Preparing the Common Technical Document for Registration of Pharmaceuticals for Human Use (CTD)—Insights and Recommendations

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has produced a unified dossier for drug applications, the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD). The CTD drug application format is now favored by the Food and Drug Administration (FDA) as well as worldwide regulatory authorities.

The technical information submitted in a CTD, and the organization of the information, is carefully specified in guidance documents. However, sponsors have latitude in how data are presented and important messages are formatted in the compilation of a CTD application. Ultimately, the timeliness of FDA's review and approval status of a drug submission is best served by preparation of a high-quality CTD. Insights and recommendations are provided to help maximize the potential for a successful outcome.

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INTRODUCTION

Efforts over the past 15–20 years by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have resulted in a unified dossier for drug applications, the Common Technical Document for the Registration of Pharmaceuticals for Human Use (CTD). Several ICH documents related to preparation of various sections of the CTD were originally issued in 2001 (1–5); many had updates in subsequent years. Although the CTD is now the preferred format for a new or generic drug application within the regions covered by the ICH, including the United States, the CTD does not in any way replace or supersede the regulations described in the US Code of Federal Regulations. The CTD is merely an agreed-upon format for the presentation of summaries, reports, and data. Indeed, the actual content of the CTD must still conform to requirements and recommendations found in the regulations and in Food and Drug Administration (FDA) guidance documents. Likewise, there may be particular components that are required by other ICH regions. Preparation of CTD submissions for various national regulatory authorities should be geared toward meeting those unique regulatory standards.

THE CTD FORMAT

For the purposes of my presentation, it has been necessary to produce an admittedly unbalanced discussion that shortchanges some sections of the CTD but that includes considerable discussion of other sections that can largely influence the ultimate success or failure of a CTD application. I have therefore focused discussion on selected aspects from a very diverse and technical exercise, which is the production of the CTD.

The format of the CTD application is modular and organized according to the general outline in Table 1. Elements within each module are specific and explicit in content and format requirements. Within the application are regional administrative information (Module 1); summary and overview discussions of chemistry, manufacturing, and controls (CMC, quality) data, nonclinical information, and clinical information relating to safety and efficacy (Module 2); and presentation of detailed technical data and study reports (Modules 3, 4, and 5). Though the content of these modules is generally well defined, according to the various guidance documents previously referred to, considerable lati-

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TABLE 1

The Common Technical Document
Module 1: Administrative Information and Prescribing Information
1.1 Table of Contents of the Submission Including Module 1
1.2 Documents Specific to Each Region
Module 2: Common Technical Document Summaries
2.1 CTD Table of Contents
2.2 CTD Introduction
2.3 Quality Overall Summary
2.4 Nonclinical Overview
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summary
Pharmacology
Pharmacokinetics
Toxicology
2.7 Clinical Summary
Biopharmaceutics and Associated Analytical Methods
Clinical Pharmacology Studies
Clinical Efficacy
Clinical Safety
Synopses of Individual Studies
Module 3: Quality
3.1 Module 3 Table of Contents
3.2 Body of Data
3.3 Literature References
Module 4: Nonclinical Study Reports
4.1 Module 4 Table of Contents
4.2 Study Reports
4.3 Literature References
Module 5: Clinical Study Reports
5.1 Module 5 Table of Contents
5.2 Tabular Listing of All Clinical Studies
5.3 Clinical Study Reports
5.4 Literature References

tude for assimilating, discussing, comparing, and contrasting data is allowed and even encouraged, in particular within Module 2. Even though CTD applications are typically huge, often hundreds of thousands of pages in length, there are opportunities to be creative, to tell a story, and to craft cohesive arguments to help regulatory bodies understand your product. The modular format, with several layers of lesser or greater detail, allows for the presentation of the

overall picture while making available all the supportive details. Because of the large size and complexity of CTD applications, it is important to cross-reference sections carefully within and between modules.

