CHAPTER

MARKETING AUTHORIZATION

6

6.1 FUNDAMENTALS

6.1.1 INTRODUCTION

In order to authorize the marketing and selling of a medicinal product, most countries require the manufacturer or distributer to register that product with the NRA [1–5]. Many countries keep an actual registry or national formulary of legitimate pharmaceutical products that may be sold on their market [6]. In most cases, these products should have been shown to be safe, pure, potent, and efficacious, as well as having correct identity and suitable quality. The process of registration or gaining marketing authorization in different countries is called by different terms that mean essentially the same thing—the product may be marketed and sold there. Even within the United States, depending on the product type, different terms are used. Various terms used are defined here:

- Licensure—Authorization to market and sell a biologic, used in the United States and elsewhere [7].
- Approval—Authorization to market and sell a pharmaceutical drug, or a medical device for which there is no precedent on the U.S. market, common term used in many countries [3,7,8].
- Clearance—Authorization to market and sell a medical device that has been found to be substantially equivalent to an already approved device in the United States [9].
- Marketing authorization or authorisation—Authorization to market and sell a medicinal product, used in Europe and elsewhere [1].
- Registration—Authorization to market and sell a medicinal product (often this term refers to a product made outside the country, particularly a nonproducing country, and imported from the producing country, with the expectation that it is already marketed in the producing country; although this term can be used synonymously with marketing authorization, as it is by ICH), used by many countries [2].

To clear up some potential for confusion, note the following: Often, people will use the term "approval" to describe an IND that is in effect under the review of the U.S. FDA. This is an incorrect use of the term. INDs are not approved, the proposed clinical trials within them are "allowed to proceed" and the IND is then considered to be "in effect." Clinical trials may be approved in various countries, but in the United States, they are "allowed to proceed" or "allowed to continue." And by allowing protocols under IND to proceed or continue, U.S. FDA is giving a tacit "approval" to the clinical trial protocol(s). (However, IRBs—subject of another chapter—do approve clinical trials.) CTAs generally are approved or they might be authorized. So, this is why there is some confusion in the terms used.

NDAs (New Drug Applications) and ANDAs (Abbreviated NDAs) are approved. So too are PMAs (Pre-Market Approvals)—a type of medical device application for those devices having no precedent

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on the U.S. market, i.e., there has not been something approved previously to which the new device may be compared and found to be substantially equivalent. 510(k)s—the other type of medical device application for those devices that can be found to be substantially equivalent to an already marketed medical device in the United States—are cleared. See Chapter 21 for more on this subject.

Finally, the type of products that are the focus of this book is biologicals. Because of the history of regulation of these products, in many countries, they are licensed. Originally in the United States, both the manufacturing facility or "establishment" in which the product was manufactured and the product itself were licensed separately. This was true for decades. The reason for this is that for biologicals, the product is the process, the process is the product—and the process occurs in the manufacturing establishment. Thus, in order to market a biological, one needed both an Establishment License and a Product License. However, with the Prescription Drug User Fee Act (PDUFA; see Chapter 1), a decision was made to streamline the approach to bring it more in line with the way pharmaceutical drugs were regulated, so that a single application was required. This application, or the Biologics License Application (BLA), covers both the manufacturing facility (establishment) and the product manufacturing process, raw materials, controls, etc. As a consequence, biologicals in the United States now receive a single license, or biologics license, that covers both the product itself and the facility in which it is made. In order for the same manufacturer to make the product in a different facility, the biologics license must be supplemented. This process (supplementing a license) will be discussed in Chapter 8, though it will be introduced in this chapter.

Whichever term is used to describe the process of marketing authorization, each means that the sponsor has gained authorization to market and sell their medicinal product within the jurisdiction the NRA granting that authorization has authority. So, don't get confused by the different terms, but just focus on the concept of marketing authorization.

In Europe, the marketing authorization dossier is referred to as Marketing Authorisation Application (MAA) and products get authorized. MAAs are given a scientific opinion by EMA, after which the EC or individual countries may authorize it for their markets. Other countries may refer to the registration dossier or they may use the same term as the EMA. Often registration is granted for products that have been manufactured, tested, and approved in other countries before an application is made to a new country, e.g., a developing country (low- or middle-income country). When regulators do not have the resources, expertise, or capacity to regulate a product throughout its developmental life-cycle, they may look to the marketing authorization in the producer's own country, as a basis for gaining confidence in evaluating a registration dossier in their country. They may also look to regional experts or the World Health Organization for technical advice to aid their decision-making on complex registration dossiers.

In Europe, variations are granted in the manner that licenses are supplemented in the United States or variations may refer to the process of approval of an ANDA in the United States (An ANDA is the type of application that a manufacturer of a generic drug would submit and these will not be discussed in this text, because biologicals don't have "generics.") Biosimilars is the term used in various places to refer to "generic" biologicals or products that are substantially similar to already licensed biologicals. A separate Chapter (20) on biosimilars will explain why they are different from generic drugs and how they are regulated differently. Other terms are also used and will be discussed in the later chapter.

Now that we have covered all the various terms used to describe the process of marketing authorization, we are ready to describe the application format. In general, throughout the book, the term Marketing Authorization Application (MAA) will be used whenever it is meant BLA, NDA, or other types of registration or marketing dossiers in a general aspect (commonalities to the processes).

