

# Memorandum

**Date:** December 2, 2013

**From:** Robert Temple, Deputy Center Director for Clinical Science

**To:** OND/OTS Review Staff

**Subject:** A Good Review Practice MAPP [Clinical Review of Investigational New Drug Applications] describes our obligation to consider breadth of patient populations in trials at EOP2 and other meetings during drug development and to discourage unnecessary exclusions of patients

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## I. Policy

FDA has a long standing interest in encouraging inclusion of a broad population sample in development programs for new drugs. This is reflected in the required (by regulation) analyses of safety and effectiveness by demographic and other relevant subgroups in marketing applications and the recognized concern with possible interactions between treatments and coexisting illnesses and concomitant treatments. FDA and ICH guidance on inclusion of both genders and the elderly also reflects this concern and the documents urge broad patient inclusion. During the interactions that take place between FDA and the sponsor during drug development, FDA should actively encourage the conduct of at least one trial in a broad population that closely resembles the people who will use the drug if it is approved and should discourage unnecessary exclusions. At present, such exclusions (see below) are far too common in clinical trials. Although certain exclusions may be appropriate and necessary (e.g., for relevant drug-drug interactions, renal or hepatic dysfunction, people on similar therapy), and patient selection can benefit from enrichment features, many exclusions are unnecessary and counterproductive, and these should be discouraged during interactions with sponsors.

The new GRP MAPP [Clinical Review of Investigational New Drug Applications] emphasizes that including a broad population in trials needs to become a regular part of our assessment of individual trials and overall development plans. Apart from attempts to end the routine use of upper age limits in trials, part of our standard procedures should be consideration of why exclusions are needed or appropriate. Where planned exclusions do not meet a test for reasonableness this should be pointed out to sponsors and protocol modifications should be encouraged. The goal is for us to become more cognizant of exclusion criteria, to examine such criteria closely, and to encourage removal of exclusions that are unnecessary.

## II. Background

A new Good Review Practices MAPP [Clinical Review of Investigational New Drug Applications], issued on Dec 2, 2013, describes good review practices with respect to analyzing IND submissions and advising sponsors during the drug development

process. The MAPP includes a series of checklists giving major considerations when reviewing an end-of-phase 2 package or a controlled trial protocol, with further discussion of the most important points. The MAPP directs us, in many sections, to encourage sponsors to utilize broad inclusion criteria and to discourage exclusions that are unnecessary. Unnecessary exclusions can create doubts about the applicability of study findings to excluded populations.

There is widespread concern that drug development studies will not provide evidence of the effects of treatment in the “real world.” This has led to the concept of “effectiveness” (as opposed to “efficacy”) trials and to a call for “pragmatic” trials, generally focused on enrolling a patient population closer to the population likely to be treated when the drug is marketed. We recognize in our draft Enrichment Guidance that careful patient selection (prognostic and predictive enrichment, encouraging compliance) can enhance study power, but enrichment does not necessitate a general exclusion of older patients, people with concomitant illness, etc., unless these factors will lead to patient drop-outs or use of medication(s) that interfere with the test drug, which will not usually be the case. We share the concern that unnecessary exclusions lead to the study of treatment populations that are not representative of the people who will use the drug if it is approved, particularly with respect to demographic characteristics, concomitant illnesses and concomitant therapies.

There is an HHS working group (broadly including FDA, NIH, CDC, CMS, AHRQ and others) that is focused on identifying barriers to enrollment of patients with multiple chronic conditions in clinical trials and to increasing the numbers of such patients in future trials. One FDA contribution to this effort, supported by FDA and the HHS Assistant Secretary for Planning and Evaluation (ASPE), Office of Science and Data Policy, was a study by Digital Infuzion of the exclusions from controlled trials. The study assessed data from clinical trials submitted in drug and biologic licensing applications (NDAs and BLAs) with electronic data during 2010, encompassing a total 147 studies and over 115,000 subjects. The studies were examined for both explicit exclusion criteria in the protocol (e.g., history of psychiatric disorder) and for the concomitant illnesses present in patients in the completed studies. The Digital Infuzion White Paper: U.S. Food and Drug Administration (FDA) Inventory of Clinical Trials Protocols and Clinical Study Data<sup>1</sup> was completed in August 2011 and has been available for more than a year.

