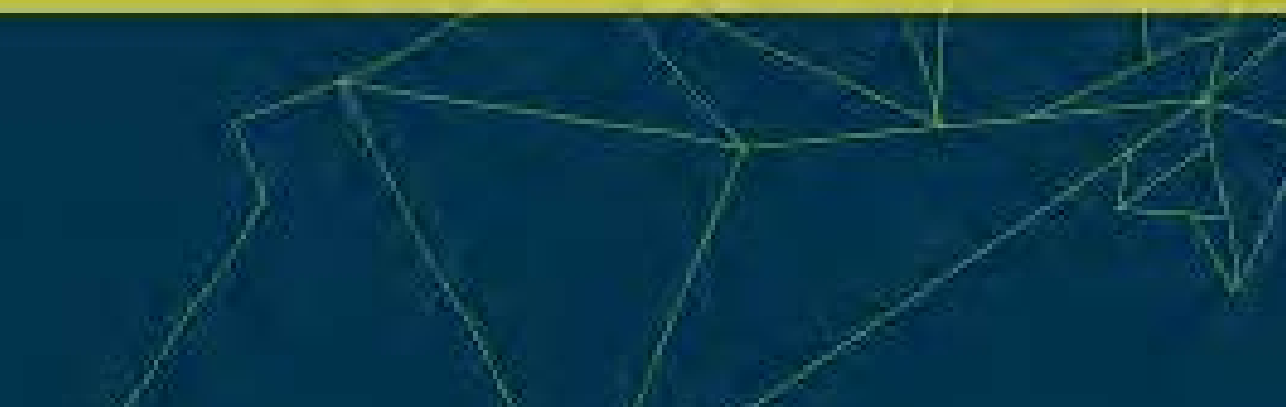
Targeted Regulatory Writing Techniques

Clinical Documentation for Drugs and Biologics

Linda Fossati Wood
MaryAnn Foote
Editors



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Targeted Regulatory Writing Techniques: Clinical Documents for Drugs and Biologics

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Foreword

This book describes the authors' standard or 'best' practices used in writing regulated clinical documents for the drug and biologics industry. The fundamental premise of this book is that the end (documents submitted to a health authority) is dependent on the beginning (the planning and strategy that go into organizing written documentation). Each regulatory document inherently exists within a constellation of related documents. This book attempts to show the relationships between and among these documents and suggests strategies for organizing and writing these documents to maximize efficiency while developing clear and concise text. At all times, and irrespective of applicable laws and guidelines, good communication skills and a sense of balance are essential to adequately, accurately, and clearly describe a product's characteristics. At no time should the reader perceive these suggestions to be the only viable solution to writing regulatory documents nor should the reader expect that these suggestions guarantee product success.

The audience for this book is the novice medical writer, or those who would like to explore or enhance regulatory-writing skills. We assume the reader will have a basic understanding of written communication, but little experience in applying this skill to the task of regulatory writing. Extensive knowledge of science, clinical medicine, mathematics, or regulatory affairs law is not required to use the best practices described in this book.

The scope of this book is regulatory writing of clinical documents and clinical sections of regulatory submissions for drugs and biologics during premarketing stages of product development. This type of writing is described within the context of a regulated environment for Europe, Japan, and the United States. Because the editors and chapter authors are most experienced with writing documents for the United States regulatory authorities, these documents are the primary focus of this book. The exception is Chapter 12 (Clinical trial procedures and approval processes in Japan), with a focus on the regulatory requirements in Japan. Many other regions of the world also require regulated clinical documents but discussion is not within the scope of this book.

Regulatory writing techniques also are used for medical devices, for nonclinical and manufacturing writing, and during the postmarketing phase of development, but these documents are outside the scope of this book. The list of documents included here is meant to represent those documents that are most frequently written by a regulatory writer. The list is by no means exhaustive, as many additional documents may be required based on product-specific characteristics or global region.

It should be noted that the opinions expressed by chapter authors may not necessarily reflect the opinions of the editors. We have taken due diligence to ensure that all information is current and correct, but we are not responsible for errors, omissions, or commissions. Discussion of a product is not endorsement for its use.

