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ROLE OF POST APPROVAL CLINICAL TRIALS FOR DRUG SAFETY

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Abstract:

MHRA (Medicines And Health Products Regulatory Agency) is the regulatory authority body for pharmaceuticals approval in the UK union. MHRA is formed by the merging of two separate agencies in 2003 i.e., Medicines Control Agency and Medical Device Agency. This agency works to maintain safety, quality and ef□cacy of the drug product before it enters into the country. The main aim of this work is to know about the practice and the regulatory requirements for the registration of a drug in the UK as per the regulations of MHRA. They are responsible for ensuring that the medicines and medical devices are acceptably safe and don't cause any harm to the patients. MHRA provides a license which is a marketing authorization to the manufacturer, required before a drug is being used by the patients of that country. Good Manufacturing Practice (GMP) is the minimum requirement that a manufacturer should possess during the period of production of the drug product. New drugs are being invented and also being distributed as per the needs of the patients. It is known that no drug product is completely safe or is 100% safe for use, but MHRA tries to minimize as many problems regarding the drug so that patients will be provided with the best drug with minimal risk.

Key words: MHRA, United Kingdom, Product license, eCT

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INTRODUCTION:

Clinical trials are experiments done in clinical research. Such prospective biomedical or behavioral research studies onhuman participants are designed to answer specific questions about biomedical or behavioral interventions, including newtreatments (such as novel vaccines, drugs, dietary choices, dietary supplements, and medical devices) and known interventions that warrant further study and comparison. Clinical trials generate data on safety and efficacy. They are conducted only after they have received health authority/ethics committee approval in the country where approval of the therapy is sought. These authorities are responsible for vetting the risk/benefit ratio of the trial - their approval does not mean that the therapy is 'safe' or effective, only that the trial may be conducted.

Depending on product type and development stage, investigators initially enroll volunteers and/or patients into small pilot studies, and subsequently conduct progressively larger scale comparative studies. Clinical trials can vary in size and cost, and they can involve a single research center or multiple centers, in one country or in multiple countries. Clinical study design aims to ensure the scientific validity and reproducibility of the results.

Trials can be quite costly, depending on a number of factors. The sponsor may be a governmental organization or a pharmaceutical, biotechnology or medical device company. Certain functions necessary to the trial, such as monitoring and lab work, may be managed by an outsourced partner, such as a contract research organization or a central laboratory.

Only 10% of all drugs started in human clinical trials become an approved drug.

Trials of drugs

Some clinical trials involve healthy subjects with no pre-existing medical conditions. Other clinical trials pertain to patients with specific health conditions who are willing to try an experimental treatment.

When participants are healthy volunteers who receive financial incentives, the goals are different than when the participants are sick. During dosing periods, study subjects typically remain under supervision for one to 40 nights.

Usually pilot experiments are conducted to gain insights for design of the clinical trial to follow.

There are two goals to testing medical treatments: to learn whether they work well enough, called "efficacy" or "effectiveness"; and to learn whether they are safe enough, called "safety". Neither is an absolute criterion; both safety and efficacy are evaluated relative to how the treatment is intended to be used, what other treatments are available, and the severity of the disease or condition. The benefits must outweigh the risks. For example, many drugs to treat cancer have severe side effects that would not be acceptable for an over-the-counter pain medication, yet the cancer drugs have been approved since they are used under a physician's care, and are used for a life-threatening condition.

In the US, the elderly constitute only 14% of the population, while they consume over one-third of drugs. People over 55 (or a similar cutoff age) are often excluded from trials because their greater health issues and drug use complicate data interpretation, and because they have different physiological capacity than younger people. Women, children and people with unrelated medical conditions are also frequently excluded. For women, a major reason for exclusion is the possibility of pregnancy and the unknown risks to the fetus.

The sponsor designs the trial in coordination with a panel of expert clinical investigators, including what alternative/existing treatments to compare to the new drug and what type(s) of patients might benefit. If the sponsor cannot obtain enough subjects at one location, investigators at other locations are recruited to join the study.