The overall results are described in the white paper and I will not attempt to summarize them here. A few frequent exclusions were, however, striking:

- 71% of studies excluded patients with a psychiatric disorder (presumably specific disorders, not all psychiatric disorders)
- 66% excluded patients with a heart disorder (again, presumably specific disorders)
- 55% excluded patients with atherosclerotic CV disease
- 38% excluded diabetics

Other common exclusions were hepatic disorder, neoplasm, and kidney disorder; these seem more understandable.

It is well-recognized that sponsors of studies seek study populations without concomitant illnesses that will interfere with assessment of their test drug by increasing the risk of dropouts, serious adverse events unrelated to treatment, need for concomitant drug therapy, etc. At the same time, overly narrow patient selection criteria can interfere with assessment of potential drug-drug and drug-disease interactions, as well as discovery of important safety concerns. For example, many drugs have potential interactions with psychiatric illnesses that could be missed if all patients with psychiatric illnesses are excluded from trials.

Most chronic conditions increase in prevalence with age, so that a particular barrier to learning about drug-chronic disease interactions is arbitrary age limits. FDA and ICH guidances have for decades encouraged inclusion of a reasonable sample of patients over 65 (the 1980's definition of elderly, now clearly outdated) and the Infuzion study found that 19% of study subjects were  $\geq 65$  (about 14% of the US population is  $\geq 65$ ) and 52% were 51 to  $\leq 65$ . Many diseases, of course, increase in frequency with age, so that if patients over 65 were included in proportion to this prevalence of diseases in them, the percentage of patients over 65 would be greater. The study did not report the proportion of patients over 75, but a recent review of diabetes trials (Craz-Jentoft, et al J Amer Geriatric Society, 2013; 61: 734-738) found relatively few patients over 75; among 440 trials in type II diabetes, 66% had an upper age limit: 26%  $< 65$ , 29% = 65-74, and 5% = 75-84. A recent set of Q and A's for the ICH E-7 Guideline for Industry: Studies in Support of Special Populations: Geriatrics,<sup>2</sup> took note of the low participation of these patients and specifically urged substantial inclusion of patients over 75 when they would be part of the expected treatment population. Greater inclusion of older patients would, of course, also increase the number of patients with MCCs.

In sum, both HHS and FDA have an interest in encouraging inclusion of a broad range of patients, specifically, patients with chronic conditions other than the one being studied, and patients of more advanced age, as well as a broader interest in minimizing exclusions, i.e., so-called "pragmatic" trials.

### III. GRP: Clinical Review of INDs

The new GRP MAPP [Good Practice: Clinical Review of Investigational New Drug Applications] provides a series of high level checklists for issues to consider during review of submissions or at industry meetings at various stages of development (pre-IND/IND original submission; end of phase 2/phase 3 planning; review of a controlled clinical trial), many of which include specific references to the breadth of the population to be studied and the need for the usefulness of proposed exclusions. The checklists are then followed by detailed consideration of critical elements, one of which is directed at Patient Population (section 7). The checklist and critical components of that section are reproduced below.