We hope that you enjoy the book and that it helps you in clarifying your thinking as you prepare your regulatory submissions.

April 2008

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Regulatory writing fundamentals

Targeted Regulatory Writing Techniques. Clinical Documents for Drugs and Biologics,
edited by Linda Fossati Wood and MaryAnn Foote

Chapter 1

Developing a target

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Introduction

Finis origine pendet (The end depends on the beginning)
Attributed to Roman poet Manlius

Regulatory writing is an integral part of the health-product development process. Most nations have a governmental authority (also called a regulatory agency) responsible for determining whether a drug or biologic is sufficiently safe to allow commercial distribution. The product's manufacturer must provide written documentation to this regulatory agency (called a submission) making an argument for safety and efficacy of the product. The regulatory agency, if it approves of the data and the claims, will file the submission and grant marketing approval. Regulatory writing is the discipline responsible for development of these regulatory documents.

Regulatory writing is important to companies that wish to market and sell their healthcare products and also is important to the general public that uses these products. Clear, concise text that communicates corporate goals and satisfies local and international regulatory requirements is critical to successful and rapid product approval for commercial distribution. Most importantly, an accurate and clear characterization of a product's safety and efficacy is an essential part of medical care.

Standard methods, also called 'best practices,' have been used by the authors of this book to write regulated clinical documents for the drug and biologics industry. The point of these best practices is to plan for the end (documents submitted to a health authority), by developing a document strategy at the beginning. The authors

attempt to show the relationships between and among these documents, and they suggest strategies for organizing and writing these documents to maximize efficiency while developing clear and concise text.

Best practices in regulatory writing are described in terms of five tasks:

- Developing a target: Determining which document(s) is needed based on five steps: classification of the product, the geographic region in which the product will be marketed, the stage of development, the intended content, and bringing these 4 steps together to determine the document(s) to be written (Chapter 1, Developing a target).
- Using a writing toolkit: Selecting and using general principles of regulatory writing (Chapter 2, Regulatory writing tips); templates and styles (Chapter 3, Templates and style guides); and developing procedures for document review (Chapter 4, Document review).
- Writing source documents: Writing the documents that form the basis for all integrated documents and submissions (Chapter 5, Protocols; Chapter 6, Clinical study reports).
- Writing integrated documents: Writing documents that integrate and summarize information from source documents (Chapter 7, Investigator's brochures; Chapter 8, Investigational medicinal products dossier; Chapter 9, Integrated summaries of safety and efficacy; Chapter 10, Informed consent forms).
- Writing submissions: Putting the source and integrated documents together (Chapter 11, Global submissions: The common technical document; Chapter 12, Clinical trial procedures and approval processes in Japan; Chapter 13, Region-specific submissions: United States of America).

Unlike many types of writing, regulatory writing is not a solitary task. All regulated documents described in this book are the result of collaboration with a team and as such reflect the cross-disciplinary efforts and expertise of the team members. The specific functional areas included on each development team vary by company and document, and occasionally by product. We suggest that team members should be included during development, with the caveat that not all are always required for each area and the best teams may be flexible, comprising members from additional functional areas .

The first step in regulatory writing is to ascertain which document needs to be written and should be determined in collaboration with clinical and regulatory staff. The writer should have sufficient knowledge to understand the context within which the document will be written. Determining the document to be written requires categorization of products using the following steps:

- Step 1: Product classification: Is it a drug, biologic, medical device, or combination product?
- Step 2: Geographic region: Will the application be submitted in Europe, Japan, or the United States, the three major regions that drive regulatory documentation? Or will it be submitted to another region of the world?
- Step 3: Stage of product development: Is the product currently being sold (also called marketed) or is it in premarketing development?
- Step 4: Source or integrated document: How many studies are being described? A source document describes one study, an integrated document describes more than one study (often with an integrated analysis of data across two or more studies) or may cross company departments.
- Step 5: Developing a target: using information from the first four steps, the document(s) required is evident.