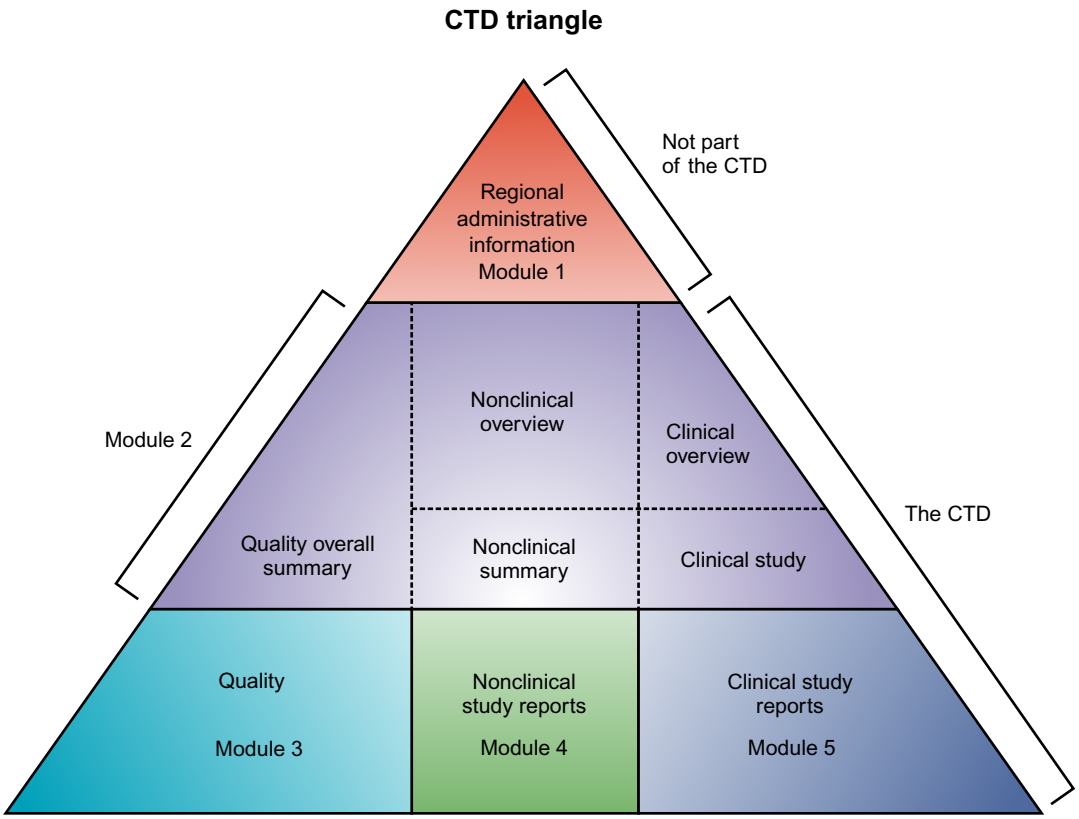
Likewise, the terms dossier or application will be favored to refer to these generally. While marketing authorization will be used, because of my background as a U.S. FDA reviewer in CBER, the term licensure will also be used and these terms (marketing authorization and licensure) should be taken as synonymous for the purposes of the book and to consider the processes generally. The purpose of using specific terms to discuss the general processes is to avoid confusion about the terms, since there are so many different terms that mean the same essential thing. The reader shouldn't let the "lingo" or jargon keep him/her from learning and understanding the concepts.

6.1.2 COMMON TECHNICAL DOCUMENT

The CTD, or its electronic equivalent (eCTD), is the format developed as part of the ICH process for how applications should be organized to gain marketing authorization in those regions that adhere to ICH [10]. The CTD is the format used for an NDA, a BLA, and an MAA. Increasingly, electronic submissions are not only accepted by regulators, but expected. The U.S. FDA already requires electronic submission of their NDAs/BLAs and will no longer accept paper submissions. INDs may be electronically submitted as well, and this is why the CTD format is beginning to be used for INDs in place of the IND format discussed in Chapter 5. Eventually, the CTD format will likely be required for INDs in the United States. In the spring of 2018, INDs will also be required to be submitted electronically, except when it is an investigator/sponsor IND, i.e., submitted by an academic rather than a company. The purpose of the CTD is so that sponsors do not need to waste time and resources reformatting the information to be submitted to different regulators. Formatting is not as important as the information itself, so the focus should be on gaining and clearly articulating the information needed to make a regulatory decision, not on reformatting it to fit each country's preferred manner in which the info should be presented to them.

The CTD comes in five modules (see Figs. 6.1 and 6.2). The first module is not officially part of the CTD, in that it will vary by country, in terms of format and content. This first module is the country-specific information required depending on the country to which marketing authorization is being applied. For example, in the United States, this module would contain the FDA form 356H, which is somewhat like the FDA form 1571 is for an IND. It is the cover form to a BLA or NDA that identifies the applicant, the product, the establishment, etc.

Modules 2–5 are the official consistent parts of the CTD and do follow the harmonized format agreed upon in ICH. These modules may be submitted identically in the United States, E.U., and Japan. Many other countries are likely to accept these as well, e.g., Canada and Switzerland. Module 2 is all summary information. Executive summaries of the three aspects about which regulators need to know are contained in this module—Quality (product), Nonclinical, and Clinical. Module 3 contains the detailed information about the product and the manufacturing facility, i.e., the Quality Module. Stability data to support expiry dating periods would be provided in this module. Module 4 contains the detailed information about the nonclinical studies, including study reports, which may be hundreds of pages in length. Finally, Module 5 contains the detailed information about all the clinical trials conducted by the sponsor to support the marketing authorization, including study reports, statistical analyses, and datasets. These too may be hundreds or thousands of pages in length and very detailed. (U.S. FDA reviewers reevaluate the clinical data themselves, to determine if they independently obtain the same statistical outcomes as the sponsor—both in regards to safety and in regards to efficacy; thus, the actual datasets are required to be submitted, to permit this independent reanalysis. There is a format—CDISC—for the datasets to be submitted to facilitate this review and analysis. Many other regulators take the results



The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

FIG. 6.1

ICH Common Technical Document format. The CTD triangle was obtained from the ICH website. The CTD format is in 5 modules, the first of which is not really part of the CTD (i.e., not harmonized), but contains the country-specific administrative information, whereas Modules 2–5 are harmonized and form the CTD for submission to all countries that have adopted the ICH procedures.

from the applicant on face value, though they may request additional analyses of the data be performed by the applicant.) [11].

Within Asia, many regulators (though not all, e.g., Japan abides by the ICH format) request use of the ASEAN CTD [12]. The ASEAN CTD (ACTD) is comparable to the ICH CTD, except that Module 2 is not included, and instead Parts II, III, and IV of the ASEAN CTD contain the overview, summary, and study reports for Quality, Nonclinical, and Clinical, respectively. Study reports for Parts III and IV may not be required if the product is already approved in the Reference Country, a term that was left to be defined at the time of publication of guidance on the ACTD format. One might consider Parts III and IV to be comparable to the related parts of Module 2, in the case that the product is registered elsewhere and is coming for registration to a new (different) country within Asia that is a member of ASEAN.

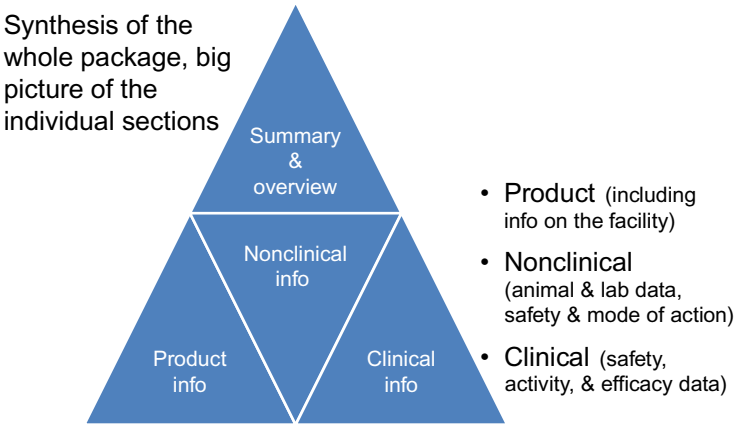


FIG. 6.2

CTD format explained. This figure explains the ICH CTD Modules 2–5. Module 2 (top of the pyramid) is the summary and overview, which synthesizes all the information (remember the three types of information regulators need to know about a product) in the whole dossier into a big picture, including the overview of each of Modules 3–5. Module 3 contains the product (Quality) information including the chemistry or microbiology, manufacturing methods, control test methods, specifications and results, and information about the manufacturing facility. The Nonclinical (Module 4) section covers all laboratory and animal safety and proof-of-principle (such as mode-of-action) study reports, i.e., the actual data. And Module 5 contains all of the clinical data in the form of study reports, including studies of safety, biological activity, and efficacy.

