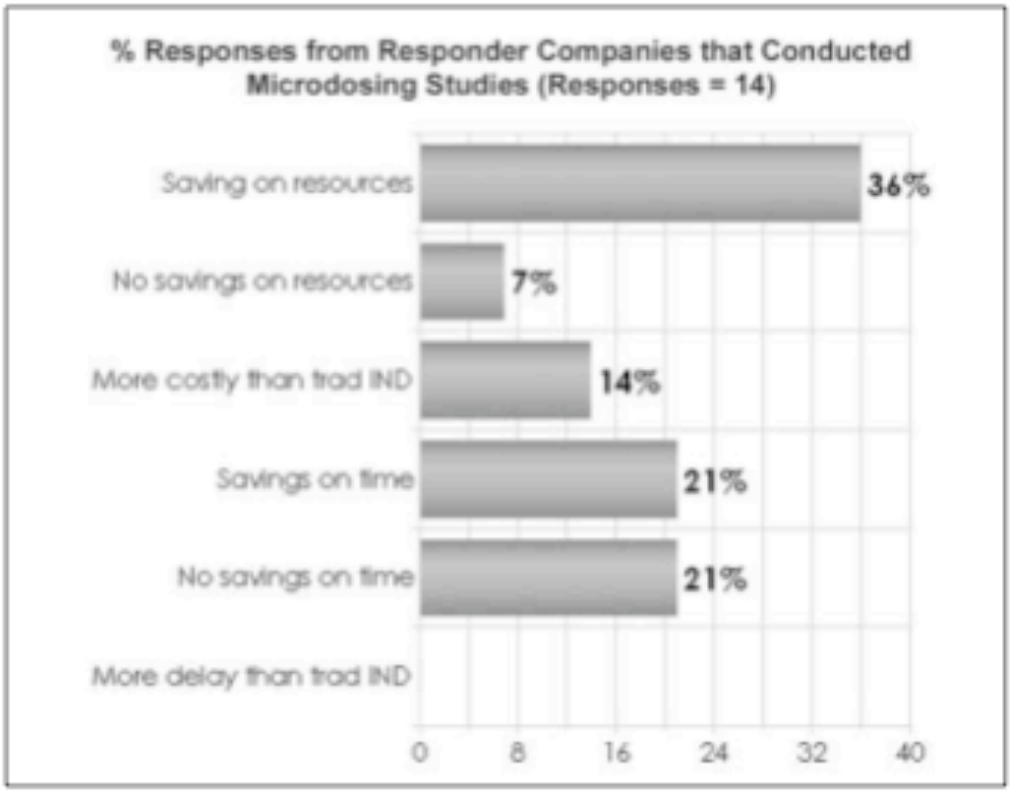


Figure 3. Compared with the traditional IND, did the conduct of the microdosing studies result in: Percentage responses from responder companies that conducted microdosing studies (14 responses)

Source: Karara AH et al. 2010; J Clin Pharm

The Journal of Clinical Pharmacology

http://www.jclinpharm.org

American College of Clinical Pharmacology Position Statement on the Use of Microdosing in the Drug Development Process

Joseph S. Bertino, Jr, Howard E. Greenberg and Michael D. Reed

J. Clin. Pharmacol. 2007; 47; 418
DOI: 10.1177/0091270006299092

Citation from the Conclusions:

At present, it would appear that studies using microdosing methodology should not be relied on as the primary or sole approach to screen new drug candidates, as the potential exists with current methodologies to possibly reject important new drugs while possibly accepting drugs that could result in significant safety issues.

Until more information is available and has undergone appropriate scrutiny, it would appear that a microdosing strategy could complement standard animal-to-human allometric scaling, refining current phase I study designs.

Human drug development is a dynamic process that capitalizes on the continuous advancements realized within the analytical pharmacology and data analysis laboratories, combined with a precise understanding of the integrated pharmacokinetic-pharmacodynamic-pharmacogenomic drug profile.

Microdosing methodology appears to be one of the many new viable “tools” in the drug development “toolbox.” The exact role and impact .... is yet to be fully realized....