Side bar: Lessons learned

It is impossible to overstate the importance of this type of rudimentary planning, which intuitively would be the logical first step when embarking on a project with such scope and impact. The editors sadly can attest to problems encountered when upfront planning for a regulatory submission was inadequate. While many submission team members may balk at the time spent in planning what documents are needed, who will write each document, how documents will be reviewed and changes agreed on, and other planning details, experience has shown us that detailed planning saves time. The maxim is every day off market for a good product is a loss of US$1 million; this statistic alone should bolster the writer's (and the team's) efforts for planning.

Step 1: Product classification

Although regulatory writers are not responsible for determining whether an investigational product is a drug, biologic, or medical device, an understanding of the distinction between drugs and biologics and medical devices is important because of the difference in documents.

Drugs

Drugs (also called pharmaceuticals) are chemical entities that affect metabolism. The European Medicines Agency (EMEA) in Europe, the Ministry of Health, Labour and Welfare (MHLW) in Japan, and the United States Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) regulate drug

testing, manufacturing, and sales. The United States Food, Drug & Cosmetic Act (FD&C Act) defines drugs by their intended use:

- Articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and
- Articles (other than food) intended to affect the structure or any function of the body of man or other animals [1].

Biologics

Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources (such as humans, animals, and microorganisms) [2]. The EMEA in Europe, the FDA Center for Biologics Evaluation and Research (CBER) in the United States, and the MHLW in Japan regulate the companies that test, manufacture, and sell biologic products.

The United States Code of Federal Regulations (CFR) defines a biologic product as any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of humans [3]. Regulation of biologics is similar to that of drugs, so documentation of clinical research and development generally follows the drug model. We describe documentation for drugs and biologics together.

Medical devices

Although writing for medical devices is beyond the scope of this book, a few basic principles of medical device development will be explained to differentiate these products from drugs and biologics.

Medical devices range from simple tongue depressors and bedpans to complex programmable pacemakers with microchip technology and laser surgical devices. If the primary intended use of the product is not achieved through chemical action or metabolism by the body, the product is usually considered to be a medical device [4].

The European Commission (EC) in Europe, MHLW in Japan, and the United States FDA's Center for Devices and Radiological Health (CDRH) are responsible for regulating firms that test, manufacture, and sell medical devices. In addition, CDRH regulates radiation emitting electronic products (medical and nonmedical) such as lasers, radiographic (x-ray) systems, ultrasound equipment, and microwave ovens [5].

Under the European Union's (EU) Medical Device Directive, a medical device is defined as any instrument, apparatus, appliance, material, or other article, whether used alone or in combination, including software necessary for its proper application intended by the manufacturer to be used for humans for the purpose of:

- Diagnosis, prevention, monitoring, treatment, or alleviation of disease,
- Diagnosis, monitoring, treatment, alleviation of, or compensation for an injury or handicap,
- Investigation, replacement, or modification of the anatomy or of a physiological process, or
- Control of conception

and which does not achieve its principal intended action in or on the human body by pharmacologic, immunologic, or metabolic means, but which may be assisted in its function by such means [6].

Device regulations differ greatly from those applied to drugs and biologics by virtue of stratifying devices into several classes that determine the degree of rigor required for approval to sell the device. The system of classification established by the EU, Japan, and the United States differ somewhat, but all attempt to quantify the degree of 'risk' posed by the device.

European Union's classification

Device classification is defined in the Medical Device Directive and is based on a complex set of rules that define device risk by duration of use and invasive characteristics [6]. Classifications range from Class I (lowest risk) to Class III (highest risk).

Japan's classification

Japan's system of medical device classification is based on level of risk, which determines whether clinical information is required [7].

- Class I: Clinical data not required.
- Classes II–IV: Ranges from relatively low risk (no clinical data required) to possible fatal risk in case of failure (clinical data required).

United State's classification

The system used in the United States considers three classes [4]:

- *Class I general controls:* Class I devices are the lowest risk devices and generally do not require FDA notification or approval before sales and distribution
- *Class II general controls and special controls:* 510(k) Premarket Notification is required before commercial distribution. The submission makes the argument that the device is "substantially equivalent" to another device legally marketed in the United States before May 28, 1976, or to a device that has been determined by FDA to be substantially equivalent. The 510(k) is notification and does not require approval from FDA before commercial distribution, but it does require FDA concurrence that the device is "substantially equivalent" to a legally marketed predicate device before commercialization.