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<sup>2</sup> <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm189544.pdf>

## A. Checklists

### 1. EOP2 meeting checklist:

- Will the planned development, together with ongoing and completed trials, provide adequate data regarding drug effects in a broad population including subpopulations of interest (see [section 7.2](#), Special Populations, Demographic Subgroups), particularly including those defined by:
  - Sex? (See [section 7.2.3](#), Women.)
  - Race? (See [section 7.2.5](#), Racial Groups.)
  - Age (various pediatric groups and geriatric groups)? (See [section 7.2.2](#), Pediatric Populations; and [section 7.2.4](#), Elderly Subjects.)
  - Body weight/body surface area?
  - Genetic difference in metabolism, risk factors? (See [section 7.2.6](#), Other Subpopulations of Interest: Genetic, Proteomic, and Concomitant Illness.)
  - Disease severity?
  - Patients with single or multiple concomitant illnesses? (See [section 7.2.6](#), Other Subpopulations of Interest: Genetic, Proteomic, and Concomitant Illness.)
  - Immunodeficiency (where appropriate)?
  - Pregnancy (if there is reason to expect use in pregnancy)? (See [section 7.2.3.3](#), Studying pregnant women.)
  - Concomitant medications? (See [section 3.2.5](#), Drug-Drug Interactions.)
  - Renal/hepatic/excretory organ impairment? (See [section 3.2.1](#), Effect of Intrinsic and Extrinsic Factors on PK and PD.)
- Are there exclusions for demographic factors (e.g., older than 75 years of age) or concomitant illness that are not needed but will decrease the breadth of the population studied? (See [section 7.2.4](#), Elderly Subjects; and [section 7.2.6](#), Other Subpopulations of Interest: Genetic, Proteomic, and Concomitant Illness.)

### 2. Controlled Trial Protocol Review (including Special Protocol Assessment) Checklist:

- Are subject inclusion and exclusion criteria appropriate (see section 7.1 Trial Population)

## B. Detailed Considerations

### 7.1 Trial Population

In general, the choice of the trial population in a phase 2 or phase 3 clinical trial should reflect the intended use of the drug. This principle should not be interpreted to preclude use of selection criteria that improve the power and

practicality of the trial. It is common, for example, to require persistence of disease over a run-in period; stability of baseline measures such as BP, exercise tests, or pulmonary function tests; or factors that improve the likelihood of compliance. In outcome trials, it is common to choose patients who are expected to have a high rate of primary endpoint events (prognostic enrichment) on the basis of clinical history, pathophysiologic observations, disease severity, or genetic or proteomic predictors. Any differences (e.g., disease stage or severity, risk factors, demographics) between the intended population and the population in which efficacy and safety are to be studied should be identified and their effect on generalizability of results and the applicability of results to a specific population and labeling examined. It should be recognized, however, that study of a broad population raises many of the same issues, even if differences in response among population subsets are well studied.

## 7.2 Special Populations, Demographic Subgroups

Regulations require *IND annual reports* to tabulate subjects entered into trials by age group, sex, and race (21 CFR 312.33(a)(2)). Reviewers should consider the distribution of subjects and ensure that there are no unjustified subject exclusions (e.g., subjects over 75 years of age), that PK differences among different subpopulations (including age, gender, race and organ dysfunction) are examined in specific trials or by population PK to determine the need for dosage adjustment in these subpopulations, and that the integrated analyses of safety and effectiveness will look for potentially important differences in dose-response. Where a condition is particularly important in a demographic subgroup, it may be appropriate to enrich the population for that subgroup. It has been recognized, for example, that many drugs for chronic illnesses are heavily used in a very elderly population (older than 75 years of age).

### 7.2.1 Subgroup Analyses vs. Special Population Trials

In general, the size of a clinical trial is established to demonstrate an overall treatment effect, not to allow assessment of effects in particular subject subgroups. Therefore, the analyses of specific subgroups will be possible principally in the integrated analyses of safety and effectiveness. A possible exception is large outcome trials in which it is usual to show effects in a variety of cohorts defined by demographics, severity of illness, use of concomitant drugs, and other factors in so-called *forest plots*. These have at times been included in labeling. Care must be taken to avoid specific efficacy claims based on such a subset analysis.