Like Module 1 of the ICH CTD document, Part I of the ASEAN CTD contains the administrative information and Table of Contents, although Part I also contains some basic product information explaining its basic pharmaceutical class and mode-of-action. Only Part II might be equivalent to the Quality portion of Module 2 and the whole of Module 3 in the ICH CTD. The use of this altered format from the ICH format reflects the regulatory processes in many Asian countries, in which there may be mutual recognition agreements between NRAs and once authorized in the producing country, other countries may agree to recognize the producing country's review and decisions regarding the Nonclinical and Clinical aspects. Thus, they may only evaluate the overviews and summaries instead of reviewing the entire dossier that the producing country would have reviewed. The regulatory regions that abide by ICH might be able to do something similar, if there was more mutual recognition of the review by the other regulatory regions, but because their legislative frameworks are so different from each other, this may never be possible. Time will tell.

However, the intent is that the ICH CTD should streamline the regulatory processes, reducing resources going into reformatting of information and focusing it on gaining and analyzing the information instead. Likewise, the ASEAN CTD should streamline the regulatory processes among those Asian countries that participate in ASEAN.

6.1.3 LABELING, ADVERTISING, AND PROMOTIONAL LABELING

In many countries, the manner in which medicinal products are labeled, advertised, and promoted is regulated. The actual containers must be labeled in a certain manner, as would be the shipping cartons

in which several containers would be distributed. Medicinal products generally must be shipped or distributed with a package insert or leaflet of prescribing information in each package of the product. The content and format of this package insert labels the product as to its intended use, administration instructions, data that supported the marketing authorization (in summary form), and so forth. Furthermore, in the United States, any type of advertising or promotional materials intended to market the medicinal product for sale must be reviewed by U.S. FDA to ensure the manufacturer or distributer is not making false claims and that the information provided is *accurate, balanced, and complete*. If you have ever seen a drug advertised in a magazine, you will have seen the "fine print" lengthy package insert in the advertisement (often on the back of the page with the graphic advertisement).

How many times have you seen a print ad or watched a commercial on television and you were not even sure what the product being sold was or for what it was intended? Are they selling a car, perfume, clothing, insurance? In the United States, drug ads or commercials must be more informative than that and tell you what the product is intended to diagnose, treat, prevent, cure, or mitigate, and what the risks of taking the product are. Even the font size in a print ad is regulated to ensure readers can read the risks of the product and that they are not buried in the "fine print." Both prescribers and consumers need to know what a medicinal product does and what the risks of taking it are.

Package inserts (PI) or package leaflets of prescribing information contain a wealth of information and are primarily directed at medical professionals, or prescribers. Sometimes, they may be accompanied by materials that are written in more lay-language so consumers can understand—a so-called patient leaflet or patient information leaflet. You may have seen this or be given such a document by a pharmacy where you acquired a drug you had been prescribed.

The U.S. PI begins with *summary* information and then is followed by more *detailed* information, referred to as full prescribing information. First, the PI summary information should identify the product name and list other required information of that sort (producer, distributor). Next comes the "boxed warning" that highlights the most significant risks, if there is one for that product. (Not all products require a boxed warning.) This is followed by recent changes to the PI, so that prescribers familiar with the product can determine if there is any new information with which they should newly become familiar. Indications and usages follow this. Next is the administration instructions and dosing info. Dosage forms and strengths in which the product comes appear after this. This info is followed by contraindications (conditions under which the product should not be given), warnings and precautions, adverse reactions noted in clinical trials (and post-marketing surveillance data, if the product has been on the market for a while), and drug interactions (effects that occur when taken with other drugs). Finally, among the summary information is the use of the product in specific or special populations (e.g., pregnant women, children, HIV-infected, or so forth) [13].

The full prescribing information begins with the boxed warning. This is followed by 17 other aspects as follows:

- Indications and Usage
- Dosage & Administration
- Dosage Forms & Strengths
- Contraindications
- Warnings and Precautions
- Adverse Reactions
- Drug Interactions
- Use in Specific Populations

- Drug Abuse & Dependence (if any)
- Over-dosage
- Description of the Product
- Clinical Pharmacology Data (summary)
- Nonclinical Toxicology Data (summary)
- Clinical Studies Data (summary)
- References cited in the PI
- How the product is supplied (e.g., in bottles, vials, syringes) and how it should be stored and handled
- Patient Counseling Information

Within Europe, the EMA requires the prescribing information be presented in the following format: name of the product, qualitative and quantitative composition of the product, the pharmaceutical form (e.g., tablets), clinical particulars (which are listed separately below), pharmacological properties (which include pharmacodynamics, pharmacokinetics, and preclinical safety information), pharmaceutical particulars (i.e., product details, which are also listed separately below), the marketing authorisation holder, marketing authorisation number(s), date of first authorisation/renewal of authorisation, and date of revision of the text [14].

The clinical particulars include:

- Therapeutic indication(s)
- Posology (dosing) and method of administration
- Contraindications
- Special warnings and precautions
- Interactions with other medicines and other forms of interactions
- Pregnancy and lactation (or fertility, pregnancy, and lactation)
- Effects on ability to drive and use machines
- Undesirable effects
- Overdose

The pharmaceutical particulars include:

- List of excipients
- Incompatibilities
- Shelf life
- Special precautions for storage
- Nature and contents of container
- Special precautions for disposal and other handling

You will note that there are many commonalities in the formats, but they are not specifically harmonized. Countries other than those in Europe and the United States each have their own formats and expected contents of the prescribing information. Likewise, the information needs to appear in the local official language. In some countries, it may be required to be provided in more than one official language.