- *Class III general controls and premarket approval:* A Premarket Approval (PMA) Application is required before commercial distribution for most Class III medical devices. In general, products requiring a PMA are high-risk devices (life-saving, life-sustaining, or breakthrough technology) that pose a significant risk of illness or injury. The PMA process is more involved than the 510(k) process and includes the submission of clinical data to support claims made for the device. The PMA is an actual approval of the device by FDA.

Combination products

The term 'combination product' includes a product that comprises [8]:

- Two or more regulated components (ie, drug/device, biologic/device, drug/biologic, or drug/device/biologic) that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
- Two or more separate products packaged together in a single package or as a unit and composed of drug and device products, device and biologic products, or biologic and drug products;
- A drug, device, or biologic product packaged separately that, according to its investigational plan or proposed labeling, is intended for use only with an approved individually specified drug, device, or biologic product where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed (eg, to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose); or
- Any investigational drug, device, or biologic product packaged separately that, according to its proposed labeling, is for use only with another individually specified investigational drug, device, or biologic product where both are required to achieve the intended use, indication, or effect.

Regulatory writing for combination products poses its own set of challenges, as the written documents must be modified from those required for each of the component products (drug/device, biologic/device, drug/biologic, or drug/device/biologic). As defined regulations or guidelines for combination products are still in their infancy in development, a best practice for writing clinical documents is to use the product classification with the most rigorous regulatory definition. This best practice generally means that combination products comprising medical devices will be written as for a drug product. The extensive, exhaustive, and at times, excessive, level of detail required for description of a drug product, however, may not be appropriate for a medical device, even a device that is under development as a combination product. Good communication skills and a sense of balance are important to determine the level of detail required.

Step 2: Regions of the world

After ascertaining the product's classification, the second step in developing a target is to identify the region in which the product will be tested and commercially distributed, as this is essential to determining the types of documentation required. The decision to submit in a particular region reflects corporate goals and is not within the regulatory writer's purview; however, the writer needs to be clear on the intended region for submission, as this may influence the documents required.

Three major regions of the world drive the regulatory environment for medical products: the EU, Japan, and the United States. Each of these three regions has a branch of government with authority over regulation of these products and individual regulations for the purpose of controlling the quality of medical products available for commercial use (Table 1). Writing documents for regions other than the major three regions requires close collaboration with staff in Regulatory Affairs. Company experience and negotiations with the health authorities should help guide the writer.

Table 1. Global regulatory authorities and regulatory initiatives by product classification

Geographic region	Drugs/Biologics	Medical devices
European Union (EU)		
Regulatory Authority	European Medicines Agency (EMEA)	Notified Bodies (NB) Competent Authorities
Regulatory Initiative	International Conference on Harmonisation (ICH)	Global Harmonization Task Force (GHTF)
Japan		
Regulatory Authority	Ministry of Health, Labor, and Welfare (MHLW): Pharmaceuticals and Medical Devices Agency (PMDA)	
Regulatory Initiative	International Conference on Harmonisation (ICH)	Global Harmonization Task Force (GHTF)
United States of America		
Regulatory Authority	Food and Drug Administration (FDA)	
	Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER)	Center for Devices and Radiological Health (CDRH)
Regulatory Initiative	International Conference on Harmonisation (ICH)	Global Harmonization Task Force (GHTF)

The EMEA, which began its activities in 1995, coordinates the evaluation and supervision of medicinal products throughout the 27 member nations of the EU [9]. Medical devices in the EU are regulated by the EC, which has issued the Medical Device Directives [6].

The Japanese MHLW regulates drugs, biologics, and medical devices under the Pharmaceutical Affairs Law (PAL; Law No. 145 issued in 1960) of the Pharmaceutical and Medicinal Safety Bureau (PMSB) [10]. This legislation describes the requirement for Clinical Trial Notification (CTN) and Marketing Approval Application (MAA). The CTN and MAA are submitted to the MHLW and then reviewed by an Independent Administrative Institution, the Pharmaceuticals and Medical Devices Agency (PMDA). MHLW has the authority to approve drugs for testing in humans, and for marketing and distribution (Chapter 12, Clinical trial procedures and approval processes in Japan).