During the trial, investigators recruit patients with the predetermined characteristics, administer the treatment(s) and collect data on the patients' health for a defined time period.

Subjects are volunteers who are not paid for participating. (However, the investigators are paid.)

Data include measurements such as vital signs, concentration of the study drug in the blood and/or tissues, changes to symptoms and whether health outcomes. The researchers send the data to the trial sponsor, who then analyzes the pooled data using statistical tests.

Examples of clinical trial goals include assessing the safety and (relative) effectiveness of a medication or device:

- On a specific kind of patient (e.g., patients who have been diagnosed with Alzheimer's disease)
- At a different dose (e.g., 10-mg dose instead of 5-mg dose)
- For a new indication

- Is more effective for the patient's condition than the standard therapy
- Relative to two or more already approved/common interventions for that disease (e.g., device A vs. device B, therapy A vs. therapy B)

While most clinical trials test one alternative to the novel intervention, some expand to three or four.

Except for small, single-location trials, the design and objectives are specified in a document called a clinical trial protocol. The protocol is the trial's 'operating manual' and ensures that all researchers perform the trial in the same way on similar patients and that the data is comparable across all patients.

Because a trial is designed to test hypotheses and rigorously monitor and assess outcomes, it can be seen as an application of the scientific method, specifically the experimental step.

The most common clinical trials evaluate new drugs, medical devices (such as a new catheter), biologics, psychological therapies, or other interventions. Clinical trials may be required before a national regulatory authority approves marketing of the innovation.

Types

One way of classifying clinical trials is by the way the researchers behave.

- In a clinical observational study, the investigators observe the subjects and measure their outcomes. The researchers do not actively manage the study.
- In an interventional study, the investigators give the research subjects a particular medicine or other intervention. Usually, they compare the treated subjects to subjects who receive no treatment or standard treatment. Then the researchers measure how the subjects' health changes.

Another way of classifying trials is by their purpose. The U.S. National Institutes of Health (NIH) organizes trials into five different types:

- Prevention trials look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vitamins, vaccines, minerals, or lifestyle changes.
- Screening trials test the best way to detect certain diseases or health conditions.
- Diagnostic trials are conducted to find better tests or procedures for diagnosing a particular disease or condition.
- Treatment trials test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.
- Quality of life trials (supportive care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.
- Compassionate use trials or expanded access trials provide partially tested, unapproved therapeutics to a small number of patients who have no other realistic options. Usually, this involves a disease for which no effective therapy has been approved, or a patient who has already failed all standard treatments and whose health is too compromised to qualify for participation in randomized clinical trials. Usually, case-by-case approval must be granted by both the United States Food and Drug Administration and the pharmaceutical company for such exceptions.

A third classification is whether the trial design allows changes based on data accumulated during the trial.

- Fixed trials consider existing data only during the trial's design, do not modify the trial after it begins and do not assess the results until the study is complete.
- Adaptive clinical trials use existing data to design the trial, and then use interim results to modify the trial as it proceeds. Modifications include dosage, sample size, drug undergoing trial, patient selection criteria and "cocktail" mix. Adaptive trials often employ a Bayesian experimental design to assess the trial's progress. In some cases, trials have become an ongoing process that regularly adds and drops therapies and patient groups as more information is gained. The aim is to more quickly identify drugs that have a therapeutic effect and to zero in on patient populations for whom the drug is appropriate.

Finally, a common way of distinguishing trials is by phase, which in simple terms, relates to how close the drug is to being clinically proven both effective for its stated purpose and accepted by the regulatory authorities for use for that purpose.

Phases

Clinical trials involving new drugs are commonly classified into five phases. Each phase of the drug approval process is treated as a separate clinical trial. The drug-development process will normally proceed

through all four phases over many years. If the drug successfully passes through phases 0, 1, 2, and 3, it will usually be approved by the national regulatory authority for use in the general population. Before pharmaceutical companies start clinical trials on a drug, they will also have conducted extensive preclinical studies. Each phase has a different purpose and helps scientists answer a different question.

