

July 20, 1998

Director, Center for Drug Evaluation and Research

FDAMA - Women and Minorities Guidance Requirements

Michael A. Friedman, M.D., Acting Commissioner

Under the Food and Drug Administration Modernization Act of 1997 (FDAMA) Sec. 115 Clinical Investigations. (b) Women and Minorities. -- Section 505(b)(1) 21 U.S.C. 355(b)(1) was amended by adding at the end the following: *"The Secretary shall, in consultation with the Director of the National Institutes of Health and with representatives of the drug manufacturing industry, review and develop guidance, as appropriate, on the inclusion of women and minorities in clinical trials . . . "*

The Center for Drug Evaluation and Research (CDER) has been assigned the responsibility for reviewing and implementing this section for the Agency. To accomplish this task, CDER established an ad hoc working group, "FDAMA Women and Minorities Working Group" with representation from the Agency and the National Institutes of Health. (A complete membership listing is contained in Attachment 1 to the enclosed report.)

The Center is submitting for your review and consideration the recommendations of the FDAMA Working Group, which have the concurrence of CDER's Medical Policy Coordinating Committee (MPCC) and are contained in the enclosed report. These recommendations also were discussed with representatives of the pharmaceutical manufacturing industry, as required by section 115(b) of FDAMA. They are in agreement that no additional guidance is needed at this time and offered to confer with the Agency if this should change in the future. The Working Group recommends that this report be made widely available, perhaps by posting it on an appropriate Web site.

I would like to emphasize that although we have concluded that additional guidance is not needed at this time, the Agency will continue to implement procedures that will enhance our ability to gather, search, and evaluate demographic data. These processes will make it possible to determine trends or indicate deficiencies, and decide whether additional guidance should be developed in the future.

Janet Woodcock, M.D.

Enclosure

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William Schultz, HF-22

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(Enclosure)

FDAMA Women and Minorities Working Group Report

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Overview

The process of implementing this section of FDAMA was logically divided into two stages. During the first stage, existing guidance was identified and evaluated to assess whether it was adequate, whether additional guidance was needed or whether there was insufficient information at this time to make such a determination. The outcome of this first stage would dictate whether another stage, which might include gathering additional data and drafting additional guidance, would be needed.

Process

The FDAMA Women and Minorities Working Group conducted a series of three meetings (2/23/98, 3/11/98, and 4/6/98) at which they accomplished the following. (See Attachment 1 for listing of members)

- Assessed the scope of its task as outlined in FDAMA, supporting documents, and legislative history.
- Compiled and evaluated existing FDA guidance on enrollment of women and minorities in clinical trials. A summary of guidance currently in effect is contained in Attachment 2.
- Evaluated available pertinent databases and reports, including the October 1992 GAO Report to Congressional Requestors (Attachment 3).
- Evaluated pertinent companion PHS documents listed in Attachment 2.

Summary of existing guidance

The 1988 "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" emphasized the importance of including analyses of demographic data in NDA applications. The 1998 regulation, "Final Rule on Investigational New Drug Applications and New Drug Applications," requires that analyses of effectiveness and safety data for important demographic subgroups, including sex and racial subgroups, be submitted to NDAs and that enrollment of subjects into clinical studies for drug and biological products be tabulated by important demographic subgroups in investigational new drug (IND) annual reports, i.e., age group, sex, and race. This final rule allows the Agency to refuse to file any NDA that does not analyze safety and efficacy information appropriately by sex.

The critical importance of including all appropriate subsets of the population in product development was most clearly articulated in the 1993 Guideline which states:

In general, drugs should be studied prior to approval in subjects representing a full range of patients likely to receive the drug once it is marketed. Although in most cases, drugs behave qualitatively similarly in demographic (age, sex, race) and other (concomitant illness, concomitant drugs) subsets of the population, there are many quantitative differences, for example, in dose-response, maximum size of effect, or in the risk of an adverse effect. Recognition of these differences can allow safer and more effective use of drugs. Rarely, there may be qualitative differences as well. It is very difficult to evaluate subsets of the overall population as thoroughly as the entire population, but sponsors are expected to include a full range of patients in their studies, carry out appropriate analyses to evaluate potential subset differences in the patients they have studied, study possible pharmacokinetic differences in patient subsets, and carry out targeted studies to look for subset pharmacodynamic differences that are especially probable, are suggested by existing data, or that would be particularly important if present.

That guidance also makes clear the Agency position that women should be included in all phases of clinical drug development. The 1998 proposed clinical hold rule, "Investigational New Drug Applications; Proposed Amendment to Clinical

Hold Regulations for Products Intended for Life-Threatening Diseases,"¹ expands upon this guidance because it would allow FDA to place an IND, or specific protocols under an IND, on clinical hold if a sponsor proposes to exclude from study women or men with reproductive potential because of a risk, or a potential risk, of reproductive or developmental toxicity from the use of an investigational drug product.

