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Commentary

Chemistry, Manufacturing, and Controls Information in NDAs and ANDAs, Supplements, Annual Reports, and Other Regulatory Filings

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Advice to the pharmaceutical industry regarding the chemistry, manufacturing, and controls and microbiology (sterility assurance) information to be included in regulatory submissions to the Center for Drug Evaluation and Research (CDER) can be found in the pertinent statutes, regulations, and guidances. The primary statute is the Federal Food, Drug and Cosmetic Act (the Act); applicable regulations appear in 21 CFR 312 and 314. Neither the Act nor the regulations provide sufficient detail on the information that should be included in these submissions. Over the past 14 years CDER has issued a series of guidelines and guidances that provide specific detail related to the recommended filing mechanisms and information that CDER expects applicants to provide. Some of these guidances are applicable to original submissions and some are applicable to post-approval changes. This article will provide an overview of The Act, the pertinent regulations, and the pre- and post-approval guidances.

KEY WORDS: Federal Food, Drug and Cosmetic Act; 21 CFR 312; 21 CFR 314, CDER CMC guidances; CDER Microbiology guidances; INDs; NDAs; ANDAs; supplements; annual reports; bioavailability; bioequivalence; USP; NF.

INTRODUCTION

The purpose of this article is to provide an overview of the type of chemistry, manufacturing, and controls (CMC) and microbiology (sterility assurance) information that should be included in Investigational New Drug Applications (INDs), New Drug Applications (NDAs), Abbreviated New Drug Applications (ANDAs), Supplements and Annual Reports to these applications, and associated regulatory filings. These filings are generally submitted to the Center for Drug Evaluation and Research (CDER) at FDA for regulatory review. Following review and approval, the information is used to assure the identity, strength, quality and purity of drugs marketed in the United States. This information also can support substance and preparation monographs in the United States Pharmacopeia (USP) (USP uses the term *preparation* for a drug product). This article focuses on applications containing non-complex active ingredients/active moieties, i.e., moieties that are neither macromolecules nor complex mixtures. Bioavailability (BA) and bioequivalence (BE) relate closely to CMC information and to safety and efficacy as well. An overview of these topics is presented briefly. Process validation and manufacture according to current Good Manufacturing Practices (cGMPs) are an important part of an overall quality control program, but these topics are not considered in this article.

STATUTE, REGULATIONS, AND GUIDANCES

The Federal Food, Drug and Cosmetic Act (the Act)

Section 505(b) (1) of the Act requires new drug applications to include the following information: 1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; 2) a full list of the articles used as components of such drug; 3) a full statement of the composition of such drug; 4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing and packing of such drug; 5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and 6) specimens of the labeling proposed to be used for such drug.

The Act also requires in Section 510 (b) that, "On or before December 31 of each year every person who owns or operates any establishment in any State engaged in the manufacture, preparation, propagation, compounding, or processing of a drug or drugs or a device or devices shall register with the Secretary his name, places of business, and all such establishments."

Section 510 (h) states, "Every establishment in any State registered with the Secretary pursuant to this section shall be subject to inspection pursuant to section 704." Section 510 (i) extends the registration of such facilities to establishments in foreign countries.

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Regulations

FDA IND regulations regarding are covered in part 21 of the Code of Federal Regulations and provide information at §312.23(a) (7) on the content and format of the CMC section. The information that should be included must be appropriate for the particular investigations covered by the IND. The amount of information will vary with the phase of the investigation but must be sufficient to assure the identity, strength, quality, and purity of the investigational drug. As there likely will be changes and modifications during the various phases of the investigation, it is understood in the regulations that final specifications for the drug substance and the drug product are not expected until the end of the investigational process. Detailed information is given to meet the drug substance, the drug product, the placebo (if any), labeling, and environmental analysis requirements.

Regulations covering NDAs and ANDAs are found in section 314 of part 21. §314.50(d) (1) provides information on the content of the CMC section for NDAs and ANDAs while §314.94(a) (9) discusses additional requirements related to the content and format of ANDAs. Detailed information is given on the drug substance, the drug product, and the environmental impact; additional information for ANDAs includes master production records, inactive ingredients, and inactive ingredient changes permitted in drug products intended for parenteral use, ophthalmic or otic use, and topical use. Changes to an approved application are covered in §314.70. Reporting mechanisms include prior approval supplements, changes being effected supplements—30 day, changes being effected supplements—0 day, and annual reports. These four categories are included in section 116 of Food and Drug Administration Modernization Act of 1997 (FDAMA). As a result of FDAMA, the Agency was required to rewrite §314.70, an effort that is on going as of the date of this article.