Phase	Aim	Notes
Phase 0	Pharmacodynamicsand pharmacokineticsin humans	Phase 0 trials are the first-in-human trials. Single subtherapeutic doses of the study drug or treatment are given to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacodynamics (what the drug does to the body) and pharmacokinetics (what the body does to the drugs).[30] For a test drug, the trial documents the absorption, distribution, metabolization, and removal (excretion) of the drug, and the drug's interactions within the body, to confirm that these appear to be as expected.
Phase 1	Screening for safety.	Testing within a small group of people (20–80) to evaluate safety, determine safe dosage ranges, and begin to identify side effects. A drug's side effects could be subtle or long term, or may only happen with a few people, so phase 1 trials are not expected to identify all side effects.
Phase 2	Establishing the efficacy of the drug, usually against a placebo.	Testing with a larger group of people (100–300) to see if it is effective and to further evaluate its safety. The gradual increase in test group size allows less-common side effects to be progressively sought.
Phase 3	Final confirmation of safety and efficacy.	Testing with large groups of people (1,000–3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow it to be used safely.
Phase 4	Safety studies during sales.	Postmarketing studies delineate additional information, including the treatment's risks, benefits, and optimal use. As such, they are ongoing during the drug's lifetime of active medical use. (Particularly relevant after approval under FDA Accelerated Approval Program)

Trial design

A fundamental distinction in evidence-based practice is between observational studies and randomized controlled trials. Types of observational studies in epidemiology, such as the cohort study and the case-control study, provide less compelling evidence than the randomized controlled trial. In observational studies, the investigators only observe associations (correlations) between the treatments experienced by participants and their health status. However, under certain conditions, causal effects can be inferred from observational studies.

A randomized controlled trial can provide compelling evidence that the study treatment causes an effect on human health.

Currently, some phase 2 and most phase 3 drug trials are designed as randomized, double-blind, and placebo-controlled.

- Randomized: Each study subject is randomly assigned to receive either the study treatment or a placebo.
- Blind: The subjects involved in the study do not know which study treatment they receive. If the study is double-blind, the researchers also do not know which treatment a subject receives. This intent is to prevent researchers from treating the two groups differently. A form of double-blind study called a "double-dummy" design allows additional insurance against bias. In this kind of study, all patients are given both placebo and active doses in alternating periods.
- Placebo-controlled: The use of a placebo (fake treatment) allows the researchers to isolate the effect of the study treatment from the placebo effect.

Although the term "clinical trials" is most commonly associated with the large, randomized studies typical of phase 3, many clinical trials are small. They may be "sponsored" by single researchers or a small group of researchers, and are designed to test simple questions. In the field of rare diseases, sometimes the number of patients is the limiting factor for the size of a clinical trial[1].

Phases of clinical research

The **phases of clinical research** are the steps in which scientists do experiments with a health intervention in an attempt to find enough evidence for a process which would be useful as a medical treatment. In the case of pharmaceutical study, the phases start with drug design and drug discovery, go on to animal testing, then start by testing in only a few human subjects and expand to test in many study participants if the trial seems safe and useful

Phases

Clinical trials involving new drugs are commonly classified into four phases. Clinical trials of drugs may not fit into a single phase. For example, some may blend from phase I to phase II or from phase II to phase III. Therefore, it may be easier to think of early phase studies and late phase studies. The drug-development process will normally proceed through all four phases over many years. If the drug successfully passes through Phases I, II, and III, it will usually be approved by the national regulatory authority for use in the general population. Phase IV are 'post-approval' studies.