REGULATORY APPROVAL BASED ON PIVOTAL PD AND PK DATA / REDEFINE THE NEED FOR THERAPEUTIC EQUIVALENCE/Phase III IN PATIENTS

European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

London, 22 February 2006
EMEA/CHMP/BMWP/42832/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: NON-CLINICAL AND CLINICAL ISSUES

European Medicines Agency
Evaluation of Medicines for Human Use

London, 22 February 2006
EMEA/CHMP/BMWP/31329/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

ANNEX TO GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: NON-CLINICAL AND CLINICAL ISSUES

GUIDANCE ON SIMILAR MEDICINAL PRODUCTS CONTAINING RECOMBINANT GRANULOCYTE-COLONY STIMULATING FACTOR

REGULATORY APPROVAL BASED ON PIVOTAL PD AND PK DATA / REDEFINE THE NEED FOR THERAPEUTIC EQUIVALENCE/Phase III IN PATIENTS

4.2. CLINICAL STUDIES

Pharmacokinetic studies

The pharmacokinetic properties of the similar biological medicinal product and the reference medicinal product should be compared in single dose crossover studies using subcutaneous and intravenous administration. The primary PK parameter is AUC and the secondary PK parameters are C_{max} and T1/2. The general principles for demonstration of bioequivalence are applicable.

Pharmacodynamic studies

The absolute neutrophil count (ANC) is the relevant pharmacodynamic marker for the activity of r-G-CSF. The pharmacodynamic effect of the test and the reference medicinal products should be compared in healthy volunteers. The selected dose should be in the linear ascending part of the dose-response curve. Studies at more than one dose level may be useful. The $CD34^+$ cell count should be reported as a secondary PD endpoint. The comparability range should be justified.

Alternative models, including pharmacodynamic studies in healthy volunteers, may be pursued for the demonstration of comparability if justified. In such cases, the sponsor should seek for scientific advice for study design and duration, choice of doses, efficacy / pharmacodynamic endpoints, and comparability margins.

REGULATORY APPROVAL BASED ON PIVOTAL PD AND PK DATA /

REDEFINE THE NEED FOR THERAPEUTIC EQUIVALENCE/Phase III IN PATIENTS

Example: Approval of Filgrastim HEXAL

Annals of Oncology Advance Access published December 17, 2009

original article

Annals of Oncology
doi:10.1093/annonc/mdp574

Development of a new G-CSF product based on biosimilarity assessment

P. Gascon[1], U. Fuhr[2,3], F. Sörgel[4,5], M. Kinzig-Schippers[4], A. Makhson[6], S. Balser[7], S. Einmahl[8] & M. Muenzberg[7]*

[1]Division of Medical Oncology, Hospital Clinic, Barcelona University, Barcelona, Spain; [2]Department of Pharmacology, University Hospital, University of Cologne, Cologne, Germany; [3]Itecra GmbH & Co. KG, Cologne, Germany; [4]IBMP – Institute for Biomedical and Pharmaceutical Research, Nürnberg-Heroldsberg, Germany; [5]Department of Pharmacology, University of Duisburg–Essen, Essen, Germany; [6]Moscow City Oncology Hospital, Moscow, Russia; [7]Sandoz International GmbH, Holzkirchen, Germany and [8]Triskel Integrated Services, Geneva, Switzerland

Received 15 September 2009; accepted 9 November 2009

Background: Zarzio®, a new recombinant human granulocyte colony-stimulating factor (filgrastim), was evaluated in healthy volunteers and neutropenic patients in phase I and III studies.

Patients and methods: Healthy volunteers in randomized, two-period crossover studies received single- and multiple-dose s.c. injections of 1 μg/kg (n = 24), 2.5 μg/kg (n = 28), 5 μg/kg (n = 28), or 10 μg/kg (n = 40), as well as single-dose i.v. infusions of 5 μg/kg (n = 26), of Zarzio® or the reference product (Neupogen®). Filgrastim serum levels were monitored; pharmacodynamic parameters were absolute neutrophil count (all studies) and $CD34^+$ cells (multiple-dose studies). Supportive efficacy and safety data were obtained from an open phase III study in 170 breast cancer patients undergoing four cycles of doxorubicin and docetaxel (Taxotere) chemotherapy, receiving Zarzio® (300 or 480 μg) as primary prophylaxis of severe neutropenia.