Guidances

CDER guidances are developed in accordance with FDA's Good Guidance Practices document (1). As noted in this document, guidances are binding neither on the pharmaceutical industry nor on the FDA, but serve as a best practices approach that, if followed, should generally serve to meet regulatory expectations on a particular topic. According to GGPs, both review staff and pharmaceutical sponsors/applicants may deviate from recommendations in guidance with suitable justification and, as needed, supervisory concurrence. The public process for guidance development at FDA conforms well to Steps 1–4 of the International Conference on Harmonization (ICH) process.

GENERAL INFORMATION

INDs and NDAs

During drug development, key CMC objectives for a pioneer manufacturer are to characterize the drug substance and drug product sufficiently so that important quality attributes are established and controlled. This effort focuses on: 1) the drug substance, to assure identity and strength of the active ingredient(s) and to control impurities arising from production and/or degradation, 2) the drug product to assure the identity and strength of the active ingredient(s) contained therein and to monitor degradants that may arise during manufacture and storage, 3) the container/closure system used to protect the pharmaceutical product during storage, 4) stability testing to assure maintenance of quality attributes during shelf-life, and 5) container labeling. For sterile pharmaceutical products, special approaches are important. Full understanding of the manufacturing processes for a finished drug product also requires an understanding and application of in-process controls and of the quality of manufacturing materials even when they are not present in the final drug product.

Out of the characterization process, pioneer manufacturers develop a set of specifications to assure the identity, strength, quality, and purity of the product and to allow batch release into the marketplace. A specification has been defined in the ICH Q6A guideline (2) as a list of tests, references to analytical procedures to evaluate those tests, and the appropriate acceptance criteria. Specifications allow a determination that a particular drug substance or drug product can be considered acceptable for its intended use. Acceptance criteria may be numerical limits, ranges, or other nonnumerical data. One specification may be developed for the drug substance and one for the drug product. Specifications may also be needed for intermediates, raw materials, reagents, and other components, including container and closure systems and in-process materials. Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, on which specifications are based, and adherence to cGMPs, *e.g.,* suitable facilities, validated manufacturing processes, validated test procedures, raw material testing, in-process testing, stability testing, and other approaches.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization. Specifications should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product. They are usually a small subset of procedures that are used in the characterization process. The reduced specification testing for batch release compared to the one-time testing for characterization is appropriate with the understanding that components and composition and method of manufacture do not change importantly between the marketed product and the clinical trial or other material used to set the specification. Acceptance criteria are based on manufacturing experience with different batches (laboratory, pilot, and, rarely, full-scale) that are prepared during the drug development process and used in nonclinical and clinical studies. As such, acceptance criteria may be based on limited data prior to approval. With additional manufacturing experience post-approval, a specification may be altered, recognizing that redocumentation of safety and efficacy may be needed if substantial deviations in tests, procedures, and criteria are proposed.

Based on characterization and specification setting processes, pioneer manufacturers compile information about the quality of starting materials and their manufacture into a finished dosage form. This information is then presented in an NDA to review chemists and microbiologists in CDER's Office of New Drug Chemistry (ONDC). The chemistry review

results in critical quality standards that are proposed and justified by the manufacturer and approved in the chemistry review process as conditions of approval, to which an approved new drug product must conform during its time in the marketplace. In addition, the chemistry review also considers in-process controls and validation of analytical procedures and, for sterile drug products, process validation to assure sterility. Both universal (description, identification, assay, impurity testing) and specific tests and criteria for drug substances and drug products are important. Agreement between a manufacturer and the FDA on a set of specifications for a finished drug product is a critical time for a manufacturer. An excessive number of procedures with narrow ranges for acceptance criteria may result in acceptable batches being discarded. Conversely, an insufficient number of tests and broad acceptance criteria may not provide a sufficient degree of public health protection. USP/NF drug substance and excipient monographs, as well as general tests and procedures, are frequently cited in an NDA and considered during the ONDC chemistry review.

ANDAs

The approaches for an ANDA applicant regarding characterization and setting specifications are similar to those followed by a pioneer manufacturer, as is the review process performed in CDER's Office of Generic Drugs (OGD). Because compendial procedures for the drug substance and drug product may be available, together with other compendial tests and standard manufacturing approaches, the amount of work needed by a generic drug manufacturer may not be as intensive as that performed by a pioneer manufacturer. Only about 65% of approved new drug products, however, have compendial procedures for drug substances and drug products. For this reason, additional characterization studies may be performed by an ANDA applicant. Different approaches between the information needed in an NDA and ANDA, with suitable justification where needed, have been described in various CDER quality guidances.

CMC/MICROBIOLOGY GUIDANCES

CDER's Chemistry, Manufacturing and Controls Coordinating Committee (CMC CC) has developed or is expected to develop approximately 50 guidances to guide pharmaceutical sponsors in developing and submitting information to INDs, NDAs, ANDAs, Supplements, and Annual Reports. These guidances will incorporate information from harmonized and updated ICH documents (see below). While these guidances are comprehensive, a complete set of recommendations to cover the development and marketing of every drug substance and drug product is unlikely. A brief overview of key guidances and their status is provided in the following sections of this report.

