Health Canada Santé Canada

GUIDANCE FOR INDUSTRY

Studies in Support of Geriatric Populations: Geriatrics

ICH Topic E7

Published by authority of the
Minister of Health

1994

Health Products and Food Branch
Guidance Document

Canada

Our mission is to help the people of Canada maintain and improve their health. *Health Canada*	HPFB's Mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by: • Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and, • Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health. *Health Products and Food Branch*

LET YOUR COMPUTER DO THE SEARCHING!

... Need to know how to market a new drug in Canada?

... Want information on the drug regulatory process?

... Need to know what the newest drugs on the Canadian market are?

... Want direct access to forms and policies?

... Need to know the requirements for labelling drugs?

All this and more is available on the

Therapeutic Products Directorate / Biologics and Genetic Therapies Directorate / Marketed Health Products Directorate Website (s)
at
http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/

Available in Canada through
Health Canada - Publications
Brooke Claxton Building, A.L. #0913A
Tunney's Pasture
Ottawa, Ontario
K1A 0K9

Tel: (613) 954-5995
Fax: (613) 941-5366

Également disponible en français sous le titre: Études à l'appui des groupes spéciaux: Gériatrie

Catalogue No. H42-2/67-1-1994E

FOREWORD

This guidance 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. The ICH Steering Committee has endorsed the final draft and recommended its adoption by the regulatory bodies of the European Union, Japan and USA.

In adopting this ICH guidance, Health Canada endorses the principles and practices described therein. This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

TABLE OF CONTENTS

1. STATEMENT OF PURPOSE

It is important to ensure that clinical testing programs are carried out according to harmonised guidances based on agreed ethical and scientific principles so that the international development of valuable innovative drugs is achieved with maximum efficiency. Harmonisation in relation to medicines for geriatric populations is an important issue because the total population of the elderly will increase significantly in the coming years in Europe, Japan and the USA. The use of drugs in this population requires special consideration due to the frequent occurrence of underlying diseases, concomitant drug therapy and the consequent risk of drug interaction.

2. GENERAL PRINCIPLE

Drugs should be studied in all age groups, including the elderly, for which they will have significant utility. Patients entering clinical trials should be reasonably representative of the population that will be later treated by the drug.

3. SCOPE OF GUIDANCE DOCUMENT

This guidance document is directed principally toward new Molecular Entities that are likely to have significant use in the elderly, either because the disease intended to be treated is characteristically a disease of aging (e.g., Alzheimer's disease) or because the population to be treated is known to include substantial numbers of geriatric patients (e.g., hypertension). The guidance document applies also to new formulations and new combinations of established medicinal products when there is specific reason to expect that conditions common in the elderly (e.g., renal or hepatic impairment, impaired cardiac function, concomitant illnesses or concomitant medications) are likely to be encountered and are not already dealt with in current labelling. It likewise applies when the new formulation or new combination is likely to alter the geriatric patient's response (with regard to either safety/ tolerability or efficacy) compared with that of the non-geriatric patient in a way different from previous formulations. The guidance document also applies to new uses that have significant potential applicability to the elderly.

It is recommended that exemptions from the guidance document be determined in advance either by sponsors or, where feasible, by the sponsor and drug registration authorities, based, e.g., on estimates of the disease prevalence by age or through examination of the age distribution of usage for other drugs of the same class or drugs used for the same indication.

4. DEFINITION OF THE POPULATION

The geriatric population is arbitrarily defined, for the purpose of this guidance document, as comprising patients aged 65 years or older. It is important, however, to seek patients in the older age range, 75 and above, to the extent possible. Protocols should not ordinarily include arbitrary upper age cutoffs. It is also important not to exclude unnecessarily patients with concomitant illnesses; it is only by observing such patients that drug-disease interactions can be detected. The older the population likely to use the drug, the more important it is to include the very old.

5. CLINICAL EXPERIENCE

Geriatric patients should be included in the Phase 3 database (and in Phase 2, at the sponsor's option) in meaningful numbers. The geriatric subpopulation should be represented sufficiently to permit the comparison of drug response in them to that of younger patients. For drugs used in diseases not unique to, but present in, the elderly a minimum of 100 patients would usually allow detection of clinically important differences. For drugs to treat relatively uncommon diseases, smaller numbers of the elderly would be expected. Where the disease to be treated is characteristically associated with aging (e.g., Alzheimer's disease) it is expected that geriatric patients will constitute the major portion of the clinical database.

The overall database of the dossier should be examined for the presence of age-related differences, e.g., in adverse event rates, in effectiveness, and in dose-response. If these relatively crude overview analyses show important differences, further evaluation may be needed.

The geriatric data used in the overview can come either from the inclusion of elderly patients in all or most of the main Phase 3 or Phase 2/3 studies or from studies conducted exclusively in geriatric patients, at the sponsor's option. Inclusion of both groups in the same studies has the advantage of allowing direct comparisons of younger and older patients using data collected in similar ways. Such comparisons are more difficult when separate studies of young and old patients are used. Certain assessments, however, e.g., studies of cognitive function, require special planning and can be best accomplished in separate studies.