6.1.4 POST-MARKETING COMMITMENTS, POST-AUTHORISATION MEASURES

When a new biological is originally licensed, authorized, or registered, often the regulators will hold the applicant to certain post-marketing commitments. A PMC (or a post-authorisation measure—PAM)

BOX 6.1

Although the terms "efficacy" and "effectiveness" are often used interchangeably, and the U.S. FDA uses "effectiveness" in the regulations & guidances; in fact, they are not the same. Efficacy is established based on how the product performs in well-controlled clinical trials under closely monitored conditions. Effectiveness is established based on how the product performs in real-world conditions, e.g., doses may be missed, timing of administration may vary from the ideal, dosing may be halted early, etc. While these things may happen during a clinical trial, they may occur more frequently in the real-world setting, where there is less control & less monitoring of use. Generally, effectiveness is lower than efficacy, for all of these reasons—lack of adherence, misuse, improper storage conditions, etc. Effectiveness may also be lower because the people taking the product in the real-world may differ from the well-controlled population enrolled into clinical trials with stringent inclusion and exclusion criteria. Don't let the nomenclature confuse you. It's about whether the product "works" or not.

is an agreement the regulator requires of the applicant so that they may continue to market a product once marketing authorization has been gained but before all data the regulators wish to evaluate are available [15,16]. The purpose of granting marketing authorization prior to having all needed data is to permit consumers access to new and improved medicines at the earliest opportunity. Examples of PMC or PAM might include gathering data in larger numbers of individuals to identify rarer adverse reactions than could be detected in the pre-marketing clinical trials or to gain a better understanding of rare adverse events already identified, gathering data to support use in specific populations, particularly children, and/or gathering data on whether the efficacy demonstrated in closely monitored well-controlled clinical trials holds up in the real-world use of the product. Often these data are gathered in the form of Phase 4 clinical studies, although they may be gained (particularly safety data) in Post-Marketing Surveillance (see below) or Pharmacovigilance (Box 6.1).

At the time the license for a new biological is granted in the United States, the licensure will be contingent on meeting agreed-upon PMC. This means the license may be revoked if the PMC are not met. How other countries deal with unmet PMC will depend on their legislative framework and what power of enforcement the NRA has. Some NRAs may be reluctant to register or authorize a product without all information they would like to evaluate is available, because once registered or authorized, they may not have as much recourse to hold applicants to PMC, if their laws do not grant them such authority. This relative lack of authority to reverse a decision once made may be part of the reason NRAs in some countries seem to wait until products have been on the market in other countries for a while before granting authorization in their country: to ensure the maximal amount of information is available upon which to make their decision.

6.1.5 POST-MARKETING SURVEILLANCE AND PHARMACOVIGILANCE

PMS and pharmacovigilance are the shared responsibility of the manufacturer/distributor and the NRA/NCL and/or public health agencies, ministries of health, or other governmental agencies responsible for medicines and health. The manufacturer must keep files on customer complaints and should investigate them to determine if there is a problem with the product or a particular lot of that product. The complaints may come from consumers or prescribers. Public health agencies may monitor customer complaints that come to them from the public and may evaluate data from Phase 4 studies that they conduct. Complaints may come to NRAs from consumers, prescribers and other medical care professionals, parents or guardians, whistleblowers, or anyone in the general public. In the case of vaccines in the United States, both

the Centers for Disease Control and Prevention[1] (CDC) and the U.S. FDA share the responsibility of monitoring vaccine safety and capture these data passively through the Vaccine Adverse Events Reporting System (VAERS) [17]. The U.S. FDA also monitors complaints about drugs through MedWatch, a similar passive reporting system [18]. The MHRA has the Yellow Card Scheme for reporting adverse events or complaints about any medicinal products, and many European countries follow a similar format [19]. In many countries, NRAs or NCLs capture Adverse Events Following Immunizations (AEFI), particularly for vaccines provided through the UN/WHO's Expanded Programme on Immunization (EPI) [20,21].

While these reporting systems are valuable tools for identifying emerging safety issues, they are limited by several facts. These facts include: that not every event will get reported, events reported may be reported incorrectly, more serious events may be reported more often than less serious events (even though the less serious events occur more frequently), there may be over-reporting on events that have caught the public's attention, and there is "no denominator" on the data. You know how many reports there are, but you don't know how many times the product was used without incident (or with minor incident) and there was no report. However, unusual reports or increased numbers of reports for particular lots can serve to detect problems, which can be followed up by targeted activities.

6.1.6 LICENSE SUPPLEMENTS (VARIATIONS) AND ANNUAL REPORTS

Although this will be the subject of another Chapter (8), briefly, once a biological is licensed (or a drug approved), the manufacturer may wish to make changes, such as:

- Changes to the manufacturing or the dosage forms
- Changes to the facility or adding a new location
- Changes to the clinical indication, new populations, new uses
- Updated labeling based on new data acquired in Phase 4 or PMS

In order to change the labeling or to make any changes in manufacturing, the license must be supplemented for this purpose. This requires the submission of an NDA or BLA Supplement. In the E.U., this is referred to as variations, rather than supplements, entailing submission of a Marketing Authorization Variation (MAV).

Annual Reports on a product that has been licensed are also required to report on the achievement or completion of PMC, new data from Phase 4 studies or PMS, or certain types of manufacturing changes that are allowable without a Supplement (or Variation) being filed. However, changes that require a Supplement (Variation) should not be reported in this manner. The Annual Report for a licensed biological allows the manufacturer or license holder to keep NRAs updated about the product. In the United States, user fees are paid at the time of Annual Reports each year that a product remains on the market. Similarly, most countries do require fees of some type, generally at the time of filing any type of application, but also annually. Some countries will only register a product for 5 years, requiring new fees to re-register the product for an additional 5 years, and for each 5-year period after that. This is true within the E.U.

6.1.7 REVIEW TEAMS AND MANAGED REVIEW PROCESSES

Because of the sheer complexity and volume of information submitted to support the licensure of a new biological, the U.S. FDA review team is often large and always, multidisciplinary. Sometimes, on the

[1]CDC also has active monitoring activities.

order of a dozen to two dozen reviewers may be assigned (this is in contrast to an original submission of an IND, which may be assigned to 2–4 reviewers). The expertise required covers the whole range of types of information being submitted for review and evaluation [22].

Licensure is also accompanied by a facility inspection (see Chapter 9). Often, the Pre-Approval Inspection (PAI) is the first time that U.S. FDA inspectors will step into a facility that is manufacturing a new product and that has never been licensed before. Often 3–4 inspectors will go and the inspection team must evaluate compliance with Good Manufacturing Practices, as well as have product expertise represented. U.S. FDA does not generally inspect manufacturing facilities during the IND phase of development and performs a paper review only up until this point immediately preceding licensure. This is a risk-based practice, with inspections on facilities that make products that will be administered to millions of people taking precedence rather than those making a developmental product for which the process, controls, and validation remain in flux [23].

Another part of the licensure process is that samples from lots that will be marketed and sold in the United States should be submitted to the NCL (CBER in the case of many biologicals). The labs at CBER will retest the lot for certain quality attributes that are part of the lot release and upon confirming those results are consistent with the manufacturer's results, they will grant authorization to release the lot to the market. Lot release will be the subject of another Chapter (16). (So, while the product may have marketing authorization, any particular lot may not be marketed until CBER releases it.) For biologicals that have been specified, there is an exemption from lot release. Specified biologicals include products like: monoclonal antibodies, synthetic peptides of 40 amino acids or less, therapeutic DNA plasmid products, or therapeutic recombinant DNA-derived products. (Many specified biologicals are reviewed by CDER, rather than CBER.)

