DEVELOPMENT AND APPROVAL OF COMBINATION PRODUCTS

A Regulatory Perspective

Edited By

EVAN B. SIEGEL, PhD
Ground Zero Pharmaceuticals, Inc.

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PREFACE

Having worked in drug, biologic, and medical device development for decades and seen the veritable explosion of combination products in testing over the last several years, it seemed logical to me to develop a book that would discuss the process of combination product development from the FDA regulatory point of view. Although a number of short monographs and books have been issued on the subject, this new book is intended to comprehensively discuss not only the technical aspects of the field, centering around Regulatory Affairs; Chemistry, Manufacturing, and Controls; Nonclinical Testing; and Clinical Trials supporting product approvals, but also the integration of these discrete fields into an efficient overall approach to the effort. It is this unique approach to the development and lifecycle management of combination product development that I hope will prove useful to professionals and benchworkers alike.

The intended readers for the book include the commercial/industrial researcher, regulatory affairs professional, university-based scientist, project manager, and corporate executive undertaking the complex process of combination product development. The book is current *vis-à-vis* FDA law, regulation, and guidance up to September 2007 and it is unlikely that it will be out of date in any major area for a long time to come.

Project teams responsible for all of the above technical areas should benefit from the integrated approach taken, and individual experts in specific technical areas can refer to the individual chapters that apply

particularly to their work. I suggest that the most efficient way to use the book is to read those sections that most specifically apply to an individual's technical field, but to also read the other chapters for an overview of the entire process. In this manner the interactions among the various discrete technical efforts can be easily seen. Summary tables throughout the book will aid in this approach.

EVAN B. SIEGEL, PHD

ACKNOWLEDGMENTS

I wish to thank the authors of the chapters that comprise this book for their willingness to review and incorporate huge quantities of material into a coherent whole, continuing to examine new material in their respective and rapidly changing fields, and modifying their chapters to reflect new scientific and regulatory initiatives in combination product development. This has resulted in a quite up-to-date volume that we sincerely hope will stand a reasonable test of time.

I would also like to express appreciation for the hard-working men and women of the US Food and Drug Administration who, every day of the year, struggle to strike a balance between the needs of patients for new therapeutics and diagnostic products and the protection of those same patients against unsafe or ineffective products in an ever more complex healthcare system. The ultimate beneficiaries of combination products are the patients and the healthcare providers who labor to cure, prevent, and mitigate disease in these individuals.

Finally to my wife, Jean, a consummate medical writer and expert medial product developer, thank you for your help with the manuscript preparation.

CONTRIBUTORS

James Barquest, PhD, Consultant, Medical Devices and Combination Products

Chaline Brown, Pharm D, Ground Zero Pharmaceuticals, Inc.

Patrick L. DeVillier, MS, A.P. Pharma, Inc.

Duane B. Lakings, PhD, Drug Saftey Evaluation Consulting, Inc.

CHAPTER 1

OVERVIEW OF COMBINATION PRODUCTS DEVELOPMENT AND REGULATORY REVIEW

EVAN B. SIEGEL, PhD
Ground Zero Pharmaceuticals, Inc.

Advances in drug, biologic, and medical device development relate to both single entities and combinations of each type of medical product. A desire for new modes of administration of therapeutics, enhancement of long-term delivery of drugs and biologics, and new routes of administration, together with commercial/competitive pressures have led to a veritable explosion of requests for reviews of experimental combination products. These developments continue to be enhanced by advances in technology and materials science, as well as in the biotechnological sophistication of manufacturing processes. All of these factors have generated requests for the Food and Drug Administration (FDA) to review combination investigational drug and device applications for human clinical testing. These reviews in turn have challenged existing regulations governing combination product development and approval, as well as intra-FDA jurisdictional decision-making.

Regulatory review of these combination products is complicated by the fact that although drugs are regulated primarily under Section 505 of the Food, Drug and Cosmetic Act and reviewed by the Center for Drug Evaluation and Research (CDER), biologics are regulated under the Public Health Service Act (Section 351) and reviewed by CDER (therapeutic biologics, synthetic peptides and proteins such as monoclonal antibodies, but not vaccines) or the Center for Biologics Evaluation and

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Research (CBER; vaccines, blood and blood products, and medical devices used for collection, processing, administration of biological products and blood products or components, cell sorters and *in vitro* tests and other medical devices involving retroviruses). The Center for Devices and Radiological Health (CDRH) regulates certain biological products and many combination products, including wound dressings with antibiotics or antiseptics, antimicrobial-coated catheters and implants, bone cements with antibiotics, drug-eluting stents, photodynamic therapy, orthopedic implants with therapeutic drugs or biologicals, dermal replacement devices with living cells, and drug delivery devices (pumps, inhalers, pen injectors). Combination product review at the FDA involves different histories and philosophies depending on the Center. For example, for evaluation of effectiveness, devices require "valid scientific evidence," drugs require "substantial evidence," and biologics must be "safe, pure and potent."