Conclusions and Recommendations

The 1993 Guideline, which is a comprehensive discussion of enrollment of women in clinical trials, was promulgated to reverse a previous FDA policy that resulted in the exclusion of women with childbearing potential from early drug studies that did not target serious or life threatening diseases. Because of the specificity of this guidance, the Working Group has chosen to report on women and minorities separately.

- **Women**

In the last five years, FDA has issued critical guidance and regulation aimed at ensuring that women are included appropriately in clinical trials and that data are analyzed to ensure that sex information is available and understood. At present, FDA believes that exclusionary policies regarding the participation of women with childbearing potential in clinical trials will be addressed by the 1998 clinical hold proposed rule, if it is finalized. Therefore, additional guidance is not indicated, and would not be useful, at this time.

The Tracking Subcommittee identified various Center mechanisms that have been used to track eligibility and/or enrollment of women in clinical trials but these were all finite projects. The Working Group recommends that the Centers consider instituting a permanent tracking system to monitor effectiveness and safety data for sex and racial subgroups submitted under the new final rule. The design and implementation of such a tracking system are currently under discussion by members of the FDA Office of Women's Health, CDER senior management team, and CDER's Women's Health Subcommittee of the Medical Policy Coordination Committee. The Office of Women's Health has recently funded a CDER project that will develop tools to search large databases for adverse events reported by sex and race. In addition, the Centers should also consider developing a program to educate reviewers on the new rule.

¹The comment period for this proposed rule closed on December 23, 1997. The comments that were received are being reviewed by a special working group.

- **Minorities**

The 1993 Guideline was promulgated specifically to reverse a long-standing regulatory barrier to the participation of women with childbearing potential in clinical trials. Unlike women with childbearing potential, there has never been a regulatory barrier to the inclusion of minorities in clinical trials and there does not exist a guidance that addresses only the issue of minority enrollment in clinical trials. The portion of the 1993 Guideline cited above clearly articulates the expectation of FDA that all appropriate demographic subgroups should be included in product development, but the fact that this statement is found in the 1993 Guideline conceivably might diminish its impact on minority recruitment.

There has been no recent methodical evaluation of minority enrollment patterns in clinical trials. The GAO report (see Attachment 3) supports the conclusion that minorities are being enrolled in proportions appropriate to their relative disease prevalence. However, that report is not current. More recently, the Office of Special Health Issues has initiated a project to review demographic data from the applications for new molecular entities (NMEs) approved by CDER during 1995-1996. The project will gather data on the participation of racial/ethnic minorities in clinical trials of the NMEs and the extent to which these populations were discussed in labeling for these drugs. It is anticipated that preliminary data will be available in the fall of this year. In addition, CDER is launching various initiatives to ensure that the Agency will have the ability to track enrollment trends. For example, under the 1998 final rule, safety and effectiveness data on racial subgroups will be required in NDAs and IND annual reports. CDER is developing a "subset page" that will be included in each NDA package where the results, and adequacy, of such analysis can be summarized in an easily accessible format. Moreover, guidance is under development that will direct industry and reviewers to ensure that appropriate mention of subset differences are included in the adverse reaction and clinical trials sections of package inserts, or that important gaps in knowledge be noted.

Certainly there are many societal and socioeconomic factors that affect the composition of study populations and there are also clear examples of products where the efficacy or safety profiles differ by racial subgroups. However, the Working Group does not find evidence of barriers to the enrollment of minorities in clinical trials that are regulatory in nature or could be addressed by regulatory guidance. The Agency will continue to evaluate available data pertaining to the enrollment of minorities in clinical trials.

**Representatives of the FDAMA
Women & Minorities Working Group**

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Rachel Behrman (lead) - Center for Drug Evaluation and Research

Julie Beitz - Center for Drug Evaluation and Research

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Kimber Richter - Center for Devices and Radiological Health

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Terry Toigo - OC, Office of Special Health Issues

SUMMARY OF AVAILABLE GUIDANCE & REPORTS

WOMEN ONLY:

- ◆ FDA - 7/88 Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications
- ◆ FDA - 7/22/93 Guideline
- ◆ FDA - 9/24/97 Proposed Rule on Investigational New Drug Applications; Proposed Amendment to Clinical Hold Regulations for Products Intended for Life-Threatening Diseases

WOMEN AND MINORITIES:

- ◆ 21 CFR 314.101(d)(2)
- ◆ FDA - 2/11/98 Final Rule on Investigational New Drug Applications and New Drug Applications - 21 CFR Parts 312 and 314

RELATED GUIDANCE:

- ◆ NIH - *Recruitment and Retention of Women in Clinical Studies - a Report of the Workshop Sponsored by the Office of Research on Women's Health*
- ◆ NIH - 3/28/94 NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research
- ◆ NIH - Informational document presenting excerpts from above guideline: *Inclusion of Women and Minorities as Subjects in Clinical Research - 96-04*
- ◆ NIH - *Outreach Notebook for the NIH Guidelines on Inclusion of Women and Minorities as Subjects in Clinical Research - 97-4160*

RELATED REPORTS:

- ◆ GAO - *Women's Health - FDA Needs to Ensure More Study of Differences in Prescription Drug Testing*