Although each module of the CTD has a specific function, the key areas for creative and informative content are Modules 2 and 3. These sections allow for integration of data between studies, presentation of both the strengths and limitations of the data, and giving the FDA reviewer an opportunity to see the big picture at any of several levels of detail. Clear and compelling presentations in these two modules are critical to the success of the application.

For generic drug applications using the CTD format, it is not necessary to produce either Module 2 or Module 4. Module 5, the clinical study reports, contains bioequivalence/bioavailability information (except for those cases in which a waiver is applicable) but no other clinical information. Comparative dissolution data are characteristically provided both in Module 3 for easy review by FDA chemists and in Module 5 for biopharmaceutics staff to readily compare with the in vivo bioequivalence results.

MODULE 1

Module 1 contains a variety of administrative documents. Some documents, such as the presentation of prescribing information (package inserts, container labels, information sheets, etc), can be region specific. Care needs to be taken that the annotated proposed labeling accurately refers the reviewers to the relevant data within the other modules. Otherwise, it is only necessary to follow directions as presented in the Code of Federal Regulations (6).

MODULE 2

Although every module of a CTD plays a vital role in supporting the ultimate approval of a new drug, Module 2 stands apart from the others in a few respects. First, as an introduction to and summary of all the data available on the drug, it will be closely reviewed across all FDA disciplines as opposed to just one or two. Module 2 can therefore influence the perspective of all FDA reviewers regardless of their particular assigned role. Second, Module 2 affords the opportunity to craft discussions, arguments, and explanations, so that supportive data can be highlighted and less-than-stellar findings put in perspective. It is preferable to tackle difficult potential issues head-on within the application rather than wait for regulatory reviewers to notice problematic data. Third, the sponsor should expect that selected sections of Module 2 may eventually become available for public disclosure. Most often, public disclosure happens by incorporation into briefing materials for an advisory committee meeting or the FDA Summary Basis of Approval document, or both.

In an ideal situation, Module 2 would be written once all of the remaining modules were complete. Unfortunately, the realities of modern drug development rarely, if ever, afford this luxury. Thus, as a sponsor prepares to undertake preparation of Module 2, one of the first and most critical steps is to engage a cross-disciplinary, interdepartmental team whose members possess both the necessary technical knowledge and the ability to collaborate effectively. Establishing an effective team can be easier said than done, but with such a team in place, the sponsor's likelihood of success can increase by countless magnitudes. As the Module 2 team moves forward, a second crucial requirement will be strong leadership. For the team to accomplish its goals, the team must clearly understand and agree on what those goals are. In other words, what are the primary marketing objectives? What are the weakest aspects of the data package, and what are the scientifically driven strategies for addressing those weaknesses? What are the immediate and long-term outcomes that the sponsor wishes to achieve for the program? If the team maintains its focus on the answers to these questions, the final Module 2 documents will more likely be on target.

Without going into all the detailed levels of information within each subsection, it is fair to conclude that CTD Module 2 serves a function similar to that of the application summary within the traditional New Drug Application (NDA)

TABLE 2

Elements of Traditional NDA Summaries and Their Corresponding Locations in the CTD

Contents of the NDA Summary [21 CFR 314.50(c)]	CTD Location
Annotated Labeling	Module 1—Administrative Information and Prescribing Information
Pharmacologic Class, Scientific Rationale, Intended Use, and Potential Clinical Benefits	Module 2, Section 2.5—Clinical Overview
Foreign Marketing History	Module 2, Section 2.5—Clinical Overview
Chemistry, Manufacturing, and Controls (CMC) Summary	Module 2, Section 2.3—Quality Overall Summary
Nonclinical Pharmacology and Toxicology Summary	Module 2, Section 2.4—Nonclinical Overview Section 2.6—Nonclinical Written and Tabulated Summaries
Human Pharmacokinetic and Bioavailability Summary	Module 2, Section 2.7.1—Summary of Biopharmaceutic Studies and Associated Analytical Methods
Microbiology Summary	Module 2, Section 2.7.2—Summary of Clinical Pharmacology Studies Section 2.7.3—Summary of Clinical Efficacy
Clinical Data Summary and Results of Statistical Analysis	Module 2, Section 2.7.3—Summary of Clinical Efficacy Section 2.7.4—Summary of Clinical Safety
Discussion of Benefit/Risk Relationship and Proposed Postmarketing Studies	Module 2, Section 2.5—Clinical Overview

format. The elements of a traditional application summary, and their placement in the CTD format, are summarized in Table 2.