Pre-Approval Guidances

Drug Substance

The February 1987 FDA "drug substance guideline" (3) was "intended to provide sponsors with procedures acceptable to the agency for complying with regulations pertaining to the submission of adequate information on the production and control of new drug substances." It "addresses new drug substances manufactured by chemical synthesis, by fermentation, or by isolation from natural sources (and combinations thereof); it does not cover drug substances manufactured by recombinant DNA synthesis (biotechnology methods)." The 1987 guideline provides information on physical and chemical characteristics, stability, manufacturer, manufacturing, process controls, drug substance controls, and solid-state drug substances and their relationship to bioavailability for NDAs and ANDAs. It also contains information on new chemical entities and known chemical entities for INDs and some information on cGMPs.

CDER's CMC CC has indicated an intent to update the 1987 guideline, incorporating the ICH Q3A guideline (4), including revisions and maintenance changes arising from ICH discussions occurring after the finalization of the ICH Q3A document. ICH Q3A "…is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state. It is not intended to apply to the regulation of new drug substances used during the clinical research stage of development. Biological/biotechnology, peptide, oligonucleotide, radiopharmaceutical, fermentation and semisynthetic products derived therefrom, herbal products, and crude products of animal or plant origin are not covered." The Q3A guideline addresses impurities in new drug substances from the chemistry and safety perspectives. The chemistry aspects include both the classification and the identification of impurities, the generation of reports, the process of setting specifications for impurities, and the analytical procedures used to control their levels. Safety aspects include the qualification of impurities that were not present in batches used during clinical and preclinical studies or of impurities that were present but are not found at substantially higher levels. Three classifications of impurities are given; organic impurities, both process and drug related inorganic impurities, and residual solvents.

Because Q3A only applies to new drug substances not previously registered, the Drug Substance Technical Committee of the CMC CC in CDER developed a guidance (5) covering previously registered drug substances. This guidance extended the provisions of Q3A on identification, qualification, and reporting of impurities to drug substances that are not considered new drug substances. It also extended the provisions of Q3A to applicants planning to submit NDAs and supplements for changes in drug substance synthesis or process and to holders of Type II drug master files (DMFs) that support such applications. (Type II DMFs include information on drug substance, drug substance intermediates and the material used in their preparation. (6)) The extension included new dosage forms of already approved drug products, or drug products containing two or more active moieties that are individually used in already approved drug products but have not previously been approved or marketed together in a drug product. A separate CMC CC guidance (7) extended the provisions of ICH Q3A to ANDAs. Both of these guidances may be incorporated in the update of the 1987 drug substance guidance.

Drug Product

Guidance on the information for the drug product that is recommended for inclusion in INDs, NDAs and ANDAs is

included in the February 1987 FDA "drug product guideline" (8). "This guideline concerns the documentation of the manufacturing process used to produce dosage forms and the accompanying quality control system intended for raw materials, in-process materials, and the finished dosage form suitable for administration…The information and data discussed in this guideline relate to the identity, strength, quality, and purity of the dosage form and the procedures for assuring that all batches manufactured conform to the appropriate specifications." The guidance provides recommendations on information to be submitted on the components, composition, specifications and analytical methods for inactive components, manufacturer, methods of manufacturing and packaging, and specifications and analytical methods for the drug product.

CMC CC is expected to update the 1987 guidance incorporating many of the concepts and recommendations in the ICH Q6A guideline. The updated guidance may also incorporate the ICH Q3B guideline (9). This guideline "provides guidance recommendations for registration or marketing applications on the content and qualification of impurities in new drug products produced from chemically synthesized new drug substances not previously registered in a region or member state." It "addresses only those impurities in drug products classified as degradation products of the active ingredient or reaction products of the active ingredient with an excipient and/or immediate container/closure system." Impurities that arise from the excipients used in the drug product are not covered by Q3B. The drug products excluded from Q3A are also excluded from Q3B. Extraneous contaminants, polymorphic form, and enantiomeric impurities are excluded as well. Extraneous contaminants are defined as those substances that should not occur in drug products and are considered as good manufacturing practice issues. The guideline includes information on analytical procedures, the rationale for the reporting and control of impurities, reporting the impurity content of batches, specification limits for impurities, qualification of impurities, and new impurities. Thresholds are given for reporting, identification, and qualification levels. These thresholds are based on the maximum daily dose of the drug substance that would be administered per day. A decision tree for safety studies is included as an attachment.