Results: The results of the studies in healthy volunteers confirm the comparability of the test and reference products with respect to their pharmacodynamics and pharmacokinetics. Confidence intervals were within the predefined equivalence boundaries. In the phase III study in breast cancer patients, the administration of Zarzio® was efficacious and safe, triggering no immunogenicity.

Conclusion: The results of these studies demonstrate the biosimilarity of Zarzio® with its reference product Neupogen®.

Key words: biosimilar, clinical trial, filgrastim, neutropenia, recombinant human granulocyte colony-stimulating factor

4.2 CLINICAL STUDIES

Pharmacokinetic studies

The relative pharmacokinetic properties of the similar biological medicinal product and the reference medicinal product should be determined in a single dose crossover study using subcutaneous administration. Comprehensive comparative data should be provided on the time-concentration profile (AUC as the primary endpoint and C_{max}, T_{max}, and $T_{1/2}$ as secondary endpoints). Studies should be performed preferably in patients with type1 diabetes. Factors contributing to PK variability *e.g.* insulin dose and site of injection / thickness of subcutaneous fat should be taken into account.

Pharmacodynamic studies

The clinical activity of an insulin preparation is determined by its time-effect profile of hypoglycaemic response, which incorporates components of pharmacodynamics and pharmacokinetics. Pharmacodynamic data are of primary importance to demonstrate comparability of a similar rh-insulin. The double-blind, crossover hyperinsulinaemic euglycaemic clamp study is suitable for this characterisation. Data on comparability regarding glucose infusion rate and serum insulin concentrations should be made available. The choice of study population and study duration should be justified.

Plasma glucose levels should be obtained as part of the PK study following subcutaneous administration.

Clinical efficacy studies

Provided that clinical comparability can be concluded from PK and PD data, there is no anticipated need for efficacy studies on intermediary or clinical variables.

