



GEORGETOWN UNIVERSITY MEDICAL CENTER

Center for Drug Development Science

Departments of Pharmacology and Medicine

June 3, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration,
5630 Fishers Lane, rm 10-61
Rockville, MD 20852

<http://www.fda.gov/dockets/ecomments>

RE: Docket No. 02D-0095

Dear Madam or Sir:

On behalf of the Georgetown University Center for Drug Development Science (CDDS: <http://cdds.georgetown.edu/>), I submit herein comments on the Draft Guidance for Industry "Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications" (Federal Register / Vol. 67, No. 63 / Tuesday, April 2, 2002 / Notices, pages 15576-7). Our comments reflect the opinion of the CDDS faculty and advisors, especially those of Professors Nicholas Holford, MD (University of Auckland, New Zealand), Lewis B. Sheiner, MD (University of California at San Francisco), John Urquhart (Maastricht University, The Netherlands), Howard Lee, MD PhD, and myself.

We appreciate and commend the high quality effort expended by the Exposure-Response Working Group of CDER and CBER in developing and presenting the draft guidance on exposure-response relationships for public comment.

CDDS's comments comprise general ones and comments relating to draft guidance text (in *italics*), identified by specific draft guidance line numbers (in **underlined bold italics**)

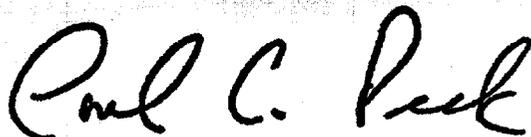
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in our commentary below. Deriving its views independently from those of the pharmaceutical industry or government, CDDS presents comments and recommendations that aim to advance the science of drug development and regulation for the benefit of patients and the public health, through optimization of effectiveness and safety determinations using advanced scientific methods.

Sincerely yours,

A handwritten signature in black ink that reads "Carl C. Peck". The signature is written in a cursive, flowing style.

Carl C. Peck, MD

Professor of Pharmacology and Medicine
Director, Center for Drug Development Science
Georgetown University Medical Center
Med-Dent NE-405
3900 Reservoir Road NW,
Washington DC, 20007

Comments on Docket No. 02D-0095
Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications
Center for Drug Development Science, Georgetown University Medical Center, Washington, DC

June 3, 2002

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Omissions

a) "Confirmatory Evidence"

The use of exposure-response data to qualify as "confirmatory evidence" of effectiveness as described in FDAMA Section 115a should be considered in this guidance. Additionally, qualities of exposure-response information that contribute to the distinction between empirical and causal evidence of effectiveness should be addressed.

b) Population Pharmacokinetics Guidance

The 1999 FDA Population Pharmacokinetics Guidance for Industry should be considered for inclusion in Appendix A of the Exposure-Response Guidance (ERG).

c) Trial designs to identify nonlinearities in exposure-response relationships

Safety risks and efficacy reductions resulting from irregular drug exposure may not be apparent in traditional supervised dose- or concentration-response study designs, which document responses during continuous exposure, but ignore responses following cessation or resumption of exposure. Particularly important are safety and effectiveness consequences encountered during drug holidays (multiple consecutive missed doses) or upon resumption of exposure due to nonlinear response patterns. Examples include hazardous rebound effects of non-ISA beta blockers, opiates, central alpha blockers, statins in unstable angina, antimicrobial resistance (TB, HIV, etc), corticosteroids, and rifampicin (hemolytic anemia). To identify such nonlinearities, consideration should be given in the ERG to encouragement of testing key input patterns for exposing such response nonlinearities during early dosing and chronic therapy. We recommend listing the following candidate exposure patterns for inclusion in Section V. "DESIGNS OF EXPOSURE-RESPONSE STUDIES", B. "Exposure-Response Study Design", Table I. "Points for Consideration in Different Study Designs from the Exposure-Response Perspective".