The ICH Q3C guideline (10) provides recommended acceptable amounts of residual solvents in pharmaceuticals based on safety considerations for the patient. "The guidance recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents. Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products." The guidance suggests "all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements." Further, the levels of these solvents should be no higher than can be supported by safety data. The guidance lists three classes of residual solvents: class 1 are those solvents that should be avoided as they are known human carcinogens, strongly suspected human carcinogens, or represent environmental hazards; class 2 solvents should be limited as they are nongenotoxic animal carcinogens or possibly are causative agents of other irreversible toxicity; and class 3 solvents are those with low toxic potential. Manufacturers have the option of testing the drug product for residual solvent levels or calculating the residual solvent levels in the drug product from the levels in the ingredients used to manufacture that drug product.

Container and Closure

Section 501(a)(3) of the Act states that a drug is deemed to be adulterated "if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health. . . ." In addition, section 502 of the Act states that a drug is considered misbranded if there are packaging omissions. Also, section 505 of the Act requires a full description of the methods used in, and the facilities and controls used for, the packaging of drugs. Section 505(b)(1)(D) of the Act states that an application shall include a full description of the methods used in, the manufacturing, processing and packing of such drug. This includes facilities and controls used in the packaging a drug product. Many packaging requirements are the responsibility of USP, e.g., 502(g) and (h). Where additional application commitments are needed, FDA issued a final guidance (11) in May 1999. The document updates and replaces a 1987 document (12) and other associated documents. It covers a variety of dosage forms (inhalation, injection, ophthalmic, liquid-based oral, topical, topical delivery systems, solid oral, powders, and other), as well as Type III DMFs (for packaging materials (6)) and bulk containers. It provides guidance on general principles for submitting information on packaging materials that are used in both human drugs and biologics. The guidance defines a container closure system as "the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system." Regarding post approval changes, the guidance refers the reader to 314.70 for NDAs and ANDAs and 601.12 for Biologics Licensing Applications (BLAs). A post-approval change document for container closure systems is under development.

Stability

In June 1998, FDA issued a draft "stability guidance" (13). The guidance is designed to replace a corresponding document published in 1987 (14). The draft guidance is comprehensive in that it covers stability information intended for INDs, NDA, ANDAs, BLAs, and supplements and annual reports to these submissions, i.e., the document covers both pre- and post-approval stability information. The draft document incorporates the ICH Q1A (15), Q1B (16), Q1C (17), and Q5C (18) guidelines. The ICH Q1A Expert Working Group has completed revision of the Q1A guideline (19). The FDA "stability guidance" will be updated based on additional ICH harmonization activities on the topic of stability testing as they are finalized. Public comments to the guidance have been considered and a final version of the guidance may appear this year.

Analytical Methodology

The 1987 "methods validation guideline" (20) "is intended to assist applicants in submitting samples and analyti-

cal data to the Food and Drug Administration (FDA) for methods evaluation. The guideline is designed to expedite a portion of the review/approval procedure for New Drug Applications (NDAs) including Abbreviated New Drug Applications (ANDAs). It does not pertain to biologic products, medical devices or radiopharmaceutical drug products." The guideline contains a number of definitions and information on the types of material to be submitted in terms of analytical samples and the content of the methods validation package. It includes three appendices covering 1) examples of common problems that can delay successful validation, 2) high-performance liquid chromatographic methods, and 3) information on other instrumentation. In August 2000, the agency issued a draft guidance (21) that updates the 1987 guideline and incorporates by reference the ICH Q2A (22) and Q2B (23) Guidelines. The ICH Q2A guideline "presents a discussion of the characteristics for consideration during the validation of the analytical procedures included as part of registration applications submitted within the European Union, Japan, and the United States." The validation characteristics, which should be evaluated, include accuracy, precision (both repeatability and intermediate precision), specificity, detection limit, quantitation limit, linearity, and range. It also provides for the possibility that revalidation may be necessary under certain circumstances. The ICH Q2B guideline is complementary to the parent document. "Its purpose is to provide some guidance and recommendations on how to consider the various validation characteristics for each analytical procedure…. In addition, the document provides an indication of the data which should be presented in a new drug application."

Microbiology

The FDA guidance on sterile process validation (24) "is intended to provide guidance for the submission of information and data in support of the efficacy of sterilization processes in drug applications for both human and veterinary drugs. The recommendations in the guidance apply to applications for sterile drug products (new drug applications, new animal drug applications, abbreviated new animal drug applications, abbreviated antibiotic applications, and abbreviated new animal drug applications). These recommendations also apply to previously approved applications when supplements associated with the sterile processing of approved drugs are submitted. Information and data in support of sterility assurance may also be necessary in investigational new drug and investigational new animal drug applications." Section 125 of FDAMA repealed section 507 of the Act. As a result, all antibiotic bulk drug substance applications have been converted into DMFs. The guidance focuses on validation of processes designed to assure sterility of a drug product irrespective of whether terminal sterilization or aseptic processing is used. Recommendations are provided based on regulations at 21 CFR 312.23(a)(7), 314.50, 314.94, and 314.70. The guidance focuses on information that should be submitted to support sterility assurance for products produced using terminal moist heat sterilization. It also provides information on other sterilization methods, e.g., ethylene oxide and radiation. Separate sections are devoted to aseptic fill manufacturing processes and maintenance of microbiological control and quality (stability considerations).

