

Advances in Drug Development

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Current Developments in Oncology Drug Research

Global Regulatory Issues

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Is oncology drug development becoming more global?

Oncology drug development, like drug development in most areas of medicine, is today a much more “global” undertaking than in the past, and the approach to the organization and conduct of clinical trials of putative new oncology therapies is much more globally coordinated. This is especially true in pediatric oncology, where there are not large numbers of patients available for clinical trials. The pediatric oncology community is engaged in efforts to enhance international cooperation in conducting transnational clinical trials in order to obtain scientifically robust data to help us all learn how best to use these new products in the fight against cancer.

What role do regulatory agencies play in international clinical trials?

The Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, and Office of International Programs of the US Food and Drug Administration (FDA) work with our counterpart agencies around the world to help ensure that regulatory requirements regarding the conduct of clinical trials meet their public health mission of ensuring: (a) patient safety during clinical trials, (b) ethical conduct of clinical trials, and (c) adequate addressing of scientific issues so that the trials can give us all the information we need to make informed decisions about putative new therapies. We also work with our counterpart agencies to help ensure that these requirements are consistent, not needlessly duplicative, and not impeding the initiation of needed clinical trials. Often investigators and cooperative groups involved in international trials identify for those of us in the regulatory agencies perceived duplications and unjustified regulatory hurdles.

Do most countries approach the regulation of clinical trials in the same way?

In the United States, in order to conduct clinical trials of a drug that has not yet been authorized for general marketing, the trial sponsor must submit an “Investigational New Drug Exemption” (IND) to the FDA, which then reviews the submitted information and provides an independent assessment of whether it is safe to proceed with the proposed

clinical trial. In addition, study investigators are required to work with an Institutional Review Board to ensure the ethical integrity of the trial. Most regions and countries with major drug regulatory authorities, such as the European Union, Switzerland, Canada, Japan, and Australia, follow essentially parallel processes. In addition, the agreement within the International Conference on Harmonization (ICH) on a standard set of “Good Clinical Trial Practices” (GCPs) helps to ensure consistently high and uniform standards of clinical trial conduct practices in those regions that have adopted this international consensus approach. In general, there are not fundamental differences in the way that clinical trials are regulated in these countries, but sometimes there are differences in the timing and the level of involvement of the various regulatory authorities.

In what aspects of trial regulation are there differences among countries?

Generally, the differences are more in the manner in which the programs are implemented rather than in the goals or designs of the programs. Sometimes these differences are just enough to be problematic in the conduct of international clinical trials. These differences may be based on regional or national traditions rather than sound science or public health, in which case we try to find a way to harmonize so that only 1 approach is taken, or to harmonize the various approaches so that they work together. If, however, there are legitimate reasons to have differences, then we try to find a way to explain the different approaches so that individuals conducting international trials will better understand the difference and be able to address them efficiently.

Do different countries generally use the same endpoints in clinical trials?

One of the most important aspects of a clinical trial is the primary efficacy endpoint chosen. Generally, where medical practice is similar, the choice of primary efficacy endpoint is usually not a difficult issue across borders. However, one must remember that the endpoint in a clinical trial sponsored by a pharmaceutical company is generally one that will give information regarding a “claim” about the product the

company wishes ultimately to make. Given different marketing strategies in different countries, the claims the company wishes to make about the product may be different enough in various countries to require different primary endpoints to be explored.

In addition, one of the differences that has been seen between the United States and some other areas of the world regarding primary efficacy endpoints in trials for products to treat serious and life-threatening illnesses for which there are no good therapies has been the greater use of and comfort with unvalidated (ie, unestablished) surrogate endpoints, or in some cases, biomarkers that have not been formally validated as surrogates, as primary efficacy endpoints for approval. This US “accelerated approval” program is based on regulations established in 1992, and has been used in the United States for various therapies for human immunodeficiency virus (HIV) infection, cancer, and life-threatening neurological diseases. As experience accrues, non-US regulatory authorities appear to be increasingly willing to accept a larger variety of endpoints as the basis for regulatory decisions.