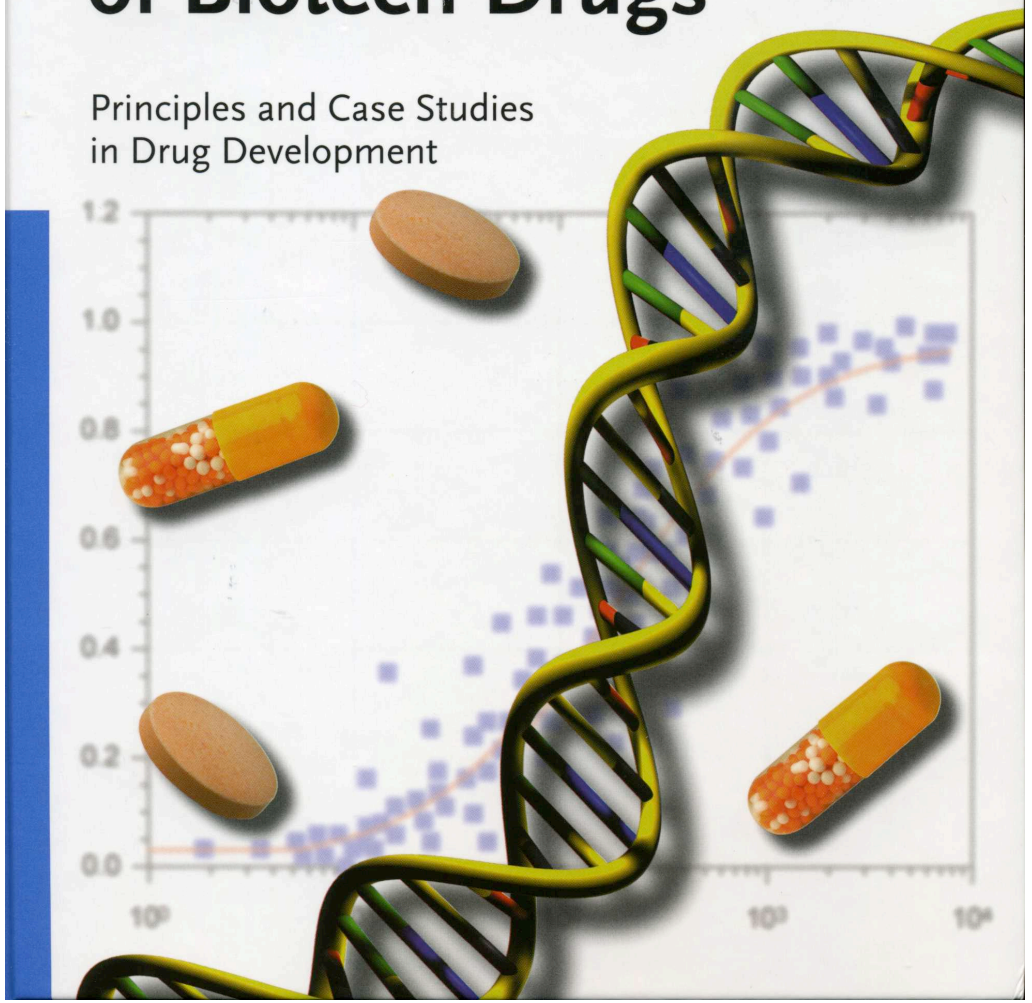
4 3 CLINICAL SAFETY

Edited by Bernd Meibohm

WILEY-VCH

Pharmacokinetics and Pharmacodynamics of Biotech Drugs

Principles and Case Studies in Drug Development