Submission of IND Information

Guidance to industry for the content and format of phase 1 INDs was provided in the November 1995 CDER guidance (25). This document provides guidance for all disciplines involved in the review of INDs, not just the CMC portion. The recommended information that should be included in the phase 1 IND is related to safety.

A draft guidance (26) focuses on the CMC portion of an IND application and emphasizes safety concerns. "The goals of the guidance are to (1) facilitate drug discovery and development, (2) ensure that sufficient data will be submitted to the Agency to access the safety as well as the quality of the proposed clinical studies from the CMC perspective, and (3) expedite the entry of new drugs into the marketplace …The amount and depth of CMC information that should be submitted to the Agency depends, in large part, on the phase of the investigation and the specific testing proposed in humans." Information directly related to safety should be reported in amendments to the IND as specified in 21 CFR 312.31. These amendments are to be submitted as needed. Other changes in phase 3 from the original submission should be reported in the annual report that is required for each IND as required in 21 CFR 312.33. Information that was reported in earlier phases of the IND need not be resubmitted unless changes have occurred. "Corroborating data and information . . . that are generated in phase 1 and phase 2 need not be submitted until the initiation of phase 3 studies. If these data are not generated in phase 1 or phase 2, they can be submitted at the time when they are generated during phase 3." The IND sponsor is responsible for assessing the impact of any change on the quality of the clinical trial material on its safety.

Drug Master File Guidances

The 1989 CDER guideline on drug master files (6) offers "guidance on acceptable approaches to meeting regulatory requirements." It "is intended to provide DMF holders with procedures acceptable to the agency for preparing and submitting a DMF. The guideline discusses types of DMF's, the information needed in each type, the format of submissions to a DMF, the administrative procedures governing review of DMF's, and the obligations of the DMF holder." DMFs provide a mechanism for the DMF holder to provide confidential information needed for the review of an IND, NDA, ANDA, NADA, ANADA, or another DMF to the FDA without revealing that information to the applicant. Regulations pertaining to DMFs can be found at 21 CFR 314.420. DMF holders are required to provide the Agency with a letter of authorization permitting FDA to reference a particular DMF on behalf of an applicant. Each DMF is expected to be updated annually. Following the Agency's administrative conversion of ANDAs for bulk antibiotic drug substances into DMFs, CMC CC issued a November 1999 guidance (27) that provides guidance "to those in industry whose approved applications for bulk antibiotic drug substances (i.e., *bulk applications*) were converted to Type II Drug Master Files". The guidance includes a general discussion of DMFs and specific information regarding Type II DMFs. It also is applicable to the submission of new DMFs for bulk antibiotic drug substances. An update of the DMF guidance may be underway.

Special Dosage Form Guidances

Two draft guidances for metered dose inhalers and dry powder inhalers (28) (October 1998) and nasal spray and inhalation solutions, suspensions and sprays (29) (May 1999) have been issued by the Agency for public comment. To date, neither of these guidances has been finalized. The former document "provides guidance for industry on the chemistry, manufacturing, and controls (CMC) documentation to be submitted in new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for metered dose inhalation aerosols and metered dose nasal aerosols (also known as oral and nasal metered dose inhalers respectively or MDIs) and inhalation powders (also known as dry powder inhalers or DPIs). This guidance also covers CMC information recommended for inclusion in the applications regarding the components, manufacturing process, and controls associated with each of these areas." Specific information is provided for components, composition, specifications for the formulation components, manufacturers, method(s) of manufacture and packaging, specifications for the drug product, container closure systems, drug product stability, drug product characterization studies, and labeling considerations. The recommendations in this guidance are applicable to INDs as well. The latter document "provides guidance for industry on the chemistry, manufacturing, and controls (CMC) documentation to be submitted in new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for nasal spray and inhalation solution, suspension, and spray drug products. The guidance also covers CMC information recommended for inclusion in the application regarding the components, manufacturing process, and associated controls with each of these areas." Specific information is provided in the same areas described above for the former guidance.

Content and Format Guidances

Two 1987 guidelines are available to assist applicants in providing CMC and microbiology information in NDAs and ANDAs (30 – 31). The former "guideline is intended to assist drug firms in preparing the chemistry, manufacturing, and controls technical section of applications to market new drugs or antibiotics for human use." Guidance is provided on the CMC information for the drug substance (description, manufacturer(s), method(s) of manufacture and packaging, specifications and analytical methods, and solid-state drug substance forms and their relationship to bioavailability), drug product (components, composition, specifications and analytical methods for inactive components, manufacturer(s), method(s) of manufacture and packaging, specifications and analytical methods for the drug product, and stability), methods validation package, and environmental assessment. The latter guideline provides advice to applicants on the preparation of the microbiology section of the application. Specific information is given on mechanism of action, pharmacokinetics, antimicrobial activity, enzyme hydrolysis rates, miscellaneous studies, assessment of resistance, clinical laboratory susceptibility test methods, *in vivo* animal protection studies, *in vitro* studies conducted during the clinical trials, conclusion, and published literature.