Regulation of drugs, biologics, medical devices, and combination products is the responsibility of the FDA in the United States. The FDA is an agency within the Department of Health and Human Services, and consists of eight centers [11], three of which are important to understanding regulatory writing of clinical material for healthcare products:

- Center for Drug Evaluation and Research (CDER);
- Center for Biologics Evaluation and Research (CBER); and
- Center for Devices and Radiological Health (CDRH).

The EMEA, MHLW, and FDA define the documentation required for testing and commercialization in their respective regions.

In addition, several regulatory initiatives have been formed that affect written documents for all of these regions (Table 1). These efforts are represented by the International Conference on Harmonisation of the Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH, drugs and biologics) and the Global Harmonization Task Force (GHTF, medical devices). The purpose of initiatives such as the ICH and the GHTF is to bring harmonization, that is, consistency in requirements to product development. Securing the right to sell a product requires that the product's manufacturer sends (or submits) a group of documents to one or more regulatory agencies. The requirements for all regions differ, sometimes substantially, so effectively securing approval for selling a product in different geographic regions of the world has traditionally been a daunting, time-consuming, and expensive task. Hence, efforts at harmonization, or aligning requirements across regions, have been initiated for both drugs and medical devices.

The ICH, created in 1990, is an agreement among the EU, Japan, and the United States to harmonize different regional requirements for registration of pharmaceutical drug products [12]. Such a joint effort by regulators, the biopharmaceutical

Side bar: Lessons learned

Many global companies have regulatory writers based in Europe, Japan, and the United States who can answer questions and provide documentation to regulatory agencies during their normal business hours when counterpart offices are closed. If this model of regulatory writing is used, it is useful, particularly in the beginning and if any managers are hired, for writers to spend some time in the other offices to learn processes and procedures and to develop some interpersonal relationships.

Because submissions are generally global, it is often useful to have some process by which regulatory documents can be worked on by writers at different times of the day, almost maintaining 24-hour/day work. The lead writer for the project would have final responsibility for overall style and quality, but experience suggests that in a global submission setting that allows the European office access to the document when the United States staff is not in the office, thus makes it possible to meet very tight timelines. Such a process also allows the regulatory writers to have a strategic global role in the submission process.

Document management processes and templates should be standardized across regions and changes suggested, discussed, and agreed to by all writing groups (and any other functional group charged with input, such as statistics). The concept of 'one document, many uses' can speed writing and reviewing time, and document management systems. Chapter 3 discusses standardized templates and boilerplate language.

industry, and trade associations is unique, and the working groups have generated a number of guidelines that drive regulatory writing.

Medical devices are not currently included in the ICH guidelines; however, the GHTF is a similar initiative that may eventually bring the various device regulations together. The GHTF was conceived in 1992 in an effort to respond to the growing need for international harmonization in the regulation of medical devices. It is a voluntary group of representatives from national medical device regulatory authorities and the regulatory industry. The GHTF has representatives from five founding members grouped into three geographical areas: Europe, Asia-Pacific, and North America. The primary function of the GHTF is publication and dissemination of harmonized guidance documents on basic regulatory practices [13].

Regulatory initiatives function to put forth guidances (also called guidelines). In contrast to regulations (which are laws), guidances are nonbinding recommendations. Because these guidances provide expanded and helpful interpretations of the regulations, they are very beneficial to the regulatory writer.

Step 3: Stages of product development

The third step in developing a writing target is to ascertain the stage of development as it relates to the ability to market the product. All new drugs and biologics, irrespective of geographic region, follow the same basic, orderly, and highly regulated process of development. Knowledge of the product development process is essential to determining the regulatory documents required at each stage, and these documents vary by geographic region.

For all three geographic regions, the process used comprises: discovery (also called laboratory or bench testing, and consists of in vitro testing of tissues, plasma, etc); nonclinical testing in live animals (in vivo testing); request for permission to test in humans; and testing in humans (Figure 1). These steps are followed by a request for approval to market the product. Each of these stages is associated with specific regulatory documentation.

