Guidance for Industry

Changes to an Approved NDA or ANDA; Specifications – Use of Enforcement Discretion for Compendial Changes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

November 2004
CMC

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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance is intended to inform new drug application (NDA) and abbreviated new drug application (ANDA) holders of the Food and Drug Administration's (FDA's) plan to use enforcement discretion with regard to section 314.70(c)(2)(iii) of the final rule entitled Supplements and Other Changes to an Approved Application (21 CFR 314.70(c)(2)(iii)).[2] This subsection describes the filing requirement that a relaxation of acceptance criteria or deletion of a test to comply with an official compendium must be reported in a changes-being-effected-in-30-days supplement (CBE-30). In the exercise of its enforcement discretion, FDA does not intend to take enforcement action if manufacturers continue to submit such changes in their annual reports. The use of enforcement discretion will give the Agency time to clarify that some of these types of postapproval changes can be submitted in an annual report, rather than in a CBE-30. The Agency intends to clarify this issue in an upcoming revision to the guidance for industry *Changes to an Approved NDA or ANDA; Questions and Answers.*

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

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[1] This guidance has been prepared by the Office of Compliance and the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] See *the Federal Register*, Vol. 69, p. 18728, April 8, 2004.

II. BACKGROUND

On April 8, 2004, FDA published in the *Federal Register* (69 FR 18728) the final rule entitled Supplements and Other Changes to an Approved Application. In the same issue of the Federal Register (69 FR 18768), FDA announced the availability of the guidance for industry entitled *Changes to an Approved NDA or ANDA* (the *Changes* guidance). The final rule sets forth requirements for postapproval changes.

Under section 314.70(c)(2)(iii) of the final rule, the relaxation of acceptance criteria or deletion of a test to comply with an official compendium that is consistent with FDA statutory and regulatory requirements must be submitted as a supplement – changes-being-effected-in-30 days (CBE-30) (see section VIII.C.1.e of the *Changes* guidance). Under 314.70(d)(2)(i) of the final rule, any change in a specification made to comply with an official compendium, except the relaxation of acceptance criteria or deletion of a test that is consistent with FDA statutory and regulatory requirements, is to be submitted as an Annual Report (see section VIII.D.1 of the *Changes* guidance).

Since publication of the final rule, the Agency has received communications from NDA and ANDA holders requesting clarification of the regulation as it applies to changes such as excipient monographs and general chapters. As written now, the regulations could be interpreted to require a CBE for any compendial change to relax or delete a test, resulting in an increase in the number of supplements, something that was not intended. The Agency plans to revise the *Guidance for Industry: Changes to an Approved NDA or ANDA; Questions and Answers* to provide more specific recommendations as to what types of changes can be submitted in an annual report instead of a CBE-30 supplement.

In addition, the Agency is aware that stakeholders have expressed concern that the final rule (i.e., 21 CFR 314.70), which published on April 8, 2004, and the accompanying *Changes* guidance do not take into consideration the recent FDA Pharmaceutical CGMP Initiative for the 21st Century. Accordingly, the Agency plans to align this guidance with the initiative in order to facilitate manufacturing changes to enhance product quality.

III. EXERCISE OF ENFORCEMENT DISCRETION

FDA intends to exercise enforcement discretion and does not intend to take action to enforce compliance with the compendial changes requirement as stated in 21 CFR 314.70(c)(2)(iii) if manufacturers submit such changes in their annual reports. FDA intends to develop further guidance to clarify the requirements of 21 CFR 314.70(c)(2)(iii).