Summary of clinical trial phases

Phase	Primary goal	Dose	Patient monitor	Typical number of participants	Notes
Preclinical	Testing of drug in non-human subjects, to gatherefficacy, toxicity a ndpharmacokinetic information	unrestricted	A graduate level researcher (Ph.D.)	not applicable (*in vitro* and *in vivo* only)	
Phase 0	Pharmacodynamics and Pharmacokinetics particularly oral bioavailability and half-life of the drug	very small, subtherapeutic	clinical researcher	10 people	often skipped for phase I
Phase I	Testing of drug on healthy volunteers for dose-ranging	often subtherapeutic, but with ascending doses	clinical researcher	20-100	determines whether drug is safe to check for efficacy
Phase II	Testing of drug on patients to assess	therapeutic dose	clinical researcher	100-300	determines whether drug can have any efficacy; at this point, the drug is not

	efficacy and safety				presumed to have any therapeutic effect whatsoever
Phase III	Testing of drug on patients to assess efficacy, effectiveness and safety	therapeutic dose	clinical researcher and personal physician	1000-2000	determines a drug's therapeutic effect; at this point, the drug is presumed to have some effect
Phase IV	Postmarketing surveillance– watching drug use in public	therapeutic dose	personal physician	anyone seeking treatment from their physician	watch drug's long-term effects

Pre-clinical studies

Before pharmaceutical companies start clinical trials on a drug, they conduct extensive pre-clinical studies. These involve in vitro (test tube or cell culture) and in vivo (animal) experiments using wide-ranging doses of the study drug to obtain preliminary efficacy, toxicity and pharmacokinetic in formation. Such tests assist pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug.

Phase 0

Phase 0 is a recent designation for exploratory, first-in-human trials conducted in accordance with the United States Food and Drug Administration's (FDA) 2006 Guidance on Exploratory Investigational New Drug (IND) Studies. Phase 0 trials are also known as human microdosing studies and are designed to speed up the development of promising drugs or imaging agents by establishing very early on whether the drug or agent behaves in human subjects as was expected from preclinical studies. Distinctive features of Phase 0 trials include the administration of single subtherapeutic doses of the study drug to a small number of subjects (10 to 15) to gather preliminary data on the agent's pharmacokinetics (what the body does to the drugs).

A Phase 0 study gives no data on safety or efficacy, being by definition a dose too low to cause any therapeutic effect. Drug development companies carry out Phase 0 studies to rank drug candidates in order to decide which has the best pharmacokinetic parameters in humans to take forward into further development. They enable go/no-go decisions to be based on relevant human models instead of relying on sometimes inconsistent animal data.

Phase I

Phase I trials are the first stage of testing in human subjects. Normally, a small group of 20–100 healthy volunteers will be recruited. This phase is designed to assess the safety (pharmacovigilance), tolerability, pharmacokinetics, and pharmacodynamics of a drug. These trials are often conducted in a clinical trial clinic, where the subject can be observed by full-time staff. These clinical trial clinics are often run by contract research organization (CROs) who conduct these studies on behalf of pharmaceutical companies or other research investigators. The subject who receives the drug is usually observed until several half-lives of the drug have passed. Phase I trials also normally include dose-ranging, also called dose escalation studies, so that the best and safest dose can be found and to discover the point at which a compound is too poisonous to administer. The tested range of doses will usually be a fractionof the dose that caused harm in animal testing. Phase I trials most often include healthy volunteers. However, there are some circumstances when real patients are used, such as patients who have terminal cancer or HIV and the treatment is likely to make healthy individuals ill. These studies are usually conducted in tightly controlled clinics called CPUs (Central Pharmacological Units), where participants receive 24-hour medical attention and oversight. In addition to the previously mentioned unhealthy individuals, “patients who have typically already tried and failed to improve on the existing standard therapies" may also participate in phase I trials. Volunteers are paid an inconvenience fee for their time spent in the volunteer centre. Pay depends on length of participation.

There are different kinds of phase I trial:

Single ascending dose (Phase Ia)

In single ascending dose studies, small groups of subjects are given a single dose of the drug while

they are observed and tested for a period of time to confirm safety. Typically, a small number of participants, usually three, are entered sequentially at a particular dose. If they do not exhibit any adverse side effects, and the pharmacokinetic data are roughly in line with predicted safe values, the dose is escalated, and a new group of subjects is then given a higher dose. If unacceptable toxicity is observed in any of the three participants, an additional number of participants, usually three, are treated at the same dose. This is continued until pre-calculated pharmacokinetic safety levels are reached, or intolerable side effects start showing up (at which point the drug is said to have reached the maximum tolerated dose(MTD)). If an additional unacceptable toxicity is observed, then the dose escalation is terminated and that dose, or perhaps the previous dose, is declared to be the maximally tolerated dose. This particular design assumes that the maximally tolerated dose occurs when approximately one-third of the participants experience unacceptable toxicity. Variations of this design exist, but most are similar.