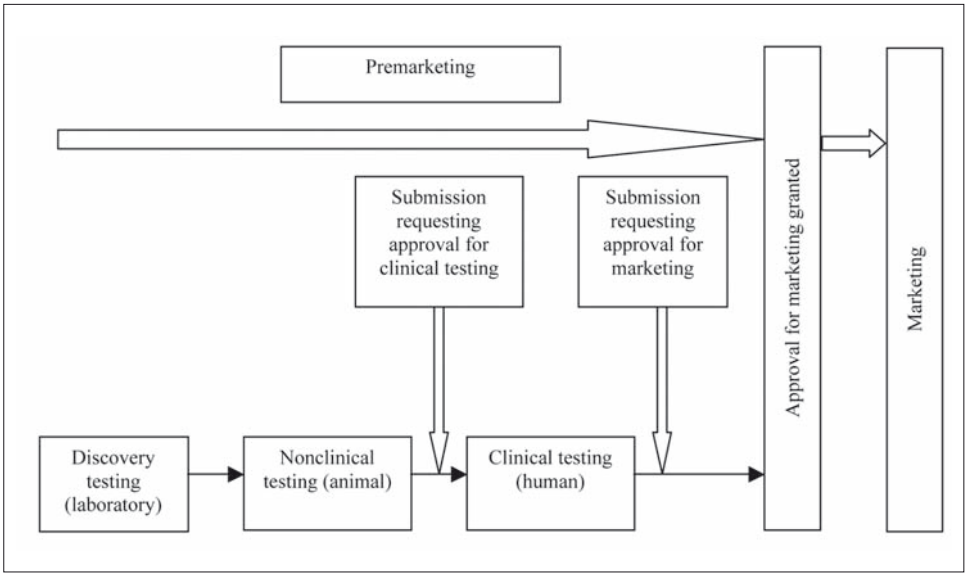

Figure 1. Approval process for drugs and biologics

Before use in humans

During the discovery (or bench) stage, before testing in live animals, a minimum of regulatory writing occurs. The protocols used are brief and reports generally consist of a few pages of text with data sheets appended and an occasional publication. Moving from this stage to nonclinical testing in animals is simple in regulatory terms, as notification of health authorities is not generally required.

Regulatory writing as a function generally starts to become an essential part of product development when animal testing begins. Nonclinical documents are similar to those written for human testing, in that study conduct is planned by the protocol, and results of testing are described in a study report. Documentation of nonclinical studies is beyond the scope of this book and readers are advised to consult other sources for further information.

Request for permission to use in humans

After testing in animals is considered adequate to ensure safe testing in humans, and before initiating human trials, the sponsor must send an assembly of documents called a submission to the health authority in the region of interest. This submission differs based on region (Table 2). After submitting these documents and waiting the region-specific time period, and in the absence of an objection by the regulatory authority, the company may begin clinical trials.

Table 2. Submissions required for use in humans by geographic region

Region	Submission
Europe	Clinical Trial Authorisation (CTA)
Japan	Clinical Trial Notification (CTN)
United States of America	Investigational New Drug Application (IND)

Clinical testing

An understanding of the phases of clinical development is important as it determines the documents required. Phase 1 clinical trials establish the preliminary safety risks for the drug, and often explore pharmacokinetics and pharmacodynamic markers. Because no drug or biologic is without toxicity, a risk:benefit profile must be established so that healthcare professionals and subjects can determine if the drug is suitable for them. Phase 1 trials also establish dose, frequency of administration, route of administration, and use with concomitant drugs and food. Phase 1 trials for drugs are usually conducted in a small number (10–30) of healthy volunteers (ie, people who are free from conditions that could complicate interpretation of data). These subjects are monitored closely at frequent time points using a large number of assessments.

Drugs that are known to have potential serious effects, drugs intended for an indication that would not benefit from testing in healthy volunteers, and biologics are generally tested in subjects with the disease. In biologics, healthy volunteers generally are not used for testing because biologics are proteins that could induce antibody production with potential adverse effects. Sometimes the very first trial, often called ‘first in man’ or, more properly, ‘first in human’ is called a phase 1a trial.

