

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

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Current *Step 4* version

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

I. INTRODUCTION	1
Purpose of Dose-Response Information.....	1
Use of Dose-Response Information in Choosing Doses.....	1
Uses of Concentration-Response Data	2
Problems with Titration Designs.....	2
Interactions between Dose-Response and Time	3
II. OBTAINING DOSE-RESPONSE INFORMATION	3
Dose-Response Assessment Should Be an Integral Part of Drug Development	3
Studies in Life-Threatening Diseases	3
Regulatory Considerations When Dose-Response Data Are Imperfect.....	4
Examining the Entire Database for Dose-Response Information.....	4
III. STUDY DESIGNS FOR ASSESSING DOSE-RESPONSE	5
General.....	5
Specific Trial Designs.....	6
1. Parallel dose-response.....	6
2. Cross-over dose-response	7
3. Forced titration.....	7
4. Optional titration (placebo-controlled titration to end-point).....	8
IV. GUIDANCE AND ADVICE	9

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

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