Exposure patterns to include in the early days of drug exposure:

- Graded doses
- Sudden exposure (e.g. rapid IV infusion)
- Gradually increasing exposure
- Sudden cessation of exposure
- Gradually decreasing exposure
- High vs low rates of increase of drug concentration in plasma

After 90-150 days of maintenance exposure:

- Repeat graded doses and contrast response patterns with those observed during early days of drug exposure. If observed dosing patterns differ substantially from those of early dosing, repeat the other patterns.
- If the drug has an exaggerated first-dose safety effect, determine how long exposure can be interrupted without the need to re-titrate.

d) Line 75 reference to "Peck 1994"

This citation on line 75 is not included in the REFERENCE section, and should appear circa line 813. The reference is: Peck, CC; Barr, WH; Benet, LZ; Collins, J; Desjardins, RE; Furst, DE; Harter, JG; Levy, G; Ludden, T; Rodman, JH; et al. Opportunities for integration of pharmacokinetics, pharmacodynamics, and toxicokinetics in rational drug development. J Clin Pharmacol. 34(2):111-9, 1994.

e) Schedule Dependence:

560 *e. Plasma concentration-time profiles*

Schedule dependence and the need to use the concentration time course to describe and predict this phenomenon are key applications in areas such as cancer chemotherapy. Any indication that relies on a clinical outcome reflecting the cumulative effect (i.e., a weighted time-integral) of drug exposure and a non-linear relationship between concentration and drug action will exhibit schedule dependence. The importance of recognizing schedule dependence is even greater than the existence of non-linearities in a drug's pharmacokinetics.

The ERG should encourage drug developers to recognize the circumstances which are likely to lead to schedule dependence and encourage clinical trial designs which can be informative for identifying optimal dosing schedules.

f) Target Concentration

The concept of a target concentration has been a mainstay of the scientific application of pharmacokinetics and pharmacodynamics to rational therapeutics [1, 2]. The identification of a target effect and from that of a (possibly individual-specific) target concentration is an essential step for the use of pharmacokinetics to guide drug dosing.

Without a target concentration there is no rational way to apply what is learned from pharmacokinetics to help in the individualization of drug dose. Further, factoring the dose to effect relationship into a dose to concentration part and a concentration to effect part allows separately focussed learning and a framework for combining pharmacokinetic and pharmacodynamic information. The ERG should therefore identify the target concentration concept as a central guiding concept for rational drug development.

Nomenclature

a) Efficacy/Effectiveness

72 output), and the full range of short-term or long-term clinical effects related to either efficacy or safety.

As used in the ERG the terms efficacy and effectiveness are used interchangeably. The ERG should place itself in consonance with the usage in the parent science, pharmacology, and use “effectiveness” to denote the demonstration that a drug has an effect and “efficacy” to refer to the drug’s maximum effect (cf. Holford & Sheiner [3]). Effectiveness may be usefully qualified as method effectiveness (the treatment effect expected if the drug is used as prescribed) and use effectiveness (the treatment effect expected from prescribing the drug e.g. as estimated by an analysis according to the intention to treat principle).

The 1998 FDA Guidance “Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products” [4] also fails to use the terms efficacy and effectiveness as defined in pharmacology, exemplified by the following excerpts:

“As used in this guidance, the term efficacy refers to the findings in an adequate and well-controlled clinical trial or the intent of conducting such a trial and the term effectiveness refers to the regulatory determination that is made on the basis of clinical efficacy and other data.”

Other disciplines e.g. epidemiology, have unfortunately added to the confusion of these terms by using “efficacy” to mean method effectiveness and “effectiveness” to mean use effectiveness [5].

The ERG should take this opportunity to improve on these definitions by using them as does the field of pharmacology, and also reinforce the notion that the maximum effect of a drug is an important exposure-response parameter (estimand).

We recommend that all uses of “efficacy” in the ERG be changed to “effectiveness” unless the context clearly refers to the maximum effect of a drug.

b) Tolerability/Tolerance

51 use is based on titration to effect or tolerance.

The term 'tolerance' should be reserved for the pharmacological phenomenon of

decreasing drug effect after chronic exposure. For the purposes of the line 51, perhaps 'tolerability' would serve better.

c) Concentration/Level

57 ...dose to blood levels in various populations, ...

It is preferable to use the word concentration instead of "level" because 1) concentration is a scientifically defined unit 2) level implies a constant or steady value but concentrations are typically varying with time.

d) Biomarker

68 other biological fluid (e.g., C_{max} , C_{min} , C_{ss} , AUC). Similarly, response refers to a direct measure of the pharmacologic effect of the drug. Response includes a broad range of endpoints, including a nonclinical biomarker (e.g., receptor occupancy), a presumed mechanistic effect (e.g., ACE inhibition), a potential or accepted surrogate (e.g., effects on BP, lipids, cardiac...)