Advances in biotech drug development

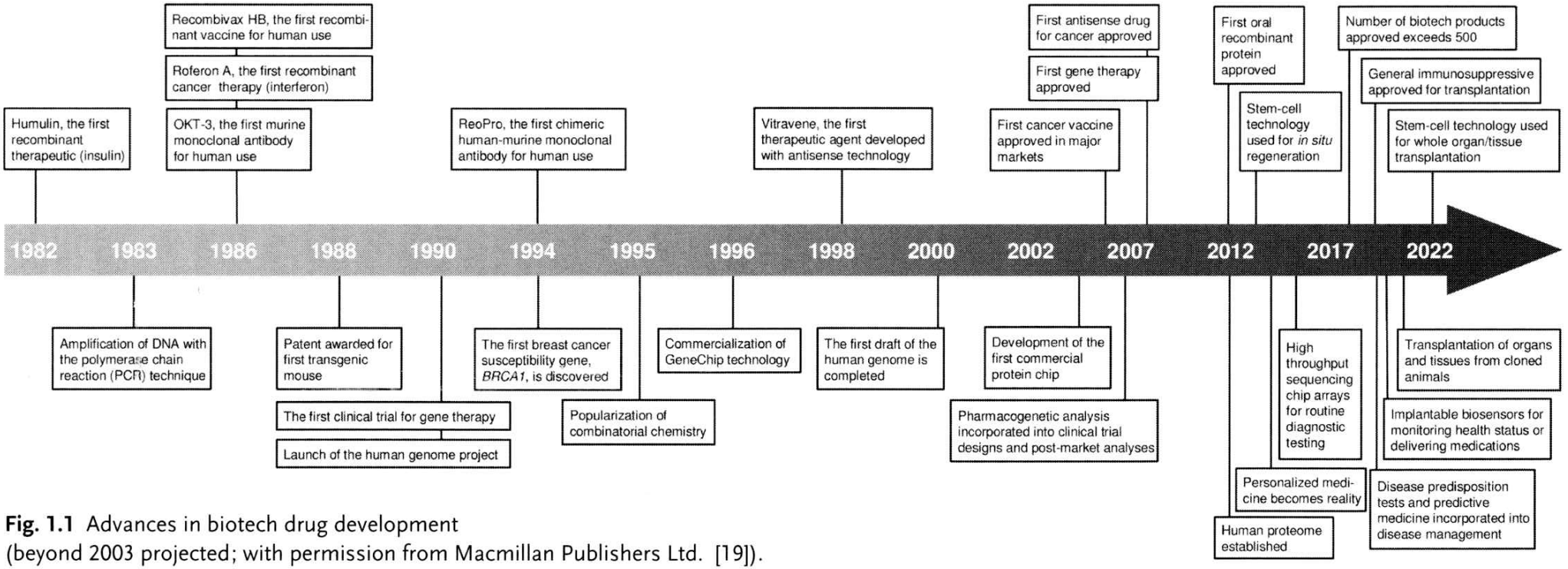
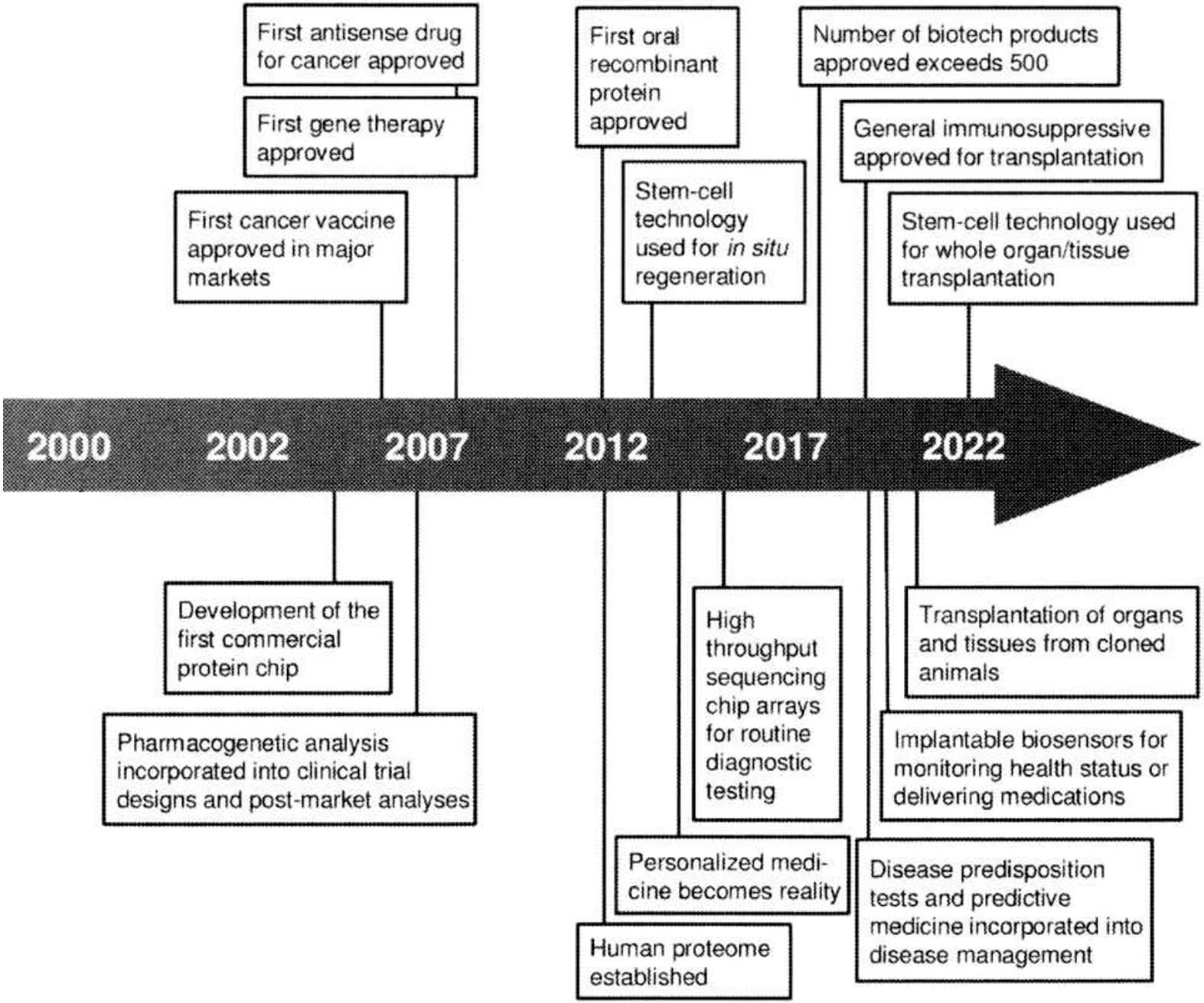
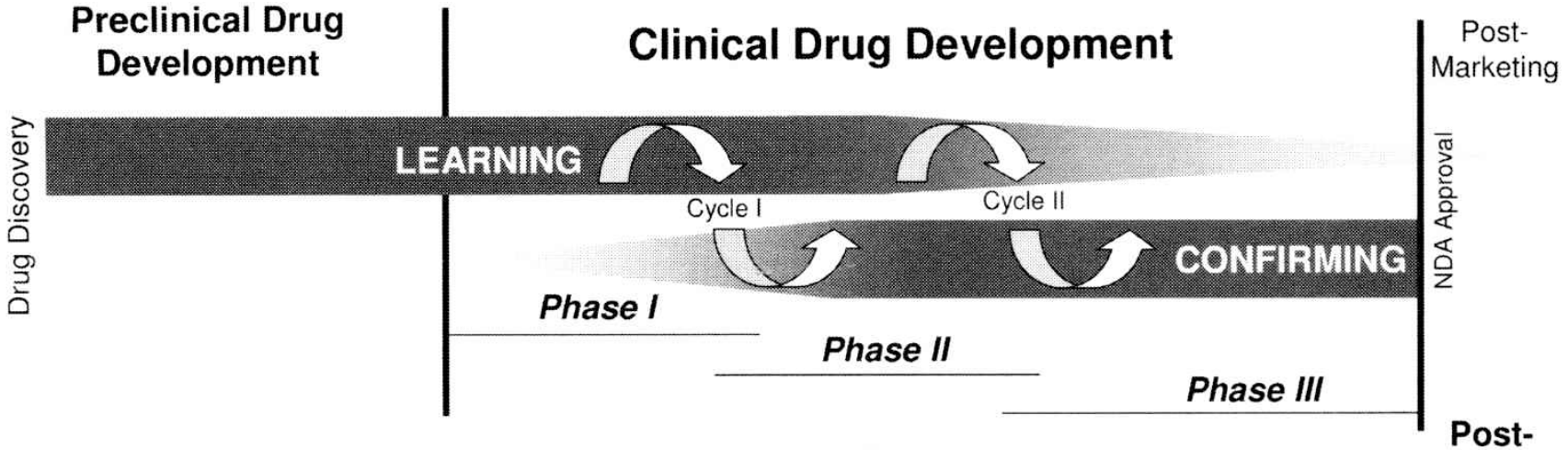


