INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

DOSE-RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION

E4

Current *Step 4* version

dated 10 March 1994

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

E4
Document History

First Codification	History	Date	New Codification **November 2005**
E4	Approval by the Steering Committee under *Step 2* and release for public consultation.	10 March 1993	E4

Current *Step 4* version

E4	Approval by the Steering Committee under *Step 4* and recommendation for adoption to the three ICH regulatory bodies.	10 March 1994	E4

DOSE-RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION

ICH Harmonised Tripartite Guideline

Having reached *Step 4* of the ICH Process at the ICH Steering Committee meeting on 10 March 1994, this guideline is recommended for adoption to the three regulatory parties to ICH

TABLE OF CONTENTS

DOSE-RESPONSE INFORMATION TO SUPPORT DRUG REGISTRATION

I. INTRODUCTION

Purpose of Dose-Response Information

Knowledge of the relationships among dose, drug-concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs in individual patients. This information can help identify an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects. Dose-concentration, concentration- and/or dose-response information is used to prepare dosage and administration instructions in product labeling. In addition, knowledge of dose-response may provide an economical approach to global drug development, by enabling multiple regulatory agencies to make approval decisions from a common database.

Historically, drugs have often been initially marketed at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose-response curve for the desired effect), sometimes with adverse consequences (e.g. hypokalemia and other metabolic disturbances with thiazide-type diuretics in hypertension). This situation has been improved by attempts to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial effects is seen, but practical study designs do not exist to allow for precise determination of these doses. Further, expanding knowledge indicates that the concepts of minimum effective dose and maximum useful dose do not adequately account for individual differences and do not allow a comparison, at various doses, of both beneficial and undesirable effects. Any given dose provides a mixture of desirable and undesirable effects, with no single dose necessarily optimal for all patients.

Use of Dose-Response Information in Choosing Doses

What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects. Selection of dose is best based on that information, together with a judgement about the relative importance of desirable and undesirable effects. For example, a relatively high starting dose (on or near the plateau of the effectiveness dose-response curve) might be recommended for a drug with a large demonstrated separation between its useful and undesirable dose ranges or where a rapidly evolving disease process demands rapid effective intervention. A high starting dose, however, might be a poor choice for a drug with a small demonstrated separation between its useful and undesirable dose ranges. In these cases, the recommended starting dose might best be a low dose exhibiting a clinically important effect in even a fraction of the patient population, with the intent to titrate the dose upwards as long as the drug is well-tolerated. Choice of a starting dose might also be affected by potential intersubject variability in pharmacodynamic response to a given blood concentration level, or by anticipated intersubject pharmacokinetic differences, such as could arise from non-linear kinetics, metabolic polymorphism, or a high potential for pharmacokinetic drug-drug interactions. In these cases, a lower starting dose would protect patients who obtain higher blood concentrations. It is entirely possible that different physicians and even different regulatory authorities would, looking at the same data, make different choices as to the appropriate starting doses, dose titration

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.