Building a complete Module 2 is an iterative process. Despite the magnitude of the tasks involved in preparing a marketing application, it is useful to remember that efficiencies can be built into the submission process. For example, a pre-NDA meeting document can serve as the basis for the eventual Module 2 summaries. Thus, developing a clear, consistent message by the time the pre-NDA meeting efforts begin is one way to maximize the efficiency of Module 2 preparations.

Quality Overall Summary (module 2.3): The Quality Overall Summary is a presentation that should include sufficient information to provide the quality reviewer as well as the other reviewers with an overview of Module 3. The general format of the Quality Overall Summary should follow the scope and the outline of the detailed body of data in Module 3, emphasizing critical key parameters of the product. The summary should summarize the data on potential and actual impurities arising from the synthesis, manufacture, or degradation of the active ingredient, and should summarize the basis for setting the acceptance criteria for individual and total impurities and state how the proposed impurity limits are qualified. Module 2.3 should also summarize the impurity levels in batches of the drug substance used in the nonclinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. Module 2.3 is also the place where explanations and justifications may be included, for example, providing justification in cases where guidance was not followed. Much of the information requested in the quality summary, including tables, figures, and flow diagrams, can be imported directly from Module 3. Other information such as a nondetailed overview description of the manufacturing process and summary of major manufacturing changes that have been made throughout development need to be presented as highlights rather than as detailed dis-

cussions so that all reviewers, not just those in CMC, are able to gain a basic understanding of the product.

The quality summary should include discussions of key issues for which it is appropriate to integrate information from manufacturing, clinical, and even nonclinical programs. An example of such a key, integrated issue would include qualification of impurities by toxicologic studies and assessment of human risk from the safety evaluations during clinical trials. Another example could be explaining the need for inclusion of a special reprocessing step because of such issues as minimizing toxic contaminants or maximizing a process that requires very expensive ingredients or has poor yields.

The quality summary separately covers drug substance (active ingredient) and completed drug product. For both entities, the quality summary attempts to convey the critical concepts of characterization, consistency (batch to batch), process control, comparability among different products throughout development (ie, a summary of Module 3 development reports), and establishing the connection between clinical drug supplies and the proposed to-be-marketed product. Whenever possible, tabular presentations are a preferred way to compare and contrast data over batches, over time, and across improvements in the manufacturing process. Comparative presentations are particularly useful to highlight both consistencies in manufacturing as well as changes undertaken to improve the product's efficacy or toxicity profile or to scale up production as one moves from nonclinical and early clinical testing to the large efficacy protocols. The quality summary normally should not exceed 40 pages of text, excluding tables and figures. For biotech products and products manufactured using more complex processes, the document could be longer, but as a rule of thumb should not exceed 80 pages of text.

Nonclinical Overview (Module 2.4): The Nonclinical Overview is a summary that should include sufficient information to provide reviewers with an overview of the detailed nonclinical data to be presented in Module 4. The overview will span the highlights of pharmacologic, pharmacokinetic, and toxicologic data, often integrating information from sponsor studies and data from the literature. Frequently, there will be conflicting data from these various sources, especially in such areas of interest as drug metabolism or mechanism of action. In these instances, the overview will need to make an attempt to put conflicting information into perspective and reconcile differences to whatever extent is possible. The module should present information used to determine to what extent toxicities may be related to unwanted components such as impurities or degradants (which theoretically could be controlled via the quality program and for which limits need to be selected and justified).