The quantity of the first dose of a particular drug administered to humans is based on observations from nonclinical toxicology studies [14]. The no-observed-adverse-effect level (NOAEL, the highest dose of the drug that does not produce a significant increase in adverse effects compared with the control group) of the drug is determined based on three criteria: overt toxicity such as clinical signs, surrogate markers of toxicity such as abnormalities in blood values, and exaggerated pharmacodynamic effects.

The NOAEL is used to calculate the human equivalent dose (HED), using mathematical methods to extrapolate the dose from animals to humans, generally based on body surface area. The selected first dose is administered to a small group of subjects (and can be as few as three subjects), and these subjects are observed for signs of toxicity for a specified period of time. Subsequent increases in the dose (called dose escalation) occur until the maximum tolerated dose (MTD) is reached. Often in phase 1 trials, serum drug monitoring is done to obtain important pharmacokinetic data, including maximum concentration in the serum and the time to maximum concentration.

Phase 2 clinical trials are designed to further explore safety of the investigational drug, to provide early data about efficacy, and provide enough data to design phase 3 trials to confirm the product's safety and efficacy. These trials have a larger sample size than phase 1 trials (generally 30–100), and the frequency and types of assessments are fewer than in phase 1. The larger sample size is intended to improve the probability that statistical analyses will be able to determine a difference between test and control groups, and therefore support the study hypothesis. Although a placebo-controlled trial would yield the best definitive answer, some investigators and regulatory authorities believe that it is unethical to withhold active treatment for some diseases. In such situations, an active control (ie, current therapies considered to be standard of care) might be used instead of a placebo.

The function of phase 2 trials is to help design successful phase 3 trials, but many drugs fail at the phase 2 stage and clinical development is terminated. Failure may have been due to a poor risk:benefit ratio (the risk of using the drug outweighs the possible benefits), poor study design, the wrong endpoint, or a lack of statistical power sufficient to show the difference between the drug and placebo or active control.

Data from phase 3 trials confirm the efficacy of a drug and further characterize the safety of the drug. Phase 3 trials have a large sample size (sometimes in the thousands), and the study designs have inclusion and exclusion criteria, time points, and assessments that tend to mimic standard medical care. The design of a phase 3 trial is crucial because the label for the drug and the marketing claims will be developed on the basis of the results of the assessments.

Request permission to market

After completion of the clinical trials, each of the geographic regions requires a submission, which requests marketing approval. Table 3 presents a list of these submissions by geographic region.

Table 3. Submissions required for marketing by geographic region

Region	Submission
Europe	Marketing Authorisation Application (MAA) Common Technical Document (CTD)
Japan	Marketing Approval Application (MAA) Common Technical Document (CTD)
United States of America	New Drug Application (NDA) Common Technical Document (CTD)

Postmarketing approval

Postmarketing clinical trials are often called phase 4 trials (or even phase 3b trials). Phase 4 trials are designed to add more data to the drug's profile: risks, benefits, and potential use in other disease settings. Phase 4 trials are important to supplement additional requirements from regulatory agencies. Sometimes marketing approval will be granted for a product with the stipulation that phase 4 work will be done within a given time frame. Although hundreds to thousands of people can be studied in phase 3 trials, it is often not possible to predict potential side effects in a large, heterogeneous population.

Postmarketing commitments made between drug sponsors and regulatory agencies often include studies in special populations, such as infants, young children, adolescents, the elderly, or subjects with liver or kidney impairment. Other phase 4 commitments may include studies to provide further information about drug-drug interactions, particularly if the drug will be used by a population with co-morbidities that also require drug therapy. Phase 1, 2, 3, and 4 studies are summarized in Table 4.

Table 4. Summary of phase 1, 2, 3, and 4 clinical trials

	Phase 1	Phase 2	Phase 3	Phase 4
Outcome	Safety Dose finding Pharmacokinetic profile Pharmacodynamic markers	Safety Preliminary efficacy Response rate	Safety Efficacy Survival	Safety Efficacy Survival
Participants	Healthy volunteers Subjects with no other treatment options Usually < 30	Subjects with the target disease Usually 30 to 100	Subjects with the target disease Usually > 100	Subjects with the target disease Often > 1000
Drug dose and schedule	Often escalating dose on a fixed schedule	Usually a fixed dose on a fixed schedule	Fixed dose on fixed schedule	Marketed dose and schedule