Multiple ascending dose (Phase Ib)

Multiple ascending dose studies investigate the pharmacokinetics and pharmacodynamics of multiple doses of the drug, looking at safety and tolerability. In these studies, a group of patients receives multiple low doses of the drug, while samples (of blood, and other fluids) are collected at various time points and analyzed to acquire information on how the drug is processed within the body. The dose is subsequently escalated for further groups, up to a predetermined level.

Food effect

A short trial designed to investigate any differences in absorption of the drug by the body, caused by eating before the drug is given. These studies are usually run as a crossover study, with volunteers being given two identical doses of the drug while fasted, and after being fed.

Phase II

Once a dose or range of doses is determined, the next goal is to evaluate whether the drug has any biological activity or effect. Phase II trials are performed on larger groups (100-300) and are designed to assess how well the drug works, as well as to continue Phase I safety assessments in a larger group of volunteers and patients. Genetic testing is common, particularly when there is evidence of variation in metabolic rate. When the development process for a new drug fails, this usually occurs during Phase II trials when the drug is discovered not to work as planned, or to have toxic effects.

Phase II studies are sometimes divided into Phase IIA and Phase IIB.

- Phase IIA is specifically designed to assess dosing requirements (how much drug should be given).
- Phase IIB is specifically designed to study efficacy (how well the drug works at the prescribed dose(s)).

Some trials combine Phase I and Phase II, and test both efficacy and toxicity.

Trial design

Some Phase II trials are designed as case series, demonstrating a drug's safety and activity in a selected group of patients. Other Phase II trials are designed as randomized controlled trials, where some patients receive the drug/device and others receive placebo/standard treatment. Randomized Phase II trials have far fewer patients than randomized Phase III trials.

Example Cancer Design

In the first stage, the investigator attempts to rule out drugs which have no or little biologic activity. For example, he may specify that a drug must have some minimal level of activity, say, in 20% of participants. If the estimated activity level is less than 20%, he chooses not to consider this drug further, at least not at that maximally tolerated dose. If the estimated activity level exceeds 20%, he will add more participants to get a better estimate of the response rate. A typical study for ruling out a 20% or lower response rate enters 14 participants. If no response is observed in the first 14 participants, the drug is considered not likely to have a 20% or higher activity level. The number of additional participants added depends on the degree of precision desired, but ranges from 10 to 20. Thus, a typical cancer phase II study might include fewer than 30 people to estimate the response rate.

Efficacy vs Effectiveness

When a study assesses efficacy, it is looking at whether the drug given in the specific manner described in the study is able to influence an outcome of interest (e.g. tumor size) in the chosen population (e.g. cancer patients with no other ongoing diseases). When a study is assessing effectiveness, it is determining whether a treatment will influence the disease. In an effectiveness study it is essential that patients are treated as they would be when the treatment is prescribed in actual practice. That would mean that there should be no aspects of the study designed to increase patient compliance above those that would occur in routine clinical practice. The outcomes in effectiveness studies are also more generally applicable than in most efficacy studies (for

example does the patient feel better, come to the hospital less or live longer in effectiveness studies as opposed to better test scores or lower cell counts in efficacy studies). There is usually less rigid control of the type of patient to be included in effectiveness studies than in efficacy studies, as theresearchers are interested in whether the drug will have a broad effect in the population of patients with the disease.

Some researchers argue that phase II studies are generally smaller than they ought to be.

Success rate

The percentage of Phase II trials that proceed to Phase III, as of 2008, is 18%.