An important part of the Nonclinical Overview is a discussion of the nonclinical testing strategy. In addition to routine nonclinical single and multiple-dose studies in standard animal models, a given drug development program may involve special types of studies or animal models based on the drug's pharmacology or known class effects. Therefore, the nonclinical testing strategy can be highly individualized and should be clearly described. Furthermore, it is common that the extent of nonclinical testing, and the selection of special studies, may have been determined in agreement with FDA at pre-IND (Investigational New Drug Appication) and pre-NDA meetings. Any such meeting discussions should be referenced so that the reviewers clearly understand the extent to which the nonclinical program fulfilled a preagreed data set.

The presentation of nonclinical data can be tedious and repetitive at times since similar data are typically collected and analyzed from several animal species. Therefore, whenever possible it is a good idea to highlight similarities and differences. Another way to help the reviewer make sense of the data is to describe a drug's effects by target organ rather than segregated by hematology/clinical chemistry/organ weight/gross/histopathology, and so on.

In many cases, it is helpful to anticipate issues that may arise during review and to try to discuss likely FDA questions as the section is being

written. For example, have all the appropriate studies been done; if not, why not (there needs to be a good reason)? Are there unique design elements to the studies that relate to the study drug, and why were the designs chosen? Is there any evidence that any one species is a better predictor of human effects (eg, more relevant anatomy or pharmacokinetics)? Such presentations often aid the reviewers in their consideration of nonclinical versus clinical findings, a difficult task since the exposures can be so different. Ethical considerations related to animal experimentation and human experimentation differ greatly, and at times, a reviewer needs to rely heavily on animal findings to fill in data deficiencies of the human program.

Clinical Overview (Module 2.5): The Clinical Overview is intended to be a relatively nondetailed summarization of the new drug product from the perspective of its use in humans. Thus, the Clinical Overview will present the clinical need for the new drug, the biological activities of the drug that support the medical application of the product, the clinical qualities (efficacy and safety) that describe the drug's use in humans, and even the intended position of the new drug in the overall therapeutic armamentarium for the clinical indication. Ultimately, the overview needs to describe the trade-off between the drug's toxicity profile (risks) and the demonstrable efficacy (benefits) in the clinical indication of interest. Whereas the more detailed clinical summary (Module 2.7) has been described as analogous to the Results section of a research publication, the Clinical Overview more closely represents the Discussion. However, it is important that the Clinical Overview sufficiently highlights the main findings (both good and bad) of the more detailed efficacy and safety summaries, so that no major surprises come to light when the FDA reviewer then reads the more detailed summary presentations. Sponsor conclusions regarding these points are not always accepted by FDA reviewers after they have reviewed the clinical summary sections and detailed study reports, and therefore the sponsor's case in the Clinical Overview needs to be soundly supported by the more detailed summaries. Similarly, potential issues of disagreement may have been clearly identified from pre-NDA and earlier meetings with the agency, and sponsors should use the Clinical Overview to make their case, often by presenting an integrated argument from the clinical data, nonclinical findings, and support from the literature.

The Clinical Overview, and in particular the subsection Product Development Rationale, is an appropriate location to discuss both relevant regulatory agency guidelines or advice from previous meetings, and future (ie, postmarketing) development plans. The Product Development Rationale is the sponsor's major opportunity to describe the strengths of the development program, including arguments about why the sponsor believes the accumulated data constitute a sufficient data package, justify the concepts desired in the prescribing information, and minimize the impact of any limitations of the results or undesirable issues that have arisen during the clinical program. The degree of clinical efficacy and conclusions of tolerability should not be exaggerated in the Clinical Overview. If certain conclusions are not particularly favorable to the sponsor's case, they should be addressed up front and honestly. It may also prove useful to discuss strategies to make use of postapproval commitment studies.