How do unvalidated surrogate endpoints work in the clinical trial process?

An unvalidated surrogate endpoint is one that has not been demonstrated by adequate and well controlled trials to predict an actual clinical benefit for patients but, based on the data available, is thought to be a likely indicator of such clinical benefit. In HIV research in the 1990s, investigators began, initially, using changes in CD4 counts as a primary efficacy endpoint. In oncology, tumor shrinkage has been used as an unvalidated primary efficacy endpoint in certain situations to grant accelerated approval with a commitment to continuing the clinical trials after approval to determine whether or not there is indeed clinical benefit for the patients.

On their own, a positive effect observed with an unvalidated surrogate endpoint does not prove that a drug will have an ultimate clinical benefit for patients with a specific disease. With HIV research, it was reasonable to think that positively changing the CD4 count would predict clinical benefit for patients suffering with HIV and related infections. In the situations in which we use unvalidated surrogates as primary efficacy endpoints for marketing authorization, given the life-threatening nature of the illnesses and the dearth of effective therapies, regulators, general practitioners, and the patient communities involved have generally been comfortable with this approach and willing to take the risks inherent in such an approach in order to market authorization. Clearly one would not take this approach if there were well documented, effective therapies available for a disease.

Thus, for certain serious and life-threatening diseases, the FDA will review a marketing application based on data showing an effect on the unvalidated surrogate endpoint. If the effect on the surrogate endpoint is confirmed, the drug will be authorized for marketing. However, this approval comes with the requirement that the trial sponsor continue the study, or initiate additional studies, in order to demonstrate whether the endpoint did indeed predict clinical benefit. If a clinical benefit is not confirmed, there are processes for removing the

product from the market, although, to date, this mechanism has not had to be used.

Finding the most predictive surrogate endpoints is one of the ultimate goals of the drug development scientific and regulatory processes. The earlier in the development process the surrogate endpoint can be measured or other predictive piece of information can be obtained, the sooner a sponsor will know whether to continue to pursue development of a particular drug, and the sooner patients can receive the drug, if the likely benefits outweigh the known risks.

Are there differences in the way that patient safety is regulated in different countries?

In general, the issue of safety does not differ very much among countries. For some of the new, cutting-edge therapies for which there is not much marketing experience on which to base regulatory decisions, such as gene therapy or certain vaccine therapies, agencies generally focus primarily on the risks inherent in the underlying disease. In oncology, if the tumor type is one for which there is no curative therapy available, or if patients have typically not responded to available therapies, we have found that patients are typically willing to take a fair amount of risk when it comes to putative new therapies. In other words, risk tolerance varies among patient groups given the underlying severity of their disease and the various therapeutic choices they do or do not have. The level of risk a patient is willing to accept, when fully and adequately informed, is one of the most important factors in regulating trials, especially with new classes of agents.

Are issues of patient privacy and informed consent similar around the world?

The general understanding about these issues is becoming more consistent throughout the major drug regulatory areas of the world. Some cultural differences lead to variations, for example, in the composition of the ethics committees in various countries. In the United States, it is considered important to have non-medically qualified individuals on ethics committees so that other perspectives can be brought to bear. Not all countries follow this practice. However, such differences should not infer a difference in their strong commitment to the ethical conduct of clinical trials.

The ethical principles to which major drug regulatory agencies are adhering are reflected in the Declaration of Helsinki, the document created by the World Medical Association on standards for bioethics. The United Nations Educational, Scientific, and Cultural Organization (UNESCO) is also developing an international code of bioethics.

Does the protection of privacy sometimes prevent effective data collection?

In various parts of the world, there may be personal privacy laws governing clinical trials that prevent certain kinds of data to flow out of that geographic area and into another. However, one of the strengths of an effective international clinical trial derives from the robustness one gets from pooling the data. Occasionally, there are challenges in working through the various systems in order to ensure that these laws, which were put into practice for good reason, do not

obstruct the pooling of data to obtain important scientific information for the good of the larger community. When there is tension between these competing good purposes, the solution may lie in making the data anonymous, or finding other ways to protect personal data from any inappropriate disclosures while allowing the medical information from the trial to be pooled.