Phase III

This phase is designed to assess the effectiveness of the new intervention and, thereby, its value in clinical practice. Phase III studies are randomized controlled multicenter trials on large patient groups (300–3,000 or more depending upon the disease/medical condition studied) and are aimed at being the definitive assessment of how effective the drug is, in comparison with current 'gold standard' treatment. Because of their size and comparatively long duration, Phase III trials are the most expensive, time-consuming and difficult trials to design and run, especially in therapies for chronic medical conditions. Phase III trials of chronic conditions or diseases often have a short follow-up period for evaluation, relative to the period of time the intervention might be used in practice. This is sometimes called the "pre-marketing phase" because it actually measures consumer response to the drug.

It is common practice that certain Phase III trials will continue while the regulatory submission is pending at the appropriate regulatory agency. This allows patients to continue to receive possibly lifesaving drugs until the drug can be obtained by purchase. Other reasons for performing trials at this stage include attempts by the sponsor at "label expansion" (to show the drug works for additional types of patients/diseases beyond the original use for which the drug was approved for marketing), to obtain additional safety data, or to support marketing claims for the drug. Studies in this phase are by some companies categorized as "Phase IIIB studies."

While not required in all cases, it is typically expected that there be at least two successful Phase III trials, demonstrating a drug's safety and efficacy, in order to obtain approval from the appropriate regulatory agencies such as FDA (USA), or theEMA (European Union),

Once a drug has proved satisfactory after Phase III trials, the trial results are usually combined into a large document containing a comprehensive description of the methods and results of human and animal studies, manufacturing procedures, formulation details, and shelf life. This collection of information makes up the "regulatory submission" that is provided for review to the appropriate regulatory authorities in different countries. They will review the submission, and, it is hoped, give the sponsor approval to market the drug.

Most drugs undergoing Phase III clinical trials can be marketed under FDA norms with proper recommendations and guidelines through a New Drug Application (NDA) containing all manufacturing, pre-clinical, and clinical data. In case of any adverse effects being reported anywhere, the drugs need to be recalled immediately from the market. While most pharmaceutical companies refrain from this practice, it is not abnormal to see many drugs undergoing Phase III clinical trials in the market.

Success rate

As of 2010, about 50% of drug candidates either fail during the Phase III trial or are rejected by the national regulatory agency.

Phase IV

Phase IV trial is also known as postmarketing surveillance Trial. Phase IV trials involve the safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold (e.g. after approval under FDA Accelerated Approval Program). Phase IV studies may be required by regulatory authorities or may be undertaken by the sponsoring company for competitive (finding a new market for the drug) or other reasons (for example, the drug may not have been tested for interactions with other drugs, or on certain population groups such as pregnant women, who are unlikely to subject themselves to trials). The safety surveillance is designed to detect any rare or long-term adverse effects over a much larger patient population and longer time period than was possible during the Phase I-III clinical trials. Harmful effects discovered by Phase IV trials may result in a drug being no longer sold, or restricted to certain uses; recent examples involve cerivastatin (brand names Baycol and Lipobay), troglitazone (Rezulin) and rofecoxib (Vioxx).
The minimum time period mandatory for Phase IV clinical trials is 2 years.

DISCUSSION:

Postmarketing surveillance

Postmarketing surveillance (PMS) (also post market surveillance) is the practice of monitoring the safety of apharmaceutical drug or medical device after it has been released on the market and is an important part of the science ofpharmacovigilance. Since drugs and medical devices are approved on the basis of clinical trials, which involve relatively small numbers of people who have been selected for this purpose - meaning that they normally do not have other medical conditions which may exist in the general population - postmarketing surveillance can further refine, or confirm or deny, the safety of a drug or device after it is used in the general population by large numbers of people who have a wide variety of medical conditions.

Postmarketing surveillance uses a number of approaches to monitor drug and device safety, including spontaneous reporting databases, prescription event monitoring, electronic health records, patient registries, and record linkage between health databases. These data are reviewed to highlight potential safety concerns in a process known as data mining[9].