U.S. FDA has a specified period of time in which to accomplish their review of a BLA. The standard review process is 10 months following the 60-day filing decision date, whereas priority review is 6 months, following the 60-day filing decision date. Part of the commitments the US Congress has made in re-authorization of PDUFA is that U.S. FDA will accomplish review in those time frames on 90% of the applications submitted. So, these timelines are goals that U.S. FDA generally accomplishes. See Fig. 6.3.

At the end of the review period, the U.S. FDA must act on the application. This action may be to provide the applicant with a Complete Review (CR) letter that indicates all review has been completed, but licensure cannot be granted yet, until the applicant responds to specific FDA questions and comments. Sometimes, this means more data must be gathered and submitted for U.S. FDA review. This could include a requirement to conduct additional clinical trials. However, if sufficient information was submitted and review questions could be readily resolved during the initial review cycle, then the license will be granted. If a CR letter is issued, then the FDA review clock is stopped until the applicant responds satisfactorily and completely. When this happens, the review clock restarts, although if the amount of information provided is considered to be a major amendment to the license application, an additional 3 months are added to the review clock. In this manner, new biologicals often take more than 1 year to be licensed.

However, it is because of the Managed Review Process that timelines such as these are achieved. The Managed Review Process is a direct result of the original authorization of PDUFA. However, the timelines have been shaved with subsequent reauthorizations, as well as increasing the percentages of applications for which those timelines must be met. The Managed Review Process is the manner in which FDA oversees the process of regulatory review to assure its quality and timeliness. The Managed

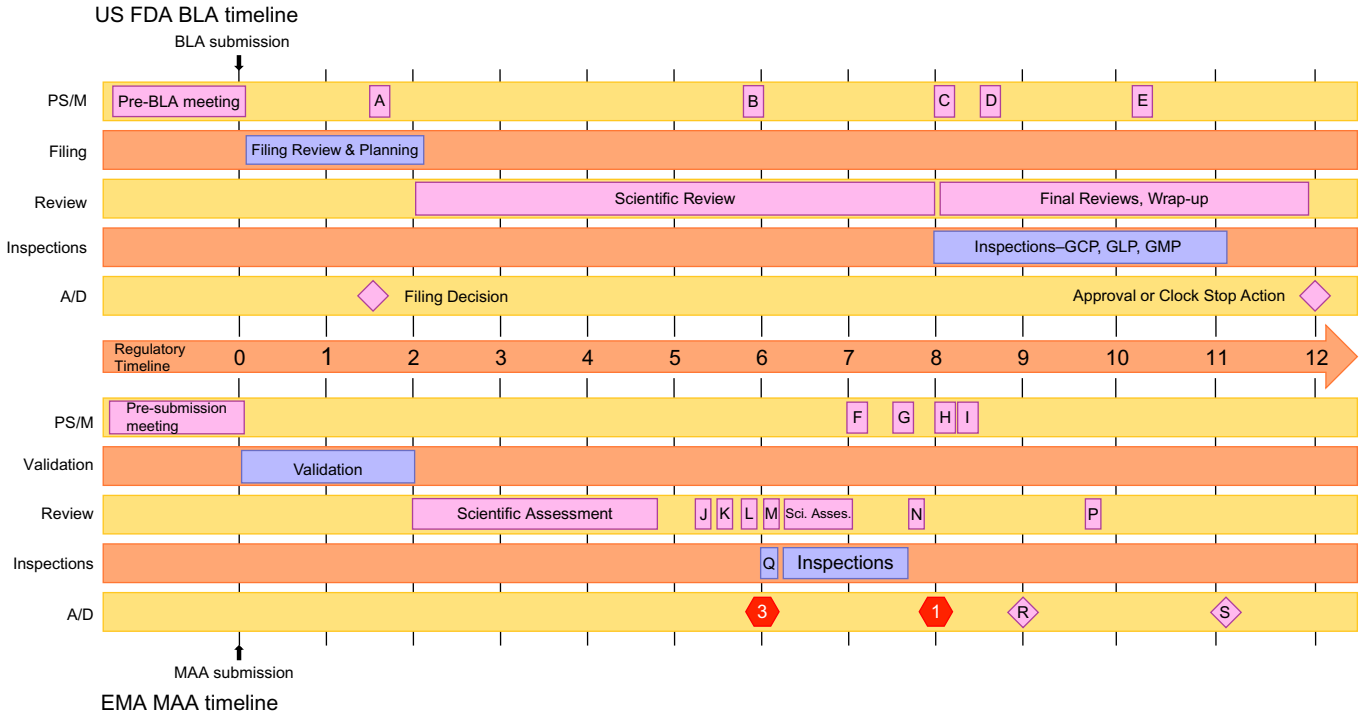


FIG. 6.3

Regulatory timelines for biologicals marketing authorization in US and EU (centralized procedure). This figure presents the *standard* timeline that the U.S. FDA or the EMA expect to meet when receiving a BLA or MAA, respectively, for review. These timelines are mandatory goals, but individual experiences may vary. The figure is separated into "swimlanes" signifying the presubmission and meeting processes (PS/M), the filing review or validation period, the scientific review processes, inspections (GCP, GLP, and/or GMP, as needed), and the actions and decisions (A/D) by the regulators. Each agency urges a meeting between the applicant and agency prior to submission and activities that would precede the actual regulatory submission (as indicated in the PS/M swimlanes). Each agency has a validation procedure that essentially starts at the time of submission but before the scientific review of the application in order to assure that the application is substantially complete and in an electronic format that permits meaningful technical review. Each agency makes a decision at the end of the validation period to accept the application for review or not. For the U.S. FDA, this is a filing decision by day 45, followed by review planning. For the EMA, this begins the period of scientific assessment by the rapporteur and co-rapporteur.

See the figure legend in next page

Review Process consists of specific activities tied to specific timelines, as well as establishing the roles and responsibilities of review team members. As an example, the first step is an administrative review, which must be completed in 60 days, to determine if the BLA is sufficiently complete to permit meaningful technical review. See Fig. 6.3 [24,25].

Many countries have similar review processes that follow specified timelines. Often, this information can be obtained from the NRA's website. For example, the EMA has a similar timeline-driven process for the regulatory review of MAAs. They also have review teams that consist of various committees and individual reviewers. Each application is assigned a Rapporteur and a Co-Rapporteur and is evaluated by the Committee for Human Medicinal Products (CHMP) and the Pharmacovigilance Risk Assessment Committee (PRAC) [1].