6. PHARMACOKINETIC STUDIES

Most of the recognized important differences between younger and older patients have been pharmacokinetic differences, often related to impairment of excretory (renal or hepatic) function or to drug-drug interactions. It is important to determine whether or not the pharmacokinetic behaviour of the drug in elderly subjects or patients is different from that in younger adults and to characterize the effects of influences, such as abnormal renal or hepatic function, that are more common in the elderly even though they can occur in any age group. Information regarding age-related differences in the pharmacokinetics of the drug can come, at the sponsor's option, either from a Pharmacokinetic Screen

(as described subsequently) or from formal pharmacokinetic studies, in the elderly and in patients with excretory functional impairment.

It is recognized that for certain drugs and applications (e.g., some topically applied agents, some proteins) technical limitations such as low systemic drug levels may preclude or limit exploration of age-related pharmacokinetic differences.

A. Formal Pharmacokinetic Studies

Formal PK studies can be done either in healthy geriatric subjects or in patient volunteers with the disease to be treated by the drug.

The initial PK study can be a pilot trial of limited size conducted under steady-state conditions to look for sizable differences between older and younger subjects or patients. A larger, single-dose PK study of sufficient size to permit statistical comparisons between geriatric and younger subjects' or patients' pharmacokinetic profiles is also acceptable.

In either case, if large (i.e., potentially medically important) age-related differences are found, the initial PK study may need to be followed by a multiple-dose PK study of sufficient size to permit statistical comparisons (geriatric vs. younger) at steady-state.

B. Pharmacokinetic Screening Approach

Sponsors may opt, instead of conducting a separate PK evaluation of the elderly, to utilize a Pharmacokinetic Screen in conjunction with the main Phase 3 (and Phase 2, if the sponsor wishes) clinical trials program. This screening procedure involves obtaining, under steady-state conditions, a small number (one or two) of drug blood level determinations at "trough" (i.e., just prior to the next dose) or other defined times from sufficient numbers of Phase 2/3 clinical trials patients, geriatric and younger, to detect age-associated differences in pharmacokinetic behaviour, if they are present. It is important to record time of dosing prior to blood concentration measurements, and relation of dosing to meals, and to examine the influence of demographic and disease factors, such as gender renal function, presence of liver disease, gastrointestinal disease or heart disease, body size and composition, and concomitant illnesses.

Small differences are unlikely to be of medical importance. Where the screen detects large differences, formal pharmacokinetic studies may be indicated unless the screen's results are sufficiently informative.

The advantage of a Pharmacokinetic Screen is that it can assess the effects, not only of age itself, but also of other factors associated with age (altered body composition, other drugs, concomitant illness) and their interactions.

7. PHARMACOKINETICS IN RENALLY OR HEPATICALLY IMPAIRED PATIENTS

Renal impairment is an aging-associated finding that can also occur in younger patients. Therefore, it is a general principle, not specific to these guidances, that drugs excreted (parent drug or active metabolites) significantly through renal mechanisms should be studied to define the effects of altered renal function on their pharmacokinetics. Such information is needed for drugs that are the subject of this guidance document but it can be obtained in younger subjects with renal impairment.

Similarly, drugs subject to significant hepatic metabolism and/or excretion, or that have active metabolites, may pose special problems in the elderly. Pharmacokinetic studies should be carried out in hepatically impaired young or elderly patient volunteers.

If a Pharmacokinetic Screen approach is chosen by the sponsor (Section 6, see above), and if patients with documented renal impairment or hepatic impairment (depending on the drug's elimination pattern) are included and the results indicate no medically important pharmacokinetic difference, that information may be sufficient to meet this Geriatric Guidance's purpose.

8. PHARMACODYNAMIC / DOSE RESPONSE STUDIES

The number of age-related pharmacodynamic differences (i.e., increased or decreased therapeutic response, or side effects, at a given plasma concentration of drug) discovered to date is too small to necessitate dose response or other pharmacodynamic studies in geriatric patients as a routine requirement. Separate studies are, however, recommended in the following situations:

- Sedative/hypnotic agents and other psychoactive drugs or drugs with important CNS effects, such as sedating antihistamines.

- Where subgroup comparisons (geriatric versus younger) in the Phase 2/3 clinical trials database indicate potentially medically significant age associated differences in the drug's effectiveness or adverse reaction profile, not explainable by PK differences.

9. DRUG-DRUG INTERACTION STUDIES

Such interactions are of particular importance to geriatric patients, who are more likely to be using concomitant medications than younger patients, but of course are not limited to this age group. Therefore it is a general principle, not specific to these guidances, that in cases where the therapeutic range (i.e., range of toxic to therapeutic doses) of the drug or likely concomitant drugs is narrow, and

the likelihood of the concomitant therapy is great, that specific drug-drug interaction studies be considered. The studies needed must be determined case-by-case, but the following are ordinarily recommended:

- Digoxin and oral anticoagulant interaction studies, because so many drugs alter serum concentrations of these drugs, they are widely prescribed in the elderly, and they have narrow therapeutic ranges

- For drugs that undergo extensive hepatic metabolism, determination of the effects of hepatic-enzyme inducers (e.g., phenobarbital) and inhibitors (e.g., cimetidine)

- For drugs metabolized by cytochrome P-450 enzymes, it is critical to examine the effects of known inhibitors, such as quinidine (for cytochrome P-450 2D6) or ketoconazole and macrolide antibiotics (for drugs metabolized by cytochrome P-450 3A4). There is a rapidly growing list of drugs that can interfere with other drugs' that metabolism, and sponsors should remain aware of it.

- Interaction studies with other drugs that are likely to be used with the test drug (unless important interactions have been ruled out by a Pharmacokinetic Screen).