ICH finalized the Common Technical Document (CTD) (32) at the meeting of the expert working group in November 2000 in San Diego, California. Any future guidances on the format and content of the CMC and microbiology sections of an application may be expected to conform to the CTD.

Post-Approval Guidances

Specifications for the drug substance and the drug product, as well as specifications for the container closure system and its components, intermediates, reagents, etc., are sufficient to support batch release into the market but may not be sufficient to assure unchanged quality in the presence of post-approval change. If changes do occur, information must be submitted either in supplemental new drug applications or in annual reports to assure that the drug product manufactured after the change is equivalent to the precursor product. Important changes in the CMC of the drug substance or the drug product may occur 1) pre-approval between clinical material and stability batches and/or the to-be-marketed dosage form; 2) between a pioneer product and an interchangeable generic product; and 3) for both pioneer and generic products after approval. A general goal is to assure that an approved drug product, to include its generic equivalents, remains pharmaceutically equivalent and bioequivalent, barring intended change, to the clinical trial material on which safety and efficacy data were generated. The general issue of post-approval change was considered in detail in FDAMA section 116 (P.L. 105-115) and in several Agency guidances. Applicants with approved NDAs and ANDAs are also required to submit certain CMC and microbiology information (and other information as well) in an Annual Report (21 CFR 314.80) even when no important changes in components and composition and/or method of manufacture have occurred. A September 1994 guidance (33) has been made available to assist applicants in submitting this information.

General Guidance

Section 116 of FDAMA required FDA to revise 21 CFR 314.70. The proposed rule and an accompanying guidance both issued on June 28, 1999, for public comment. Based on the comments, FDA issued a finalized guidance on November 19, 1999 (34). This guidance focuses on filing recommendations for Prior Approval Supplements, Changes Being Effected Supplements, and Annual Reports for a broad category of post-approval changes. The filing mechanisms are based on the potential for the change to have an adverse effect on the identity, strength, quality, and purity of the drug as they may relate to the safety and effectiveness of the drug. An applicant is expected to validate (assess) the effect of the change and to include the validation data in the submission. Unlike the documents discussed subsequently in this section, the guidance does not indicate the recommended type and amount of information recommended for inclusion in submissions in the presence of specific changes or groups of changes. The final rule revised 314.70 is expected to publish in 2001, accompanied by a notice of availability of an updated guidance. The guidance will be updated to be consistent with any changes introduced to the proposed rule in response to the comments received.

Bulk Active Chemical Post Approval Changes Guidances (BACPACs)

Two guidances are planned to provide recommendations to applicants on the information and filing mechanisms in the

presence of post-approval changes that affect the drug substance synthesis. The first of these (35), finalized in February 2001, covers post-approval changes that affect changes in synthetic steps up to and including the final intermediate. A companion document (36) will cover changes in synthesis between the final intermediate and the drug substances intended for use.

Scale Up and Post Approval Changes Guidances (SUPACs)

While the BACPAC guidances focus on changes in synthesis of the drug substance, a set of SUPAC guidances focus on changes in components and composition, manufacturing site, manufacturing scale, and/or method of manufacture of certain drug products. At this time three SUPAC guidances (37–39) covering immediate release solid oral dosage forms, modified release solid oral dosage forms, and nonsterile semisolid dosage forms have been finalized. Additional clarification of the first of these guidances was provided in an FDA document (40) issued in 1997. Also published is a SUPAC addendum that provides recommendations on when manufacturing equipment may be considered to have the same design and operating principles (41). A further guidance (42) covers post-approval changes associated with changes in moving laboratory testing from one site to another. As noted in their titles, the SUPAC guidances cover both CMC and bioequivalence (BE) information, given that changes covered by these guidances may also affect relative bioavailability (BE)) between the pre- and post-change products. Additional post-approval guidances may be developed for sterile aqueous solutions (43), container closure systems (44), and analytical procedures (45).