Day 1 is the start of the procedure, which only begins after the validation period (see Section 6.1.8). Days 80, 94, and 100 are dates for various review reports to be completed. Day 115 is when a draft list of questions from the reviewers needs to be composed. The CHMP commits to the list of questions to be sent to the Applicant by Day 120 and the review clock stops. Day 121 is the day (not the calendar day after the clock stop) when the Applicant submits the response to the list of questions and other documents required. Between Day 121 and Day 180 are several additional review steps, with Day 180 being another

FIG. 6.3, Cont'd

Once the scientific reviews are undertaken, then there is some divergence between the two processes in recognition that the U.S. FDA is a single federal agency solely responsible for the authorization, whereas EMA and the CHMP represent numerous countries of the EU all under the governance of the EC. These timelines include clock-stops (decision point by month 12 for U.S. FDA and octagonal stop signs for EMA), but not the time the applicant may take during the clock-stops. Thus, these are the timelines for the regulators. However, the EMA does indicate that the first clock-stop between days 120 and 121 normally takes 3 months (hence the 3 in the first octagon) and the clock-stop between days 180 and 181 normally takes 1 month (hence the 1 in the 2nd octagon). These months are not included in the timeline itself, as shown. Thus, the EMA process generally exceeds 12 calendar months, whereas the U.S. FDA is expected to take action (approval or clock-stop for first round reviews) within 12 calendar months from submission and within 10 calendar months as counted by PDUFA milestones (i.e., from filing at day 60). Exceptions to these rules are not shown in the figure, so an individual applicant's experience with the regulatory marketing authorization process may vary in time from the goal timelines. Priority reviews may be undertaken on shortened timelines not shown in this figure. A: Filing meeting by day 45 followed by planning review. B: Mid-cycle meeting. C: Late-cycle meeting. D: Advisory Committee meeting, if needed. E: Wrap-up meeting (final decisions made, negotiations on labeling if needed). F: EMA/QRD subgroup meeting on English-language product information (~day 165). G: CHMP discussion and day 170 comments. H: CHMP discussion for List of Outstanding Issues and/or Oral Explanations by applicant (day 180). I: Oral Explanations by applicant (if needed, day 181—clock restart after ~1 month clock-stop). J: Comments by CHMP on joint assessment from rapporteur and co-rapporteur. K: Peer Review by CHMP members of CHMP comments; Report from BWP to CHMP on Quality section. L: List of Questions to applicant (this is followed by a clock-stop that normally takes 3 months). M: Clock-restart when applicant replies and replies go to rapporteur and co-rapporteur for 30 days for further scientific assessment, joint assessment report by day 150. N: Final inspection report to CHMP; Report from BWP to CHMP on Quality section; day 170 comments from CHMP prepared. P: Decisions on final translations of product info for all member states and transmission of CHMP opinion to EC. Q: Request for inspections, if needed (day 120). R: CHMP opinion (positive or negative) by day 210. S: EC decision by day 277 followed by member states regulatory actions for valid marketing authorization.

clock stop when a list of outstanding issues to be sent to the Applicant is adopted by the CHMP, as well as the overall conclusions of the scientific review. Again, Day 181 is not the next calendar day, but the day the Applicant provides written or oral responses and the clock resumes. And then, by Day 210, the CHMP adopts a scientific opinion and scientific assessment report. If the opinion is favorable, then the EC may grant marketing authorization to the centrally reviewed biological product. So, in fact, the 210 days (plus the 60-day validation period) will take considerably more than the 9 months it appears on face value as taking, once you factor in the time it takes the applicant to respond to the initial list of questions and the list of outstanding issues. And then, the individual countries' NRAs must have time to take action on marketing authorization in their country. This process often takes more than 1 year too. See Fig. 6.3 [1].

6.1.8 FILING OR REFUSE-TO-FILE

If a sponsor submits an NDA or BLA to U.S. FDA that is grossly incomplete or does not contain the necessary data, or in the appropriate format, to facilitate the regulatory review, FDA has the option to refuse-to-file the NDA or BLA. This helps to assure that the U.S. FDA Managed Review Process is smooth and that their time and resources are not being wasted attempting to review something that is unreviewable, rather than spending their time and resources reviewing important and properly submitted applications. U.S. FDA has 60 days (45 days for fast track applications) to make the decision whether to file or refuse-to-file (RTF) a submitted NDA/BLA. The submission must be sufficiently complete to permit a meaningful review by FDA. If it is, it will be considered "filed;" if not, it will be refused to be filed. Most BLA or NDA applications (except those for Orphan Drugs) require the payment of a User Fee to FDA to perform the review. If the application is RTF'd, the sponsor loses their User Fee and has to pay it again the next time they attempt to file their application (hopefully, when it is actually complete). This is intended to dissuade sponsors from filing frivolous or premature NDAs or BLAs. [Often company officials' bonuses are tied to the timing of filing their NDA/BLA, so they may be inclined to file prematurely, thus, wasting U.S. FDA's time.] This is another reason why pre-BLA or pre-NDA meetings are so important—to assure that the sponsor is actually ready, in U.S. FDA's opinion, to submit their application [26].

The EMA has a similar process of validating an MAA once submitted to them. The initial month after submission is involved in this validation process. Once validated, an MAA is processed further (assigning rapporteurs, etc.), but if the MAA is substantively incomplete in some manner (e.g., missing clinical data), the MAA may be declined or what they refer to as negative validation [27]. In fact, there are four scenarios for the validation process: the application may be deemed to be valid the first time with no request for additional supplementary information, only can be deemed valid after supplementary information is requested and provided during the validation timeline, not able to be deemed valid and validation is suspended (because the additional supplementary information requested cannot be provided in the validation timeline), or negatively validated (i.e., invalid) and declined. This last category is akin to the U.S. FDA's RTF. The EMA also strongly encourages applicants request a presubmission meeting to be sure that the EMA and the applicant are in accord with regards to whether or not the application is ready to be filed, or to identify what gaps need to be filled. It is particularly important with the EMA for an applicant to request this presubmission meeting, because the EMA may not have been involved in the clinical trial process. Although the EMA will provide protocol assistance upon request (and remittance of fees), they do not approve or authorize clinical trials. So, because they may not have had input into the clinical development of a product, they may well expect a different data package than other regulators may have requested. Thus, it is crucial to find this out before submission of the MAA.

Many NRAs, in fact, will initially do an administrative review to ensure that the application submitted to them is complete before they begin their technical review. Many NRAs also have application fees. Often, these fees are forfeited if the application is not deemed reviewable due to incompleteness.

Other NRAs may not have a process for refusing to review an application that has been submitted, but the outcome of the review may be some type of rejection and substantial numbers of substantive criticisms and additional requirements, with concomitant loss of time after the application is submitted and before it is ultimately granted marketing authorization (if ever). It is always a good idea to request a meeting with the relevant NRA prior to submitting any application, in order to ensure that the applicant understands the NRA's expectations and requirements. Many applicants are reluctant to do this, because it adds to the timeline for submissions, but that attitude is often one of being "penny-wise, pound-foolish." Saving time in the short run often leads to huge losses of time in the long run. To put it in "company" terms—which is better to do the fastest: to be able to tell your stockholders (or your CEO) that you filed an application or to start selling the product and making money for the company? The sooner you file doesn't necessarily equate to the sooner you sell.