As an alternative to assessing effects in special populations through subgroup analyses or as an approach to confirming a differential effect noted on such an analyses, sponsors can choose to evaluate specific groups of subjects in small trials. For example, a sponsor can conduct specific trials of the drug's effects in elderly subjects, commonly done for sedative-hypnotic drugs and in subjects with varying degrees of renal function. In general, apart from enrichment attempts, sponsors should be encouraged to conduct major efficacy trials in demographically heterogeneous subject populations and in patients with a wide range of concurrent illnesses and treatments, to ensure that the results are reasonably generalizable. Within those trials, subset analysis can help identify important differential treatment effects and safety issues.

In particular, reviewers should closely examine exclusions in phase 3 trials to consider whether they are really needed. It has been common, for example, to exclude patients older than 75, but there is no good reason to do this. Similarly, exclusions of patients with a history of psychiatric or cardiovascular illness, unless dictated by the drug's pharmacology, decrease the opportunity to detect important drug-drug interactions and should be discouraged.

#### 7.2.4 Elderly Subjects

Although elderly subjects comprise a significant portion of the consumer population for drugs, they are often underrepresented in clinical trials. Data collected from elderly subjects can be of particular value because elderly subjects are more likely to have organ impairment, take a larger number of concomitant medications, and be susceptible to certain drug-related toxicities. In general, subjects over 65 years of age are considered elderly for the purpose of data evaluation, but it is particularly important to have data on subjects 75 years of age and older. For drugs intended for a population that includes the elderly, substantial numbers of elderly subjects should be included in trials by the time of the marketing application. ICH E7 should be consulted about the inclusion of elderly subjects in clinical trials. A recent amendment to this guidance strongly emphasizes the need for exposure of patients above 75 years of age. As noted earlier, arbitrary upper age limits for trial entry are almost never justified and should be discouraged.

#### 7.2.6 Other Subpopulations of Interest: Genetic, Proteomic, and Concomitant Illness

Although special populations of interest traditionally have been defined on the basis of demographics or in some cases physiological features (e.g., plasma renin activity, systolic versus diastolic function in heart failure, organ dysfunction including renal and hepatic impairment), the rapidly evolving technologies of pharmacogenomics and growing recognition of drug-disease interactions and various risk factors for outcome under the broad heading of *individualization* of therapy is expected to increase efforts to assess the effect of such factors on drug effects. Genetic factors are known to determine how drugs are absorbed, distributed, metabolized, and eliminated and can significantly affect PK, dosing, and drug interactions. Genetic factors can also affect the pharmacologic actions and PD effects of a drug, most strikingly seen up until now in cancer treatments but also for some adverse effects in non-oncologic drugs. We anticipate seeing increasing amounts of data regarding the effect of genetic, proteomic, and other factors on drug effects.

When evaluating such data, reviewers should scrutinize the validation of the submitted test methodologies and the multiplicity of hypotheses that arise when many genes are analyzed. Interpretation of pharmacogenetic data requires evaluation of results in the context of what is known with respect to the clinical pharmacology of the drug, disease biology, and genetic variability. Reviewers are encouraged to consult with the clinical pharmacology reviewers in the Genomics Group, in the Office of Clinical Pharmacology, for submissions containing pharmacogenetic or biomarker trial objectives and/or data.

If the reviewer or the sponsor thinks a label might indicate that genetic (or other) testing is essential for the safe and effective use of a drug (e.g., to define the

indication, to determine dosing, to identify high-risk patients or to identify likely responders), then the sponsor should be reminded that both the drug and the companion test must, in most circumstances, be approved at the same time. When such testing may be appropriate, reviewers should contact the Office of Combination Products, with a consult to the Center for Devices and Radiological Health, as early as feasible in the drug development and review process. Further information is available in the Guidance for Industry and FDA Staff: In Vitro Companion Diagnostic Devices, <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262292.htm>.

The growing interest in individualization of treatment is also reflected in the increasing examination of effects in population subsets defined by concomitant illness or disease severity in addition to the traditional demographic groups, especially in outcome trials, with resulting so-called *forest plots* appearing in published reports and in drug labeling.