The NIH/FDA conference held in 1999 [6] established a consensus on the use of the terms biomarker and surrogate endpoint. No distinction was made between effects such as receptor occupancy and inhibition of an enzyme (such as ACE). We wonder what distinction is sought by distinguishing, in this context, between receptor occupancy and enzyme inhibition. We suggest:

"including a biomarker (e.g., receptor occupancy, or ACE inhibition), a potential or accepted surrogate endpoint (e.g., effects on BP, lipids, cardiac..."

This would then be compatible with the later remarks in the ERG in section 570 D. Measuring Response.

Concepts Which Appear to be Over Simplified

a) Use of C_{max} and C_{min}

507 2. Exposure Variables

By referring to C_{max} and C_{min} as exposure measures, this implies their official approval for this purpose. It should be pointed out that for many drugs there is little data on which to base such a supposition. Further, the ERG does not adequately distinguish between estimands (target concentrations, for example) and estimators (measurements made at certain times in an inter-dose interval). Specifically, for example, a concentration

Comments on Docket No. 02D-0095

Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications
Center for Drug Development Science, Georgetown University Medical Center, Washington, DC
measured at the expected time of the maximum concentration is a downwardly biased estimator of the true maximum.

b) Use of Trough Concentration to Predict AUC

537 ... *Trough levels are often proportional to AUC, because they do not reflect drug absorption processes, as peak levels do in most cases.*

See the above comment. Does the ERG want to take a stand on what is a good estimator and what is not? If so, we would opine that the immediate pre-dose concentration is not a particularly good estimator of average C_{ss} (or, therefore Clearance or AUC) [7], despite the fact that the recommendation is supported by the FDA Guidance on population pharmacokinetics [8]. A sample in the middle of the dosing interval will generally be better than a trough and in many cases will be close to the average C_{ss}.

c) Definition of Surrogate Endpoint

629 *A well-validated surrogate will predict the clinical benefit of an intervention both quantitatively and qualitatively (Prentice 1989), with consistent results in several settings.*

The Prentice definition of a surrogate endpoint is generally regarded as more stringent than is practical, and in any event is not needed to justify the assertion here. We suggest leaving out the reference and substituting Lesko & Atkinson [9].

Recommendation

In order to optimize the utility of exposure-response information derived in drug development, consideration should be given to FDA encouragement of a sponsor-regulator meeting at the end of phase 1, as recommended at a recent workshop on confirmatory evidence (see

(http://cdds.georgetown.edu/conferences/confevidence_final.html) or the Drug Information Journal, Volume 36, 2002.)

References

1. Sheiner L, Tozer T. Clinical pharmacokinetics: The use of plasma concentrations of drugs. In: Melmon K, Morelli H, editors. *Clinical Pharmacology: Basic Principles of Therapeutics*. New York: Macmillan; 1978. p. 71-109.
2. Holford NHG. The target concentration approach to clinical drug development. *Clinical Pharmacokinetics* 1995;29(5):287-91.
3. Holford NHG, Sheiner LB. Understanding the dose-effect relationship: Clinical application of pharmacokinetic-pharmacodynamic models. *Clinical Pharmacokinetics* 1981;6:429-453.
4. Food and Drug Administration. Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. <http://www.fda.gov/cder/guidance/1397fnl.pdf> 1998:1-23.
5. Porzsolt F. Clinical economics: estimating the value of health care services. http://biostatistik.uibk.ac.at/roes/papers/RoES_2001_Porzolt_Paper.pdf 2001:1-6.
6. National Institutes of Health, Food and Drug Administration. Biomarkers and Surrogate Endpoints: Advancing Clinical Research and Applications. <http://www4.od.nih.gov/biomarkers/> 1999. See also: Biomarkers Definitions Working Group: "Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. *Clin Pharm Ther* 69 (3): 89-95, 2001.
7. Lee PID. Design and power of a population pharmacokinetic study. *Pharmaceutical Research* 2001;18(1):75-82.
8. Food and Drug Administration. Population Pharmacokinetics. <http://www.fda.gov/cder/guidance/1852fnl.pdf> 1999:1-35.
9. Lesko LJ, Atkinson AJ. Use of biomarkers and surrogate endpoints in drug development and regulatory decision making: criteria, validation, strategies. *Annual Review of Pharmacology and Toxicology* 2001;41:347-66.