Postmarketing Studies and Clinical Trials — Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act

Introduction

This guidance provides information on the implementation of new section 505(o) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 355(o)), added by section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA). Section 505(o)(3) authorizes FDA to require certain postmarketing studies and clinical trials for prescription drugs approved under section 505 of the Act and biological products approved under section 351 of the Public Health Service Act (the PHS Act) (42 U.S.C. 262). This guidance provides information about the requirements for postmarketing studies and clinical trials under section 505(o)(3) of the Act. The guidance also describes the types of postmarketing studies and clinical trials that:

● will generally be required under the new legislation (postmarketing requirements (PMRs)) and

● will generally be agreed-upon commitments (postmarketing commitments (PMCs)) because they do not meet the new statutory criteria for required postmarketing studies and clinical trials.

Section 901 of FDAAA also created new sections 505-1 and 505(o)(4) of the Act, which authorize FDA, under certain circumstances, to require risk evaluation and mitigation strategies (REMS) to ensure that the benefits outweigh the risks of a drug and safety-related labeling changes (SLC) respectively. This guidance does not address REMS and SLC provisions. FDA wishes to clarify that PMRs, REMS, and SLCs are required under separate sections of the Act and while all are intended to address serious safety risks, they are separate provisions that have different goals and must meet separately defined statutory criteria. REMS are not a special type of PMR, nor are PMRs elements of a REMS.

This guidance does not apply to nonprescription drugs approved under a new drug application (NDA), nor does it apply to generic drugs approved under section 505(j) of the Act. Section 505(o) of the Act applies only to prescription drugs approved under section 505(b) of the Act and biological products approved under section 351 of the PHS Act.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

On September 27, 2007, the President signed FDAAA (Public Law 110-85) into law. Section 901 of Title IX of FDAAA amended the Act by adding new section 505(o). Section 505(o)(3) authorizes FDA to require certain postmarketing studies and clinical trials for prescription drugs approved under section 505(b) of the Act and biological products approved under section 351 of the PHS Act.

A. Past Practice

In the past, FDA has used the term postmarketing commitment (PMC) to refer to certain studies (including clinical trials), conducted by an applicant after FDA has approved a drug for marketing or licensing, that were intended to further refine the safety, efficacy, or optimal use of a product or to ensure consistency and reliability of product quality. These PMCs were generallyagreed upon by FDA and the applicant. Prior to the passage of FDAAA, FDA required postmarketing studies or clinical trials only in the situations described below:

• Subpart H and subpart E accelerated approvals for products approved under 505(b) of the Act or section 351 of the PHS Act, respectively, which require postmarketing studies to demonstrate clinical benefit (21 CFR 314.510 and 601.41, respectively);

• Deferred pediatric studies, where studies are required under section 505B of the Act (21 CFR 314.55(b) and 601.27(b)); and

• Subpart I and subpart H Animal Efficacy Rule approvals, where studies to demonstrate safety and

efficacy in humans are required at the time of use (21 CFR 314.610(b)(1) and 601.91(b)(1), respectively).
Section 130(a) of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act) amended the Act by adding a new provision requiring reports of certain postmarketing studies for human drug and biological products (section 506B of the Act (21 U.S.C. 356b)). Section 506B of the Act provides FDA with additional authority to monitor the progress of a PMC by requiring the applicant to submit a report annually providing information on the status of the PMC, which was defined to include agreed-upon commitments and required studies (including clinical trials). This report must also include the reasons, if any, for failure to complete the commitment. This provision is implemented at 21 CFR 314.81(b)(2)(vii) and 601.70. 9 Under section 506B(b) and (c), FDA is required to track these PMCs and report on them annually in the Federal Register.

B. New FDAAA Authority and Requirements

1. FDA May Require Applicants to Conduct Studies and Clinical Trials

Section 505(o)(3) of the Act authorizes FDA to require postmarketing studies or clinical trials at the time of approval or after approval if FDA becomes aware of new safety information. Section 505-1(b)(3) of the Act defines new safety information to include data about a serious risk, or an unexpected serious risk associated with use of the drug . Even if a serious risk is known at the time of approval of the drug, more may be learned after approval about its frequency or severity that can be considered new safety information.