Bioavailability and Bioequivalence

Product quality BA and BE are discussed extensively in an October 2000 FDA guidance (46). These type of BA and BE studies focus on the performance of a drug product and thus are closely related to CMC CC quality guidance. Product quality BA studies benchmark the performance of pivotal clinical trial batches and may or may not be comparative. BE studies are always comparative and are based on an equivalence approach in which measures such as area under the curve (AUC) and maximum concentration (C_{max}) are compared between test and reference drug products. Conceptually, BA and BE studies may be viewed as one-time product characterization studies that support a dissolution test (to include procedures and acceptance criteria) in the drug product specification. While the objective may be one-time characterization, a BE study is analogous to a test in a specification where the BE test uses procedures (pharmacokinetic, pharmacodynamic, comparative clinical, and/or *in vitro* studies) with defined acceptance criteria. Acceptance criteria for a CMC procedure are usually based on manufacturing capability. In contrast, acceptance criteria for a BE study are usually based on clinical judgment (e.g., an 80–125% BE limit) as to when a dosage adjustment would be needed if drug delivery were less than or greater than the specified limit. BA and BE studies provide a key link between quality attributes for the drug product, safety, and efficacy outcomes.

Additional Guidances and Approaches

Procedures

A guidance covering CMC IND meetings (47) was issued by CDER in May 2001. The guidance provides recommendations for the conduct of formal meetings between sponsors of INDs and CDER to discuss CMC information. The guidance covers pre-IND, end of Phase 2, and pre-NDA meetings. These meetings can address scientific issues that arise during the course of a clinical investigation, aid in the resolution of problems, and facilitate evaluation of drugs. These meetings often coincide with critical points in the drug development and/or regulatory process. This guidance is expected to make these meetings more efficient and effective by providing recommendations for developing information to support the purpose, request, information package, format, and focus of the meeting. The guidance is related to or otherwise conforms with Section 119 of FDAMA, regulations at 21 CFR 312.47 applicable to meetings on investigational products, FDA's guidance on formal meetings for PDUFA products (48), FDA's guidance on fast track drug development programs (49), and CDER's Manual of Policy and Procedures (MAPP) on formal meetings (50).

United States Pharmacopeia

Practitioners established the *U.S. Pharmacopeia* in 1820 to promote the availability of unadulterated and appropriately named and prepared therapeutic products. Since the early 1900's USP approaches have been tied to activities of the FDA in the Act. Section 201 (j) of the Act defines the *United States Pharmacopeia (USP)* and the *National Formulary (NF)* as official compendia. These texts provide quality standards for therapeutic products and excipients approved under the provisions of the Food, Drug & Cosmetic Act, and other therapeutic products as well. Through the adulteration and misbranding provisions of the Food, Drug & Cosmetic Act, FDA can take regulatory action against firms whose drug products do not comply with a *USP* or *NF* standard. The letters "USP" or "NF", by themselves, are not trademarked and also can be used by companies for non-drug products if they wish as a representation of the quality of their products subject only, for the most part, to regulatory constraints. Each specification consists of one or more tests, with associated procedures, and acceptance criteria. Many of these tests are available as public standards, or become public standards, in the *USP-NF*. A manufacturer must document or be able to document that an approved drug or biologic conforms to its private specifications or public standards at the time of release of a batch into the marketplace and throughout the shelf-life, as indicated in approved product labeling and container labels. The processes by which application specifications become official substance and preparation monographs in the *USP* have been described in a separate publication (51). Pharmacopeial standards expressed in substance and product monographs and compendial general and informational chapters and in other compendial documents provide approaches that may be referenced in an application without special justification. Validation data are needed to assure that a compendial test is suitable for a specific substance or product cited in a regulatory filing. Given the complexity of many

modern dosage forms, the quality of a finished drug product may inevitably be controlled by a combination of pharmacopeial standards and application commitments.

INTERNATIONAL CONFERENCE ON HARMONIZATION

As established in the ICH, in national regulatory systems, and in the World Health Organization, efficacy, safety, and quality have become core topics in drug development and regulatory assessment. In ICH terminology, efficacy covers clinical safety and efficacy, safety covers non-clinical pharmacology/toxicology, and quality covers information about the identity, strength, quality, and purity of new drug substances and new drug products. Information developed on these three topics by a pharmaceutical sponsor intending to market in the United States serves many purposes, one of which is to satisfy regulatory authorities that a new drug product may be allowed market access. While efficacy and safety information is summarized in product labeling, quality information is summarized in specifications for the drug substance and the drug product.

ICH Guidelines

ICH has finalized many guidelines that provide recommendations on the information needed to support the CMC sections in NDAs and ANDAs. In addition to the guidelines mentioned above for chemical substances, ICH guidelines provide recommendations on topics for biotechnology pharmaceutical products, including Q5A (52), Q5B (53), Q5D (54) and Q6B (55). Taken together, these guidelines provide a broad set of recommendations to global pharmaceutical manufacturers who wish to market pharmaceuticals in the European Union, Japan, and the United States.