6.1.9 PUBLIC TRANSPARENCY OF SCIENTIFIC OPINION OR LICENSURE DECISION

At the end of the licensure/registration process, an NRA will render their decision to authorize marketing or not. To provide for public transparency of the decision-making of national agencies beholden to the public they protect, often there are documents prepared to be posted on agency websites or otherwise publicly obtainable. Herein will be described briefly such documents from the U.S. and from the EMA.

The U.S. FDA prepares a compilation of documents for posting on their website documenting their review and decision-making process, in addition to posting the agreed-to package insert and the approval letter. U.S. FDA posts something referred to as the summary basis for regulatory action (formerly known as the summary basis of approval). The summary basis for regulatory action provides reviews of key review team members (though parts may be redacted due to the company confidential information contained) and is generally written by the Chair of the review committee, compiling the reviews into this summary. This document explains what data were available for review and why decisions were made on the basis of the reviewed information. This document also lists the review team members. Transcripts and sometimes, briefing packets and meeting summaries for public Advisory Committee meetings where products pending licensure were discussed are also posted on the U.S. FDA's website.

EMA also prepares a number of documents posted on their website to provide transparency into their review decisions too. One such compilation of documents is the European Public Assessment Report (EPAR). The EPARs provide authorization details, product information, and an assessment history for the product. Another document is the Summary of Product Characteristics (SmPC), from which package leaflets are prepared. Meeting summaries are also posted on the EMA website.

6.2 SOME DETAILS

6.2.1 RECALLS OR MARKET WITHDRAWALS

Most NRAs have some authority to recall products off their market if problems occur. Often, the recall may involve certain product lots or products made during a certain time frame when some problem,

discovered later, is found. An example might be the discovery of visible impurities (e.g., metal, broken glass, any other material that should not be present) in several containers within a lot (e.g., vials containing liquid), once consumers or pharmacies receive the containers. Another example might be that a lot prematurely expires (as found on real-time stability testing of that lot), because the lot has lost potency or for some other reason is expired before the label expiry. Such lots should not be used past the current date despite the expiry with which the container was originally labeled. A final and quite serious example is when a product has been placed into containers labeled with the labels from a different product and this lot has been distributed before the mislabeling is discovered, because this could result in the wrong medicine being taken or administered instead of the medically indicated product, which could result in severe consequences [28].

Recalls can be voluntary. With regards to U.S. FDA's authority, recalls may be initiated by the license holder themselves or at U.S. FDA's request. Or they can be enforced by U.S. FDA. These recalls have classifications depending on severity of the health hazard associated with the problem, with Class I being the most severe and Class III being the least. Market withdrawal is the classification in which the hazard is so minor that the U.S. FDA would not take a legal action against the company, or for example, the company found evidence of tampering, but without evidence of manufacturing or distribution problems on their part.

The EMA also has a process they call batch recall for quality defects and a classification system, in which specific defects are categorized as Class 1 to 3, in decreasing severity as with U.S. FDA's system. However, many products on the market in Europe will go through processes in individual member states, rather than the centralized (EMA) process. EMA is to be notified when a product upon which EMA rendered an opinion that resulted in gaining marketing authorization in member states, if a member state recalls lots (batches) of that product, or whenever they receive a warning letter from a non-European country (country not within the European Economic Area—EEA) [29].

6.2.2 LICENSE REVOCATION OR SUSPENSION

Most NRAs have both the authority to grant a license and to revoke it. Some licenses are only granted for a period of time, typically 5 years. When U.S. FDA licenses a biological, it remains licensed, as long as the annual fees are paid, until either the applicant requests that the license be revoked (so they no longer have to pay the fees for a product they are no longer marketing) or because the U.S. FDA has found cause to revoke the license. Generally, if the revocation is being initiated by the NRA, the license holder will have some recourse to protest the revocation prior to it being done. But, ultimately, the NRA will have the authority to remove products from the market, if medically or scientifically justified [30].

Sometimes, a license might be suspended by U.S. FDA until certain issues have been addressed, e.g., issues that arise due to a facility inspection that uncovers violations against GMP or other illegal activities. There is a process for this as well—to give the license holder an opportunity to respond to the suspension order. Suspensions can last indefinitely until the problems have been resolved [30]. Further legal actions can be taken, including implementation of a Consent Decree, during which U.S. FDA may require that some products made in a facility not be marketed, distributed, or sold, until the conditions are met. It can take years to resolve these issues of noncompliance [31].

6.2.3 RISK MANAGEMENT PLANS OR RISK MINIMIZATION ACTION PLANS

The ICH recommends applicants submit a Risk Management Plan (RMP) when seeking marketing authorization and regulators have begun to require or expect this. This concept emerged as part of the Quality by Design (QbD) approach to product development in which risk assessments are key and pivotal to success [10]. Risk assessments will be discussed in Chapter 14. EMA provides summaries of Risk Management Plans to the public. The expectation is that Risk Management Plans are regularly updated as more information becomes available to inform the risk assessment and hence planning to mitigate risks. The Risk Management Plans actually impact and are provided for explaining the plans for pharmacovigilance—which occurs after the product gains marketing authorization and is in the marketplace. U.S. FDA refers to this as Risk Minimization Action Plans (RiskMAPs). These are discussed further in Chapter 17 in Section 17.2.18.

6.2.4 PHARMACOVIGILANCE

The public may imagine that once marketing authorization is granted, everything there is to know about a product's safety and effectiveness is known. In reality, only so much can be learned in the controlled setting of clinical trials, and much more will be learned once a product is on the market and being used under real-world conditions. This post-marketing phase of "development" or gaining data and product understanding continues for the entire life-cycle of the product. The difficulty though is collecting such data without the confines of a randomized, controlled clinical trial (see Chapter 17 for discussion of an RCT). The interpretation of the data outside this credible and reliable method of data collection is challenging, yet the majority of data on a product will ultimately be obtained this way (for products that remain on the market for many years). Pharmacovigilance begins from the moment of marketing authorization and a system for collecting these data needs to be in place before marketing authorization is granted, so that the license holder is ready to collect data from the moment the product goes on the market in any country [2].

In fact, in recent years, as the U.S. FDA has rushed to get new drugs available and accessible for patients in dire need, the number of products with black box warnings and the number of products that have been removed from the market after marketing authorization was granted has increased substantially. Around 20 drugs were removed from the market in the United States in the 2000s following marketing authorization [32]. This has resulted in a shift toward increased scrutiny on drug safety within the agency and an increased precautionary attitude of reviewers. Most of these were chemical drugs and not biologicals, for which perhaps a precautionary attitude has always been more pervasive. Nonetheless, the need to monitor medicine safety (and continued effectiveness) in the post-marketing period has drawn considerable attention worldwide in the past decade or so.