ANNUAL BURDEN ESTIMATES

Instrument	Number of respondents	Number of responses per respondent	Average burden hours per response	Total burden hours
Tribal Leaders	40	1	1	40
Program Managers and Front Line Workers	120	1	1	120
Funding Officials	20	1	1	20
Child Welfare/Human Service Collaborators	60	1	1	60
Court Officials	20	1	1	20

Estimated Total Annual Burden Hours: 260.

In compliance with the requirements of section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995, the Administration for Children and Families is soliciting public comment on the specific aspects of the information collection described above. Copies of the proposed collection of information can be obtained and comments may be forwarded by writing to the Administration for Children and Families, Office of Information Services, 370 L'Enfant Promenade, SW., Washington, DC 20447, Attn: ACF Reports Clearance Officer. All requests should be identified by the title of the information collection.

The Department specifically requests comments on: (a) Whether the proposed collection of information is necessary for the proper performance of the functions of the agency, including whether the information shall have practical utility; (b) the accuracy of the agency's estimate of the burden of the proposed collection of information; (c) the quality, utility, and clarity of the information to be collected; and (d) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques or other forms of information technology. Consideration will be given to comments and suggestions submitted within 60 days of this publication.

Dated: March 26, 2002.

Bob Sargis,

Reports Clearance, Officer.

[FR Doc. 02-7907 Filed 4-1-02; 8:45 am]

BILLING CODE 4184-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Administration for Children and Families

Office of Planning, Research, and Evaluation, Grant to the University of Georgia

AGENCY: Office of Planning, Research and Evaluation, ACF, DHHS.

ACTION: Award announcement.

SUMMARY: Notice is hereby given that a noncompetitive grant award is being made to the University of Georgia to conduct a study to identify rural counties in the Southern Black Belt experience persistent poverty and to examine their social, demographic, and economic conditions.

As a Congressional setaside, this one-year project is being funded noncompetitively. The university has several facilities and resources on campus for undertaking the feasibility study. The university also will rely upon several outside sources with specialized expertise to conduct various activities related to the project. The cost of this one-year project is \$250,000.

FOR FURTHER INFORMATION CONTACT: Hossein Faris, Administration for Children and Families, Office of Planning, Research And Evaluation, 370 L'Enfant Promenade, SW., Washington, DC 20447, Phone: 202-205-4922.

Dated: March 22, 2002.

Howard Rolston,

Director, Office of Planning, Research, and Evaluation.

[FR Doc. 02-7906 Filed 4-1-02; 8:45 am]

BILLING CODE 4184-01-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 02D-0095]

Draft Guidance for Industry on Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications." The guidance is intended to provide

recommendations for sponsors of investigational new drug applications (INDs) and applicants submitting new drug applications (NDAs) or biologics license applications (BLAs) on the use of exposure-response information in the development of drugs, including therapeutic biologics.

DATES: Submit written or electronic comments on the draft guidance by June 3, 2002. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies of the draft guidance to the Division of Drug Information (HFD-240), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857 or the Office of Communication, Training, and Manufacturers Assistance (HFM-40), Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist that office in processing your requests. Submit written comments on the draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT: Lawrence J. Lesko, Office of Clinical Pharmacology and Biopharmaceutics, Center for Drug Evaluation and Research (HFD-850), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5690, or David Green, Center for Biologics Evaluation and Research (HFM-579), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301-827-5349.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Exposure-Response Relationships: Study Design, Data Analysis, and

Regulatory Applications." This guidance provides recommendations on the use of exposure-response information in the development of drugs, including therapeutic biologics. The guidance describes: (1) The uses of exposure-response studies in regulatory decisionmaking, (2) the important considerations in exposure-response study designs to ensure valid information, (3) the strategy for prospective planning and data analyses in the exposure-response modeling process, (4) the integration of assessment of exposure-response relationships into all phases of drug development, and (5) the format and content of reports of exposure-response studies.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the agency's current thinking on study design, data analysis, and regulatory applications of exposure-response relationships. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit to the Dockets Management Branch (address above) written or electronic comments on the draft guidance. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guidance and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

III. Electronic Access

Persons with access to the Internet may obtain the document at <http://www.fda.gov/cder/guidance/index.htm>, <http://www.fda.gov/cber/guidelines.htm>, or <http://www.fda.gov/ohrms/dockets/default.htm>.

Dated: March 25, 2002.

Margaret M. Dotzel,

Associate Commissioner for Policy.