In some cases, FDA may be concerned about a risk and believe that it is serious, but may not know enough about the risk to determine how to address the risk in labeling and what information would be appropriate to include. In such a case, FDA can require a postmarketing study or clinical trial to obtain more information. See purposes set forth in 505(o)(3)(A) below.

If there is information on chemically-related or pharmacologically-related drugs, FDA may consider this drug class safety information when requiring a study or clinical trial. See 505(o)(3)(A).

Section 505(o)(3)(A) states that postmarketing studies and clinical trials may be required for any or all of three purposes listed in section 505(o)(3)(B):

• To assess a known serious risk related to the use of the drug

• To assess signals of serious risk related to the use of the drug

• To identify an unexpected serious risk when available data indicates the potential for a serious risk

For the purposes of implementing section 901 of FDAAA, clinical trials and studies are defined as follows:

• **Clinical trials** are any prospective investigations in which the applicant or investigator determines the method of assigning the drug product(s) or other interventions to one or more human subjects.

• **Studies** are all other investigations, such as investigations with humans that are not clinical trials as defined above (e.g., observational epidemiologic studies), animal studies, and laboratory experiments.

Clinical trials are one type of clinical investigation, as defined at 21 CFR 312.3(b). For the purposes of this guidance, FDA has separately defined these terms as listed above because statutory provisions below from section 505(o)(3) of the Act differentiate between studies and clinical trials.

2. Applicants Are Required to Report on the Status of Studies and Clinical Trials

The applicant is required to provide certain information to FDA with regard to required postmarketing studies and clinical trials (section 505(o)(3)(E)(ii)). Under section 505(o)(3)(E)(ii), this information must include:

• For all required postmarketing studies and clinical trials, a timetable for completion

o A timetable for completion is a set of milestone dates by which we measure progress of studies and clinical trials and compliance with requirements. These goal dates generally include, but are not limited to, final protocol submission date, study or clinical trial completion date, and final report submission date. FDAAA does not include provisions to amend or change milestone dates for purposes of reporting as required under 21 CFR 314.81(b)(2)(vii)(a)(8)(ii-iii) and 21 CFR 601.70(b)(8)(ii-iii). Therefore, status reporting under these regulations will remain based on the **original** schedule.

For each study required under section 505(o)(3), periodic reports on the status of the study, including whether any difficulties in completing the study have been encountered

• For each clinical trial required under section 505(o)(3), periodic reports on the status of the clinical trial, including:

o whether enrollment has begun,

o the number of participants enrolled,

o the expected completion date,

o whether any difficulties completing the clinical trial have been encountered, and

o registration information with respect to the clinical trial under section 402(j) of the PHS Act (42 U.S.C. 282(j))

In addition, FDAAA requires that applicants report on each study and clinical trial "otherwise undertaken

by the applicant to investigate a safety issue". Reports on these studies and clinical trials would previously have been required under 21 CFR 314.81(b)(2)(viii).

CONCLUSION:

Any medicinal agent to be marketed in the United Kingdom
has to follow the guidelines and regulations framed by MHRA,
a regulatory authority which approves the drug products. The
objective of this review article is to highlight information regarding
the requirements, the different types of submissions for the
registration of a medicinal product in a market in the UK. It also
includes all the details about the fee for the application and the
time period for the approval of the application after the submission
of the application. By knowing the requirements of the MHRA
guidelines and regulations, it is easy for a product to get into the
UK market.

Drug safety is a major public health concern, especially in today's society with vast amounts of new drugs coming onto the market. And no drug isperfectly safe; however, it is possible to improve the post-market drug surveillance system sothat people are only exposed to those drugs that have benefits outweighing their health risks.Congress and officials at the FDA need to take a look at the process and be willing to commit to the FDAAA changes to improve post-market drug safety. With the current rates of ADEs and poor reporting, the nation cannot afford for the post-market drug surveillance system to lag behind. The FDA keeps trying small changes to the system, but these simply are not enough. A major overhaul needs to happen so that this imperative public health concern is properly protected.

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