The ICH provides guidelines on pharmacovigilance in the E2 series with E2C being about the PBRERs, E2D about post-market safety data management including about expedited reporting, and E2E about pharmacovigilance planning [2]. The other E2 documents deal with clinical trial safety data collection and reporting, but these three documents focus on post-marketing pharmacovigilance. The frequency of reporting likely differs by country and by product, but annual, every other year, or twice yearly reporting are most common. Importantly, data should be collected globally from all countries where the product is marketed, even though there may be demographic differences in safety and effectiveness. Especially for products that may have an orphan indication in any given country, combining the data from all countries in which the product is marketed may permit more meaningful data evaluation.

The EMA requires submission of a Pharmacovigilance System Master File (PSMF) and has specific requires for a responsible party to be identified and maintenance of records. They provide Guidelines on Good Pharmacovigilance Practices (GVP) in modules, including modules on the system itself and its quality assurance, the PSMF, inspections, audits, risk management systems, reporting and management of adverse events, PBRERs, Post-Authorisation Safety Studies, signal management, additional monitoring requirements, public participation, safety-related actions, international cooperation, safety communication, and risk minimization. In addition, there are product-specific guidelines on vaccines, biological medicinal products, and advanced medical therapy products (which includes gene therapies and cell therapies). A guideline specific to the pediatric population is also available. All of these guideline modules can be obtained from the EMA website [33].

The U.S. FDA also provides a guidance document on the subject of good pharmacovigilance practices [34].

Most countries will expect some sort of reporting on post-marketing data on the continued safety and effectiveness of the product on their market by the registration holder or the procurement agency that supplies medicinal products to the public (in the case that a product is not directly marketed in the country, but available through a procurement agency). In addition, most countries take the role of pharmacovigilance as part of the responsibilities of the NRA or the Ministry of Health (MOH). The public (consumers) is also expected to play a role, as are the healthcare practitioners, who should report adverse events to the NRA or MOH. More information may be obtained in Section 17.2.17.

6.3 CASE STUDIES

6.3.1 TIMELINES TO APPROVAL COMPARING U.S. FDA AND EMA

Marc Beishon wrote an interesting comparative article on the approval processes of the U.S. FDA and EMA [35]. Although the article focuses on a particular class of anti-oncotics, which are all small molecules, rather than biologicals, the discussion and concepts in the article are thought-provoking about the medicine approval process in two major regulatory regions. While there are sometimes disagreements between the regulators, most differences seem to be more procedural than scientific. The fact that the EMA is an organization representing numerous countries, all of which have differing regulatory legacies, different "political" sensitivities and realities, and different experiences—it should not be surprising that this multicountry collaborative process takes longer.

The discussion by the author about transparency and trust is an important one. One needs to remember that the decisions are made by specific humans involved in the regulatory review, and all humans have fallibilities. Transparency in decision-making can aid in identifying poor decisions and rectifying them quickly. But, more importantly, explaining the complicated and challenging decision-making process that regulators must undertake can bolster public trust in these governmental institutions at a time when most governments and government agencies are not trusted by the public. If you hear a television commercial telling you that something is FDA-approved, the marketer includes that in the advertising because they know that the United States public by-and-large still trusts and values the U.S. FDA and their opinions and decisions. Part of this is because of the public hearings that their advisory committee meetings afford. The public has a voice in the process.

EMA also holds public hearings and publishes on their website the agendas and meeting summaries of their committee meetings. They too engage in transparency to build public trust in the regulatory process.

It is challenging to convey science-based decisions to a lay audience, but to the extent feasible—i.e., without disclosing company-confidential information—many regulatory agencies do engage the public in their decision-making process and consider the public's concerns when deciding. Many agencies publish information about approved medicines on their websites and some publish their review documents and meeting summaries. However, regulatory harmonization is still a challenge and medicines will continue to become available in some regions before others due to relative lack of regulatory convergence. This can be for a number of reasons including differing process and timelines, differing legal frameworks, differing scientific opinion and understanding, available expertise and relative confidence in decisions, and no doubt, a number of other factors that have nothing to do with the medicine itself. Part of the role of the WHO is to try to reduce these factors to reach as much regulatory convergence as is feasible so that medicines become available to the public in whichever country in the world, not just the developed countries first with a long-lag for the developing world (low- and middle-income countries). Emerging markets may push these issues farther faster, as they wish to compete with the large markets.

6.3.2 DRUG WITHDRAWALS

Appendix G of the U.S. FDA's Report on "Managing the Risks from Medical Product Use: Creating a Risk Management Framework" [36] contains several examples of market withdrawals for blood products, three specific drugs, and a medical device. While these examples do not include any biotechnology products or vaccines, the cases nonetheless bear review.

The case of Xigris is also an interesting one in which the risk/benefit seemingly changed over time post-authorization with improving standard-of-care. Thus, benefit that had been seen supporting initial licensure/authorization was not re-confirmed in a study undertaken a decade later for continued market authorization in Europe. Essentially, it was speculated that benefit was greatly reduced due to advances in standard-of-care, so while the safety was unchanged, the benefit no longer outweighed risk [37–39]. Interestingly, it would seem that the general impression of physicians and statisticians is that despite the trial results, the risk/benefit remains favorable. Several reviews, which can be found through PubMed, suggest that the fault was not with the product but with the trial design. Even though on the face of it, the follow-up trial was designed the same as the original trial, there were nuances in the analyses, it would seem, that made the studies incomparable.

6.4 CONCLUSIONS

Marketing authorization is required in most countries in order to lawfully market a medicinal product in that country. The process of gaining marketing authorization will vary from country to country and even the term given to the granting of marketing authorization varies (e.g., approval, licensure, registration, clearance). However, the procedures for marketing authorization are more harmonized internationally than are those for clinical trial approval. The ICH provides a Common Technical Document (CTD) format to align the regulatory submission requirements among the United States, Japan, and the E.U., as well as several other countries that have adopted the ICH guidelines, e.g., Canada and Switzerland. Within Asia, for those countries that are part of the Association of South East Asian Nations (ASEAN), there is also an ASEAN CTD format for submissions, as well as significant mutual recognition agreements that permit streamlining the registration process further.

Once on the market, the holder of the marketing authorization continues to have responsibilities, such as pharmacovigilance activities, to continue to monitor the safety and effectiveness of their mar-

keted product. Any changes to the product after the initial marketing authorization also need to be submitted to gain authorization to make such changes, and these are described further in Chapter 8. Facility inspections of the manufacturing site(s) where the product under review for marketing authorization takes place near the time of authorization and subsequently on a periodic basis (this will be described further in Chapter 9). Product labeling is also reviewed near the time of authorization and thereafter, whenever changes are made.

This chapter covers the aspects of the procedures for granting marketing authorization. In addition to those mentioned already above, the review processes themselves within the U.S. FDA and EMA were described, including the process of validating the application (EMA) or filing or refusing to the file the application (U.S. FDA). Once on the market, products may be recalled, withdrawn, or suspended from the market if anything untoward happens or is discovered during the post-marketing period. Medicinal products continue to be regulated after they are developed and once they have gained marketing authorization in order to assure consumers of the quality, safety, and effectiveness of the medicines they use.

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