Fig. 1.1 Advances in biotech drug development
(beyond 2003 projected; with permission from Macmillan Publishers Ltd. [19]).

Advances in biotech drug development



DRUG DEVELOPMENT BASED ON PK/PD



Preclinical PK/PD

- Development of mechanism-based models
- Evaluation of *In vivo* potency and intrinsic activity
- Evaluation of *In vivo* drug interactions
- Identification of bio-/ surrogate markers and animal models for efficacy/toxicity
- Dosage form and dosage regimen optimization
- Integrated information supporting 'go/no go' decision

Transitional PK/PD

- Extrapolation of preclinical data to humans
- Allometric scaling
- Dose selection/ escalation

Clinical PK/PD

Analytical PK/PD

- Characterization of dose-concentration-effect relationship
- Evaluation of dosage forms and administration pathways
- Therapeutic index
- Food effects
- Gender effects
- Special populations (children, elderly)
- *In vivo* evaluation of active metabolites
- Drug/Drug interactions
- Drug/Disease interactions
- Tolerance development
- Evaluation of drug analogues
- Population PK/PD
- Bridging studies

Predictive PK/PD

- Simulations
- Trial forecasting

Post-Marketing PK/PD

- Post-marketing surveillance

AAPS-FDA Workshop White Paper: Microdialysis Principles, Application, and Regulatory Perspectives

