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The FDA Perspective on the Development of Stereoisomers

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ABSTRACT The current regulatory position of the Food and Drug Administration is discussed with regard to the approval of racemates and pure stereoisomers. Circumstances in which stereochemically sensitive analytical methods are necessary to ensure the safety and efficacy of a drug are described. Regulatory guidelines are interpreted for applications for the approval of a pure enantiomer in which the racemate is marketed, for the approval of either a racemate or a pure enantiomer in which neither is marketed, and for clinical investigations to compare the safety and efficacy of a racemate and its enantiomers. Examples of the basis for such regulation are drawn from historical situations (thalidomide, benoxaprofen) as well as currently marketed drugs (arylpropionic acids, disopyramide, indacrinone).

KEY WORDS: optical isomers, stereochemistry, enantiomers, Food and Drug Administration, drug development, drug regulation

Since the discovery of the optical isomerism of tartaric acid by Louis Pasteur in 1848, the significance of stereoisomerism in relation to biological activity has been recognized by scientists. It was soon seen that the separation of a racemate into its component stereoisomers presented a challenge of immensely greater magnitude than did the development of a stereospecific synthesis. As a result, efforts to resolve such mixtures were largely bypassed for more than a century. The rare instance of a successful separation was often treated either as happenstance or as the success of trial and error. In either event, a systematic approach to the problem was not seen as feasible, except in a few special cases. Commercial exploitation was certainly unthinkable.

The result of this perception, particularly among scientists working on the development of new drugs, was that their research efforts were directed more by the technical feasibility of the experiment than by a concern with the biological effect of the drug. Questions of whether clinical efficacy and safety were greater in one member of an enantiomeric pair were asked only when a synthetic route that was both stereospecific and economic was available.

The successful development of chiral stationary phases for high-performance liquid chromatography in the late 1970's altered this situation. The separation on a routine basis of optically pure material from a racemate in amounts adequate for clinical investigations became feasible. Enantiomeric purity could be determined for the bulk drug, for its formulations, and often in biological fluids. The investigator could now ask the question, "Why should I separate a racemate?", knowing that it was not an exercise in rhetoric.

The primary regulatory focus of the Food and Drug Administration is on considerations of both clinical efficacy and consumer safety in making its determination of whether to allow a drug to be marketed. Because the chiral environment found in vivo affects the biological activity of a drug, the approval of stereoisomeric drugs for marketing can present special challenges. The case of thalidomide is an example of a problem that may have been, at least, complicated by ignorance of stereochemical effects. Much has been learned from the tragedy associated with its marketing. A variety of other conclusions about the behavior of a drug in vivo may be affected by the "isomeric ballast" present in a racemate, to use a phrase popularized by Ariëns.[1,2] In particular, it will be shown how the use of racemates can lead both to erroneous models of pharmacokinetic behavior and to the potential for opportunities to manipulate pharmacological activity. Through all this, it should be remembered that it is within the realm of technical feasibility to design experiments that will answer, with little ambiguity, the question, "Is a stereochemically pure drug more effective and/or less toxic than the racemate?"

When, as often results from synthetic processes, an equimolecular mixture of enantiomers is prepared, it is referred to as a *racemate*. Although we use this as a general term today, it is interesting to recall that Pasteur's original effort was an attempt to discover the difference between tartaric acid, a natural product, and its isomer, which was then called "racemic acid."

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Two types of racemates are identified by stereochemists. A "racemic mixture" refers to the rather unusual situation that Pasteur found in which each individual crystal of the solid is optically pure, and rotates polarized light. On the other hand, a "racemic compound" contains equal numbers of "plus" and "minus" molecules in each unit cell of the crystal. This case is far more commonly encountered. Unfortunately, carelessness in the use of such nomenclature has led many chemists to assume that most, if not all, racemates are separable by simple selection of optically pure crystals.

In discussing the physical and chemical properties of enantiomers, the concept of a "stereochemically sensitive" test must be introduced. In using chemicals in the manufacture of pharmaceuticals, we work in the macroscopic world. Considerations of stereochemistry are significant at the molecular level. But they must be translated into tests that can be applied, for example, to a drum of a white, crystalline powder in QC testing. Polarimetry may be the tool of choice to assess optical purity in the research laboratory, and will clearly discriminate between enantiomers. Other properties may be used when it is necessary to distinguish between an enantiomer and a racemate. On the production line, the complex of tests that is applied may or may not logically require such a test.

Optical rotation is clearly a stereochemically sensitive test, for it will discriminate between plus and minus enantiomers. So is melting range, which will discriminate between either pure enantiomer and the racemate, although, obviously, it cannot discriminate between the enantiomers. Among the more sophisticated techniques, X-ray powder diffraction, laser Raman spectroscopy, and nuclear magnetic resonance using chiral lanthanide shift reagents are all stereochemically sensitive. So, too, are chiral high-performance liquid chromatography (HPLC) methods. It is well established that the order of elution of enantiomers is more predictable than their retention times relative to a standard. Retention time may be highly affected by the chromatographic conditions. As a result, the use of chromatographic retention time on a chiral column may not be as generally applicable as an *identity* test as it is on standard columns. However, comparison of such times on a chiral stationary phase to those observed for the two peaks in a racemate may have the potential for being an identity test that is suitable for regulatory purposes.