The size and complexity of the Clinical Overview will be greatly influenced by whether the new drug may present dilemmas to the FDA reviewers: whether the drug belongs to a well-known pharmacologic class or is a non-new clinical entity or is a novel new drug in terms of chemistry, mechanism of action, and clinical characteristics; whether efficacy is based on clear clinical endpoints according to FDA guidances or prior sponsor communications, including Special Protocol Assessments, and is robust; and whether toxicities are well defined and of clear quantitative importance. For a drug that fits neatly into a standard pharmacologic class with anticipated efficacy and safety profiles, the Clinical Overview can be quite succinct and straightforward. A reasonable target size for the entire Clinical Overview section would be ap-

proximately 30 pages. However, in the instance that the new drug is truly novel, or presents efficacy to existing therapies but at a marked trade-off with medically important risks and toxicities, the Clinical Overview (and in particular, the Benefits and Risks Conclusions subsections) will need to make a clear case for why the risks are worthwhile. In such a case, the overview may need to present the sponsor's position with more detailed justifications.

Drugs that are effective clinically generally present risks of intolerability and often demonstrate clinically relevant toxicities. However, many of the most dangerous toxicities of a drug are sufficiently uncommon to occur at rates in the approximate range of 1 in 5,000 to >10,000 treated subjects; no drug development program has the resources to evaluate the true risk of such uncommon toxicities during clinical testing. FDA reviewers will very carefully scrutinize the sponsor's safety assessment, and the Clinical Overview is where the sponsor's commitment to diligent toxicity evaluation is best expressed.

Nonclinical Summary (Module 2.6): Whereas the Nonclinical Overview section (Module 2.4) is a relatively brief, integrated assessment of pharmacologic, pharmacokinetic, and toxicologic data, the summary module is more comprehensive. A typical Nonclinical Summary might comprise 100–150 pages altogether. Tabular presentations of data may be organized by species, route of drug administration, duration of treatment, age/gender, or other groupings that may be particularly informative for the new drug.

Nonclinical data can be voluminous, with multiple animal species, a wide range of single and multiple doses administered, histopathology of every known organ, and so on. As a result, presentation of individual study data can be impractical and uninformative. The more useful approach is to highlight parameters that can be compared across studies, specifically identify noteworthy findings, and focus the discussion and conclusion section of the module on interpretations of the data, the significance of observed findings, and potential issues of particular importance. Fortunately, FDA has provided examples of useful appendix formats for the presentation of complicated nonclinical data (*7*) to aid in making interpretations and conclusions readily understood. Ultimately, the true utility of the Nonclinical Summary is to support conclusions of the overview that have implications for the safe use of the drug in humans and make the link to critical aspects of the quality (manufacturing) aspects of the development program.

Clinical Summary (Module 2.7): The Clinical Summary is the detailed presentation of clinical results pertinent to the new drug. These results derive from sponsor studies, meta-analyses when appropriate, published literature, post-marketing data for other geographic regions than that covered by the studies conducted for the CTD, and, in appropriate instances, clinical data from referenced listed drugs. Within the Clinical Summary are different "layers" of study summarization, including an overview of study designs, detailed presentations from each individual study, and comparison of results across studies to highlight the degree to which individual studies provide consistent supportive data. If there is more than one indication for a new drug, clinical summaries for separate indications can be considered together if the indications are closely related, but are more typically presented independently.

Data presentations are representative but also targeted when particularly relevant clinical data need to be highlighted. The Clinical Summary section needs to present a relatively comprehensive efficacy and safety evaluation of the drug and as such can be quite extensive, typically numbering in the hundreds of pages.

Special considerations are important for the Integrated Safety Summary (ISS) and Integrated Efficacy Summary (ISE). Detailed efficacy results and safety results are independently presented and integrated within the CTD document. However, discussion of trade-offs between efficacy and toxicity is not presented here but rather within the less detailed Clinical Overview subsection of Module 2.

The ISE provides the opportunity to highlight data from various studies that are supportive of a

drug's clinical utility and to discuss results of various studies that may not be consistent or reinforcing of the general conclusions. Subsections of the comparison across studies that can be particularly important regarding efficacy (or lack thereof) discuss and contrast data from the perspectives of study populations, demographic subpopulations, and other contributing study characteristics that might differ between studies.