Chandra S. Chaurasia, PhD, RPh, Markus Müller, MD, Edward D. Bashaw, PharmD, Eva Benfeldt, MD, PhD, Jan Bolinder, MD, PhD, Ross Bullock, MD, PhD, Peter M. Bungay, PhD, Elizabeth C. M. DeLange, PhD, Hartmut Derendorf, PhD, William F. Elmquist, PhD, Margareta Hammarlund-Udenaes, PhD, Christian Joukhadar, MD, Dean L. Kellogg Jr, MD, PhD, Craig E. Lunte, PhD, Carl Henrik Nordstrom, MD, Hans Rollema, PhD, Ronald J. Sawchuk, PhD, Belinda W. Y. Cheung, PhD, Vinod P. Shah, PhD, Lars Stahle, MD, PhD, Urban Ungerstedt, MD, PhD, Devin F. Welty, PhD, and Helen Yeo, PhD

Keywords: *Microdialysis; regulatory aspects; tissue pharmacokinetics*

Journal of Clinical Pharmacology, 2007;47:589-603

The White Paper defines the role of *μ*D

- in drug discovery and development
- in PK-PD evaluation
- monitoring of human organ chemistry during intensive care
- in topical application of drugs (e.g. dermal microdialysis)
- in paracrine endocrinology and metabolism

Regulatory aspects

Ultimately, the acceptance of *μ*D as a regulatory tool will be dependent on the correlation of the results from *μ*D with clinical response.
Thus, validation will be the key to regulatory acceptance of the methodology.

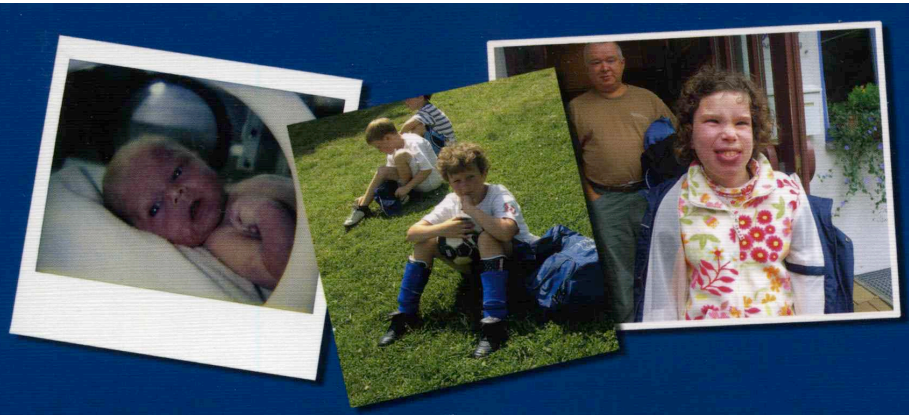
Clinical Microdialysis in Skin and Soft Tissues: An Update

Stephan Schmidt, BS, Rebecca Banks, BS, Vipul Kumar, PhD, Kenneth H. Rand, MD, and Hartmut Derendorf, PhD, FCP

Traditionally, plasma or serum drug concentrations have been used for the assessment of bioavailability and bioequivalence. Since in the majority of cases the site of drug action is in the tissue rather than the blood, the use of corresponding free, unbound concentrations in the tissue is a much more meaningful approach. This can become especially important for topical drug administrations, where locally active drug concentrations can significantly exceed free concentrations in plasma. The ability to measure these free concentrations at the site of drug action over time makes microdialysis a very valuable tool for the assessment of bioavailability and bioequivalence. This has been recognized by industry and regulatory authorities, resulting in a recommendation of the microdialysis technique as a tool for bioequivalence determination of topical dermatologic products. The aim of this article is to provide an updated review of the microdialysis technique, its applications in skin and soft tissues, and the resulting impact on clinical drug development.