In evaluating clinical trial findings, do regulatory agencies readily accept international data?

For the most part, FDA regulations specify that foreign data is perfectly acceptable, providing that the population studied is reflective and predictive of the US population. In most situations, human physiology is the same and where the trials are conducted is irrelevant to the evaluation of clinical benefit and risk. The various ICH agreements are reflective of this principle in most of the major drug regulatory agencies. At the FDA, we are seeing an increasing amount of data from various parts of the world, and the FDA has approved therapies for the US market based on clinical data collected entirely outside the United States.

In certain situations, data from one country will not be applicable to the population of another country. Sometimes data from trials for certain infectious diseases cannot be broadly extrapolated because the microbes have different sensitivity patterns in different parts of the world. In oncology, these kinds of differences are uncommon.

Are pharmaceutical companies tending to develop drugs for global use from the outset now?

With most new drugs in development, companies now tend to conduct global development programs. The data presented to the regulatory agency come from patients in many countries. In addition, it is reported that because of the numbers of patients available and the cost of conducting trials, many companies are conducting trials overseas in regions such as the former Soviet Union, Eastern Europe, Central America, and South America, where the cost of clinical trials is not as high as it is in Western Europe and North America.

What role has the ICH played in global regulation?

The ICH began in the early 1990s and is an ongoing initiative of the drug regulatory agencies and the major innovator pharmaceutical manufacturers in the European Union, the United States, and Japan, along with the World Health Organization and the drug regulatory authorities from Canada and Switzerland. This initiative focuses on harmonizing the technical and scientific requirements for drug registration in those areas of the world. The work of this initiative has resulted in many agreed consensus documents, including the GCPs mentioned above, on the efficacy, safety, and quality of new drug products that are now implemented throughout the regions involved and many other regions of the world. Prior to the development of these harmonized GCPs, conducting international clinical trials was extremely difficult and frustrating for sponsors because of differing views on what constituted good clinical practice in various countries. A great deal of the frustration came from sponsors trying to follow a host of local requirements when conducting an international

trial under 1 protocol. The ICH GCP guidelines have made the acceptance of clinical trial data from other parts of the world much easier because each regulatory agency now understands more fully the standards under which the clinical trials were conducted and the data were collected.

How is the ICH responding to findings on the role of genetics in a patient's response to therapy?

The ICH has begun to address this issue. In certain situations, ICH has recommended a "bridging study" to evaluate different pharmacokinetic and/or pharmacodynamic responses in different populations to help determine if the results and recommendations from a trial in one population can be extrapolated appropriately to another.

What may become more interesting than differences among populations are the genetic differences among individuals who would be considered to be of the same race or cultural group, as we gain better understandings of the genetic basis of disease and therapy, and improve our ability to evaluate a patient's individual genetic pattern. Currently, clinical trials are not designed routinely to look at individual effects. Drugs are approved based on a population effect, and the risk-to-benefit ratio is evaluated on a population basis. In the coming years, the scientific community will need to determine how to study and regulatory agencies will need to determine how to authorize a drug that is developed for individuals with a particular genetic feature or pattern in order to maximize the efficacy potential of the drugs and/or minimize a potential risk of the product. This paradigm is entirely different from the drug development paradigm of the past several decades.

What are the specific challenges that this new paradigm presents?

Many issues will come into play with this change, including science issues and challenges regarding new ethics, personal privacy, and future insurability concerns. There are enormous benefits to learning more about individual genetic make-up, including the ability to predict a patient's positive and negative responses to therapy and the diseases to which they may be prone. Systems must be implemented that allow such information to be used to a patient's benefit and not to discriminate against people. This will be one of the biggest challenges to drug regulators, manufacturers, practitioners, and patients alike in the early 21st century.

Suggested Reading

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