In contrast to the integrated efficacy discussions, the ISS highlights a different set of study characteristics. In order that the reviewer can assess the extent to which safety data are broadly generalizable, the integrated safety presentation discusses the extent to which infrequent but important adverse events would likely have been detected, given the total number of exposed subjects, and highlights patient subpopulation differences that might influence the toxicity profile or dosing recommendations. Thus, the integrated presentation of safety needs to tabulate clearly the extent of exposure to the experimental drug (dose, duration, number and type of patients), identify adverse events that reproducibly occur in most or all of the studies versus those that appear sporadically, and provide any insights regarding observed serious adverse events, such as their relationship to dose or duration of treatment and susceptibility of particular demographic groups to particular adverse events. Although statistical parameters such as the frequency of adverse events or the mean of specific laboratory abnormalities can be informative, it is equally important that the integrated safety section includes clear presentation of the extremes, that is, the range of severity of adverse events or the minimum or maximum values for any given laboratory parameter. FDA reviewers pay particular attention to the difference between common but mild abnormalities versus rare but potentially severe or even fatal drug reactions.

When incorporating results of international studies, it may be necessary to introduce discussion targeting language differences. For example, adverse event terms and event codes may differ regionally, and it could be important to clarify whether event terms are synonymous. There also may be regional differences in investigators' philosophies on assigning causality to an adverse event, and such differences will need to be discussed.

MODULE 3

Module 3 is a highly defined module (3) containing both drug substance (active ingredient) and drug product sections, with each containing required presentations of drug technical information, processes and key parameters, and various validation studies. These reports provide the detailed evidence that a drug's characteristics are well known and well controlled, such that one can assure that the next lot produced is essentially the same as the last lot. Drug manufacture control and reproducibility is the essential message that Module 3 must convey if FDA reviewers are to conclude that a new drug warrants marketing. For an older drug, much manufacturing information can be cross-referenced to an existing Drug Master File from the active ingredient manufacturer and not reiterated in Module 3.

It is beyond this review to summarize all the Chemistry/Manufacturing/Controls (CMC) sections that make up Module 3; however, a few sections are of particular interest. Section 3.2R contains "Regional Information," that is, additional drug substance and drug product information reflecting the specific requirements of different regulatory authorities. Applicants are encouraged to maintain their awareness of these needs as they evolve and to participate in an active dialogue with these authorities for additional country-specific requirements for their products. Some examples of region-specific requirements are presented in Table 3.

Module 3, and the development work that provides the data for the module, is unique in that it often tells a story rather than simply being a collection of data. For most drugs, the manufacturing development program has truly evolved, often such that substantial differences exist between a drug substance or product early in development versus that which is proposed for marketing. The challenge inherent in describing manufacturing development changes is

TABLE 3

Section 3.2R. Regional Information	
US	**EU**
Executed Batch Records	Process Validation Scheme for the drug product
Methods Validation Package	Certificate(s) of Suitability for Medicinal Products containing or using, in the manufacturing process, materials of animal and/or human origin, such as for Transmissible Spongiform Encephalopathy Agents; Other Materials of Animal Origin; Albumin and Other Human Tissue Derived Materials
Comparability Protocols	
Where validation is still to be completed, a summary of the studies intended to be conducted	

to convince FDA reviewers that it is appropriate to consider and to integrate nonclinical and clinical data obtained at various points during development, having studied drugs that might have been significantly different at these points.

Part of the difficulty in assimilating a cohesive and coherent Module 3 is the common situation that the generation of CMC data comes from various sources. Although sometimes all chemistry development is undertaken in-house, it is more common that the module must rely on the contributions of both in-house and outside parties. As drug development accelerates, the pressure to generate batches of drug substance and drug product for nonclinical and clinical trials increases greatly. GMP standards are high, including documentation requirements for the analytical and stability programs supporting manufacturing. At the same time, technical experts in manufacturing are investigating more efficient process schemes and, frequently, look to alternate contractors to shave costs and prevent being boxed into a single-sourced strategy for the CTD, if possible. All of these changes require documentation and evidence of control, if possible beginning at the initiation of the project and planned proactively as far out in time as possible. For purposes of putting together Module 3, it is particularly important to get it right from the start. It is extraordinarily difficult to have to go back in time to some primary source and try to reconstruct after the fact, particularly if the people responsible are no longer available or if other links are missing.