[FR Doc. 02-7883 Filed 4-1-02; 8:45 am]

BILLING CODE 4160-01-S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Health Resources and Services Administration

Fiscal Year 2002 Competitive Cycle for the Graduate Psychology Education Program 93.191a

AGENCY: Health Resources and Services Administration, HHS.

ACTION: Notice.

SUMMARY: The Health Resources and Services Administration (HRSA) announces that applications will be accepted for the Graduate Psychology Education Program (GPEP) for Fiscal Year 2002.

Authorizing Legislation: These applications are solicited under section 755(b)(1)(J) of the Public Health Service Act as amended, and the FY 2002 Appropriations Act, Public Law 107-116 which provides \$2 million to support graduate psychology education programs to train health service psychologists in accredited psychology programs.

Purpose: Grants will be awarded to assist eligible entities in meeting the costs to plan, develop, operate, or maintain graduate psychology education programs to train health service psychologists to work with underserved populations including children, the elderly, victims of abuse, the chronically ill or disabled and in areas of emerging needs, which will foster an integrated approach to health care services and address access for underserved populations. The Graduate Psychology Education Program addresses interrelatedness of behavior and health and the critical need for integrated health care services. Funding is available to doctoral programs or doctoral internship programs as defined and accredited by the American Psychological Association (APA). Funding may not be used for post-doctoral residency programs.

Eligible Applicants: Eligible entities are accredited health profession schools, universities, and other public or private nonprofit entities. Each Graduate Psychology Education Program must be accredited by the American Psychological Association (APA). As provided in section 750, to be eligible to receive assistance, the eligible entity must use such assistance in collaboration with two or more disciplines.

Funding Preference: A funding preference is defined as the funding of a specific category or group of approved applications ahead of other categories or

groups of applications. This statutory general preference will only be applied to applications that rank above the 20th percentile of applications recommended for approval by the peer review group.

As provided in section 791(a) of the Public Health Service Act, preference will be given to any qualified applicant that: (1) Has a high rate for placing graduates in practice settings having the principal focus of serving residents of medically underserved communities; or (2) during the 2-year period preceding the fiscal year for which such an award is sought, has achieved a significant increase in the rate of placing graduates in such settings. "High Rate" refers to a minimum of 20 percent of graduates in academic year 1999-2000 or academic year 2000-2001, whichever is greater, who spend at least 50 percent of their worktime in clinical practice in the specified settings.

"Significant Increase in the Rate" means that, between academic years 1999-2000 and 2000-2001, the rate of placing graduates in the specified settings has increased by a minimum of 50 percent.

Estimated Amount of Available Funds: \$1,900,000.

Estimated Number of Awards: 15-19.

Estimated Average Size of Each Award: \$100,000-\$130,000.

Estimated Funding Period: One year.

Application Requests, Availability, Date and Addresses: Application materials will be available for downloading via the Web on March 29, 2002. Applicants may also request a hardcopy of the application material by contacting the HRSA Grants Application Center, 901 Russell Avenue, Suite 450, Gaithersburg, Maryland, 20879, by calling at 1-877-477-2123, or by fax at 1-877-477-2345. In order to be considered for competition, applications must be received by mail or delivered to the HRSA Grants Application Center by no later than May 22, 2002. Applications received after the deadline date may be returned to the applicant and not processed.

Projected Award Date: August 30, 2002.

FOR FURTHER INFORMATION CONTACT:

LCDR Young Song, Division of State, Community and Public Health, Bureau of Health Professions, HRSA, Room 8C-09, Parklawn Building, 5600 Fishers Lane, Rockville, Maryland 20857; or e-mail at ysong@hrsa.gov. Telephone number is (301) 443-3353.

Additional Information: A Technical Assistance Videoconference Workshop is being planned for sometime in April, 2002. Detailed information regarding this workshop will be in the application

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 * Declared value limit \$500
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 FedEx Pak* Includes FedEx Small Pak, FedEx Large Pak, and FedEx Sturdy Pak
 Other Pkg. Includes FedEx Box, FedEx Tube, and customer pkg.
6 Special Handling
 Include FedEx address in Section 3
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 HOLD Weekday at FedEx Location Not available for FedEx First Overnight
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Does this shipment contain dangerous goods?

One box must be checked.

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 Yes As per attached Shipper's Declaration
 Yes Shipper's Declaration not required
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 Cargo Aircraft Only
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