While the ICH quality guidelines are broad, information in this article indicates they cover only a relatively small number of CMC topics. For example, neither container and closure nor microbiology topics are covered. ICH quality guidelines also do not cover post-approval change recommendations, nor do they provide specific recommendations for certain complex pharmaceutical substances and products. Many of the ICH quality guidelines specifically exclude investigational drug products used in clinical research, biologicals, oligonucleotides, radiopharmaceuticals, fermentation and semi-synthetic products, herbal products, and crude products of animal or plant origin. ICH guidelines also do not cover information needed in an ANDA and do not provide recommendations on BA and BE. Even when an ICH guideline covers a topic, it may not cover the topic as extensively as may be needed for a regulatory filing. For example, the initial ICH Q1A stability document provides recommendations suitable only for temperature zones I and II but not III and IV. To address some of these issues, ICH has created mechanisms for revision and maintenance of ICH guidelines. According to these mechanisms, the ICH Q1A document has been revised to incorporate guidance on accelerated storage condition testing times, commitment batches, low temperature storage conditions, and liquid products stored in semi-permeable containers and for editorial consistency. Additional topics currently under discussion include bracketing and matrixing, statistical analysis and interpretation of data, uniform storage statements, and expansion to climatic zones III and IV. Further revisions are in progress for Q3A and B to allow updating and clarification of areas not adequately addressed in the original round of harmonization. Additionally, a maintenance plan for Q3C is in place that will allow movement of a particular solvent from one class to another based on new scientific data and for the introduction of new solvents into the appropriate class.

The ICH Common Technical Document

In addition to the ICH topics in safety, efficacy, and quality, ICH created a fourth area of harmonization termed regulatory communications. Topics in this area include a terminology for adverse event reporting (*M1*) (56), electronic standards (*M2*) (57), timing of nonclinical and clinical trials (*M3*) (58), and a topic termed the CTD (*M4*) (59). Now finalized, the CTD provides a table of contents and summaries for submission of information generated according to the ICH safety, efficacy, and quality documents. The CTD is also designed to accommodate information based on regional needs and guidances. With three sections termed CTD-Efficacy, CTD-Safety, and CTD-Quality (CTD-Q), the CTD provides a core set of information for Marketing Authorization Applications in the European Union, for NDAs (and by extension ANDAs) and BLAs in the United States, and the Gaiyo in Japan. The quality part of the CTD has proven challenging. Several reasons exist for this, including different approaches in regulatory control of quality information vis-a-vis Good Manufacturing Practices (GMPs) in the three ICH regions, absence of harmonized approaches in many quality areas, the broad range of pharmaceutical substances and products for which guidance is needed, a need to accommodate both pioneer, multi-source, and self-medication pharmaceuticals, dissimilar pharmacopoeial approaches in the three ICH regions, and other factors as well. The ICH CTD-Q Expert Working Group has successfully resolved these barriers by developing an agreed table of contents, with annexes that lead the way toward future harmonization.

DISCUSSION

This article has provided an overview of many draft or final FDA quality guidances. The general intent of these guidances is to provide a comprehensive set of recommendations on the information needed in IND, NDA, ANDA, and post-approval regulatory filings. Many of these guidances incorporate harmonized ICH guidances and will be updated as future ICH harmonization occurs. A general objective of these guidances is that quality information needed to support a regulatory filing as well as review approaches and standards are optimally understood by pharmaceutical sponsors/applicants. Availability of standardized information as recommended in the gudiances facilitates the submission of CMC and microbiology information electronically both in text and as data in structured databases. With realization of this objective, rapid access to quality sections of an application by regulatory review and inspectional staff will be facilitated. Taken together, guidances for industry, guidance for reviewers, and information technology strategies support an overall objective of promoting high quality, consistent filings, rapid access to information in a filing over many years, and a logical, well-

planned, well-understood regulatory review process. The general effort in CDER, coupled with the efforts of many others in FDA, ICH, and elsewhere has relied on: 1) full understanding of past and current approaches; 2) good conceptualization of scientific and technical issues; 3) extensive drafting and redrafting; 4) public comments to build internal and public consensus; 5) training; 6) implementation and tracking; and 7) revision and updating. The amount of resources necessary to achieve progress to date and to complete the overall effort has been and will continue to be substantial.

Given the complexity of emerging new drug substances and products, resource needs in the future may be even more substantial. A key factor to future success will be the availability of high quality science and technical information to support new guidance development and updating and to allow, where feasible and justified, reduction and/or clarification in regulatory burden. While the amount of CMC work needed to develop and market a new drug in the United States is substantial, the effort should be seen in the context of a single drug product—initially manufactured by the pioneer and then followed by generic equivalents where both can remain in the marketplace for many years. The iterations of this product over time in terms of its identity, strength, quality, purity, and bioequivalence should be tied to the clinical trial material on which safety and efficacy data were based. That the US system achieves these objectives is a substantial science, technological, and policy achievement made possible by pharmaceutical sponsors working with regulators and the pharmacopeia. The general outcome is the availability of remarkably high quality pharmaceutical products that meet the health needs of the US public.

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