Keywords: *Microdialysis; skin; soft tissues; pharmacokinetics*

Journal of Clinical Pharmacology, 2008;48:351-364

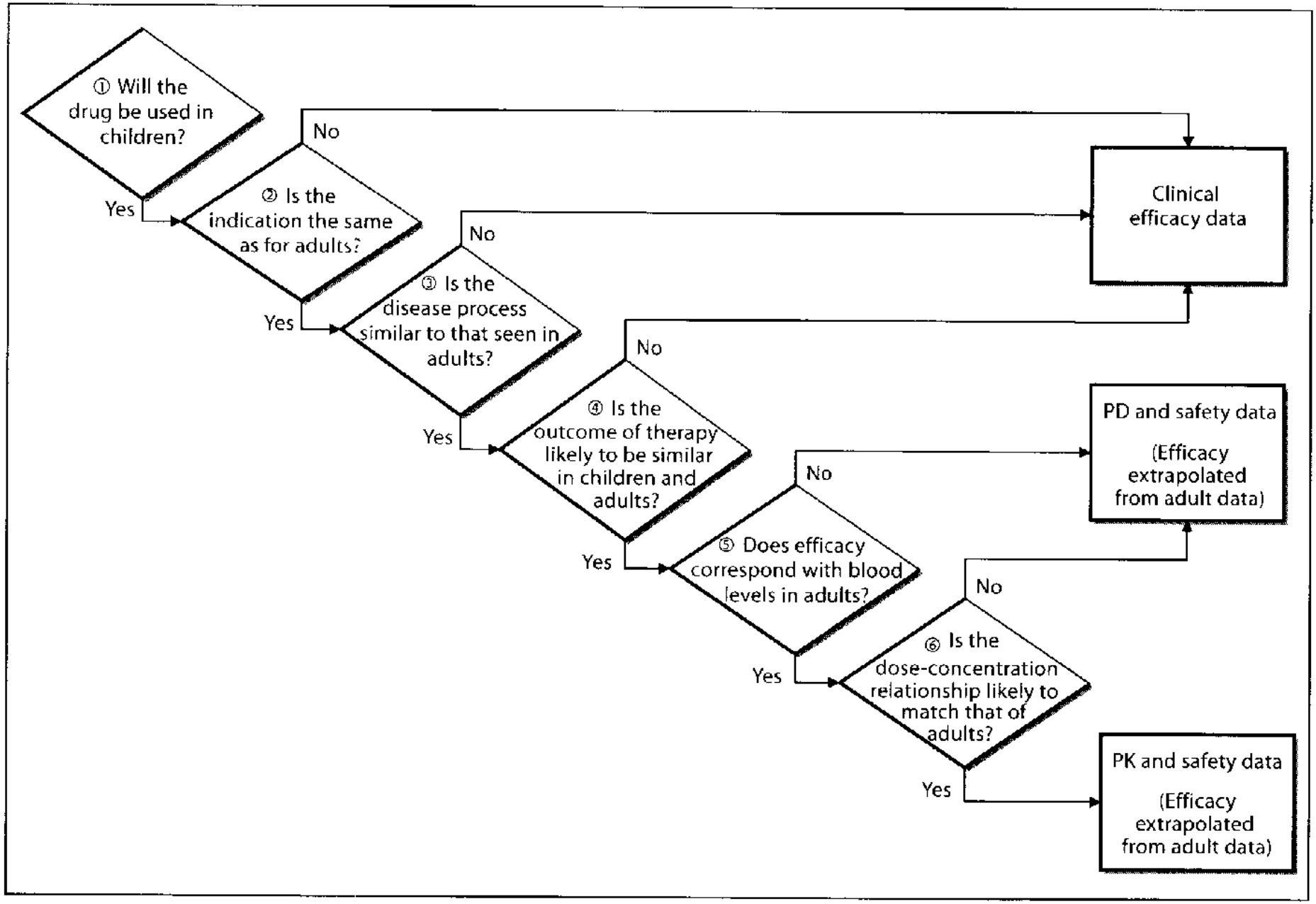


Guide to Paediatric Clinical Research

Editors
K. Rose
J.N. van den Anker

KARGER

Decision tree for paediatric clinical drug development



CONCLUSIONS

The past 20 years have provided a solid basis
for applied human pharmacology tasks

We will experience a paradigm shift in drug development

The role of applied human pharmacology and clinical pharmacology
will dramatically increase

There will be increasing requirements concerning our discipline
in a much more complex setting

We will have to face and to shoulder this task in the next 20 years