The formal definition of "combination product" for FDA purposes involves a product comprising two or more regulated components (e.g., drug/device, biologic/device, or biologic/drug) provided as a single entity, single package, intended for use with an approved product, or intended for use with an investigational product. We will also use the term to connote drug/drug, biologic/biologics, and so on, as active principles either incorporated into a single entity or co-packaged. This situation might be called "combined therapy." The reason for this is that, increasingly, sponsors are resurfacing old products for new uses, including their use in complex products that involve two or more active principles. This book would be incomplete without a detailed discussion of the chemistry, manufacturing and controls; nonclinical; clinical; and regulatory issues related to such products. It will discuss the means by which FDA's Office of Combination Products (OCP) and Centers decide on the primary reviewing Division for a combination product and how Centers and Divisions can work together to deal with the often complex regulatory issues presented by a combination product.

Historically, the FDA has endured a number of controversial inter-Center disagreements regarding the proper placement of primary review for combination products. The evolution of handling requests for jurisdictional decisions regarding such products has moved from individual decisions in the Center first approached by the sponsor through memoranda of understanding, negotiations between Centers and, finally, the formal establishment of the OCP stemming from the passage of the Medical Device User Fee and Modernization Act (MDUFMA) of 2002. This Act both required and empowered the FDA to focus its mission of regulating

combination products in a hypothetically more logical and consistent manner. The passage of the Act led to a series of standard operating procedures and policies generated by the FDA to guide its reviewers in regulating combination products. Formal guidelines for industry have also been released, and additional such guidelines are expected in 2008 and 2009. The lead regulatory group at the FDA is selected based on the "mode of action" of the proposed combination product. The formal definition of mode of action is "the means by which a product achieves an intended therapeutic effect or action." If multiple modes of action are supported, one will take precedence as the primary mode of action based on criteria in the applicable regulations for dealing with product reviews. The assignment of a primary reviewing Center at the FDA will be based on the primary mode of action (PMOA), if known; regulatory precedent with reference to similar products; and, finally, the Center with the most expertise in dealing with effectiveness and safety questions related to the proposed combination product. Subtle differences, for example, in co-packaging or product conformation, may change the PMOA.

In considering the desirability of working with the various Centers, a sponsor should remember the following points.

- CDER drug products can have new drug marketing exclusivity of up to five years conferred at approval, and both CBER and CDER products can be subject to both orphan drug and pediatric exclusivity.
- CBER biologics are not, as yet, subject to generic competition.
- CDRH products may have lower overall development costs, and a possibly faster route to market.
- Combination products regulated by two or more Centers may possess both the advantages and disadvantages of single entity products regulated by only one Center.

As new laws, regulations, and guidances are developed, sponsors will often find that combination product reviews at the FDA are somewhat of a moving target. Sponsors and reviewers must work within the existing regulatory framework at any time during the development and review process, but the "rules" may change midway through. For example, timeframes for review may shift, user fees may change for the provisional product by the time it reaches the marketing application(s) stage, and the different locations and review cultures of the Centers have yet to be fully integrated. Developing procedures for intercenter cooperation, joint and collaborative review, harmonization of the review of multiple applications

for some combination products, and additional memoranda of understanding will help to ameliorate the complications of combination product review in the months and years to come.

As a sponsor starts to develop a combination product, we recommend that the following points be taken into account.

- Consider regulatory requirements early in the development process, using guidance and precedents.
- Tailor testing and analyses to the combination product and its individual constituents (e.g., drug, device, biologic).
- Recognize that existing guidance documents that cover individual constituents alone may be useful but will not likely address all issues for the combination product.
- Consider manufacturing issues early in the development process.
- Consider whether the individual constituents are already approved, indicated for the same use and target population as intended for the combination product, and whether the combination product will be administered via a new route of administration or as a new dose or formulation.
- For the device constituent in a combination product, consider whether its design is similar to or different than that for an approved device, or if it is manufactured from new materials.
- Consider potential interactions among components in the new combination product, including leachable materials, changes in stability, energy emission that can affect stability, or drug or biologic adhesion to device materials.
- Use the many guidances available, including device-specific guidances, to make the review more efficient and reduce requests for more information. For example, biocompatibility and software issues are the subject of multidisciplinary guidances.
- Refer to the many voluntary consensus standards accepted by the CDRH.
- Schedule early meetings with the FDA Centers, recognizing that for combination products other Center resources may need to be involved so scheduling may take longer than for single-component products.

CHAPTER 2

DETAILED REGULATORY APPROACHES TO DEVELOPMENT, REVIEW, AND APPROVAL

JAMES BARQUEST, PhD
Consultant, Medical Devices and Combination Products

2.1 INTRODUCTION

The regulation of drugs, medical devices, and biological products by the Food and Drug Administration (FDA) has generally been divided both legally and organizationally within the Agency. Legally, there are differences in the regulatory definitions and applicable regulatory controls. Organizationally, the FDA has established separate entities within the Agency that are responsible for the regulation of drugs, biologics, and medical devices. This separation is reasonable given the differences in the safety and effectiveness issues associated with each product type and the specialized technical and scientific expertise necessary to assure competent regulation within each product area. The development of new products consisting of a combination of more than one type of regulated article (drug, device, or biological product) presents a number of regulatory questions regarding the assignment of jurisdiction within the Agency and applicable regulatory controls. This chapter covers the hierarchy of law, regulation, guidelines, informal guidance, and precedent in dealing with

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