A final aspect of Module 3 that contributes to its uniqueness is the necessity for development reports. Pharmaceutical development reports include drug substance (active ingredient), drug product, and analytical reports. These reports need to tell the historical story of the evolution of these three development aspects during the lifetime of the product's development. FDA reviewers need to understand clearly how the drug has evolved and, ultimately, be able to agree that all nonclinical and clinical data derived during development are somehow informative and relevant to the drug product that ultimately would reach the market. Because it is rarely the case that a drug remains the same during the years of development, it is important that all ongoing chemistry and manufacturing changes are documented and the ramifications of product differences understood. When the history of changes has led to improved purity and tightening of release specifications the story is easy to tell; if this is not the case, considerable creativity may be required. Development reports may benefit from the input of the English major as much as the chemist. If development reports are poorly prepared or unconvincing, the result can easily be an almost endless cycle of FDA queries and sponsor responses, prolonging the review cycle and delaying approval times.

MODULES 4 AND 5

Modules 4 and 5 are collections of nonclinical and clinical study reports. As such, these modules do not require any new writing or editing but rather present the relevant animal and human reports so that regulatory reviewers can review a greater level of detail than that presented in overview and summary form in Module 2. Various graphs, tables, figures not presented in Module 2, and individual animal or patient listings can be found in the reports of Modules 4 and 5. Components and format of the actual study reports, not discussed here, are presented in FDA guidance documents (8,9).

A couple of items are worth discussing relevant to preparation of Module 5. First, the M4E Guidance (4) discusses organization of studies within the module that have aspects of more than one subsection, for instance, studies presenting both relative bioavailability data and detailed pharmacokinetic data. Although such organization is not strictly dictated, when a study has more than one of these broad objectives, the placement of the report within the Module 5 organization is determined by the primary objective of the study. There needs to be careful cross-referencing between sections, as appropriate, since studies are not to be presented in more than one location in Module 5.

Second, whereas the content of study reports in specific subsections of Module 5 is generally self-evident, the content of Other Study Reports (section 5.3.5.4) deserves special consideration. Clinical reports that present information not readily fitting in the other subsections can include interim analyses or other descriptions of ongoing studies in the indication subject to the NDA, reports with relevant information (usually safety) on studies of the drug in other clinical indications, and published reports of clinical experiences not conducted by the sponsor and not included elsewhere in Module 5. Most abbreviated clinical reports such as for aborted studies are placed within their most relevant specific subsections rather than in Other Study Reports.

CONCLUDING REMARKS

A drug application organized according to CTD format is not any more difficult than a standard NDA; guidances provide much assistance. However, in places, there can be significant advantages to considering the "art" of the presentation as well as the science. These are the sections that have been highlighted in this article. Recommendations in this article are based on the experience of the author rather than any existing literature.

The most important approach to maximize the chance that a CTD application is received favorably is to strive for clarity, to avoid exaggerations, and to discuss rather than hide negative findings and deficiencies. Avoid claims that cannot be substantiated, and keep in mind the advice that if something is not documented it is rumor.

If reviewers look favorably on an application's content and presentation and can follow the trail from statement to documentation, there is the best chance for the most rapid approval. A further benefit of a high-quality CTD application is that FDA requirements for additional data, which become imposed at the time of review, may well end up as a postmarket requirement as opposed to a preapproval obligation. If the reviewers are generally uncomfortable with the CTD, review issues are more likely to result in new preapproval data obligations that delay approval.

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The author has disclosed that he has participated in numerous fee-for-service relationships with pharmaceutical clients related to aiding in the production of drug applications. He has no specific relationships to disclose.