In order to fully present the Food and Drug Administration's perspective on stereoisomerism, a brief consideration of the historical background of the Food, Drug, and Cosmetic Act seems appropriate. It is necessary to mention only a few of the highlights of its history to show where FDA has been with regard to the application of the Act to the regulation of the molecular structure of drugs. From its initial passage in 1906, the Pure Food and Drug Act has been a dynamic document. FDA's original mandate under the "Wiley Act" was to guarantee the purity of foods and drugs. For the latter, this was approached through labeling of the active ingredients and designation of the U.S. Pharmacopeia as an official compendium of drug standards. Following the tragic "elixir of sulfanilamide" incident, FDA's authority was extended to safety by the passage of the FD&C Act in 1938. Under this successor to the Wiley Act, New Drug Applications (NDA's) were first required for the marketing of drugs. The Kefauver–Harris Drug Amendments of 1962 extended our authority further to the premarketing review of efficacy, provided authority for the monitoring of the investigational use of drugs, and required the use of established names. In 1972, our authority was extended to include OTC drug monographs, and the review of generic drugs or new versions of marketed drugs was changed in 1984 to provide for abbreviated applications for drugs approved after 1962.

Through all of these changes, the FD&C Act has remained blind to questions of stereochemistry. The definition of a "drug" in the Act[3] does not specifically consider the question of its stereochemical composition. The Code of Federal Regulations (CFR) also avoids this question. Whether a drug substance is considered to be the racemate or a pure stereoisomer has, therefore, usually been left to the judgment of those who are, in the language of the Act, "experts qualified by scientific training and experience."[4]

The use of established names for the active ingredients in drug products was, as noted, first required by the Kefauver–Harris Drug Amendments of 1962. These names are generally those adopted by the U.S. Adopted Names Council. However, the FDA is specifically mandated to continue to publish official names when,

> two or more official names have been applied to a single drug, or to two or more drugs that are identical in chemical structure and pharmacological action, and that are substantially identical in strength, quality and purity.[5]

This has resulted in the general practice that an enantiomer is not given the same established name as the racemate.

Last year, FDA issued a set of guidelines on the submission of New Drug Applications. The question of stereochemistry was approached directly in the guideline on the manufacturing of drug substances.[6] The FD&C Act requires a full description of the "methods used in the manufacture of the drug," which includes testing to demonstrate its identity, strength, quality, and purity. Therefore, we require that submissions show the applicant's knowledge of the molecular structure of the drug substance. For chiral compounds, this includes identification of all chiral centers. The enantiomer ratio, although 50–50 by definition for a racemate, should be defined for any other admixture of stereoisomers. The proof of structure should consider stereochemistry, and provide appropriate descriptions of the molecular structure. The guidelines do not discuss conditions under which a determination of absolute configuration is desirable or essential. Obviously, though, it would be appropriate data for supporting the manufacture of optically pure drugs.

For approved NDA's in which the marketed drug is a racemate, FDA policy is already clear. An optically pure enantiomer of an approved racemate may be marketed only under a new NDA. This application is likely assigned to chemical type 2 (like a new ester). Consider the various chemistry, manufacturing, and controls issues in such an application. The synthesis of the new drug must be fully described. If the manufacturing process is actually a commercial scale resolution of the racemic bulk drug as synthesized under the approved NDA, then the

resolution may be considered as an additional step or steps in the manufacturing process. Obviously, the controls on the purified bulk drug cannot be completely identical for the racemate and the enantiomer, since the optically pure drug must be distinguishable from the racemate. It is equally obvious that many of the controls could reasonably be identical. Clinical trials must be carried out under a new Notice of Claimed Investigational Exemption for a New Drug (IND) for the specific optical isomer as appropriate to show efficacy and bioequivalence.

Suppose, on the other hand, that a drug is already marketed in its optically pure form. What is necessary for it to be marketed as a racemate? This is purely speculative, since no such application seems to have ever been submitted. It seems unlikely that such a step could ever be shown to improve safety. The focus would have to be on a comparison of efficacy and the resulting risk/benefit ratios of the enantiomer and racemate. As with the opposite case, manufacturing information would have to be submitted. At least one test would be necessary to distinguish the racemate and the enantiomer.

Now, turn to the situation prior to approval of the NDA. In practice, the decision about whether to develop the racemic or optically pure form of a drug is made by the firm well before the time that an application to market a new drug is submitted. In the course of drug development, a manufacturer should consider both enantiomers, as well as the racemate, to be potential drugs. The choice may even be to carry out at least limited preclinical and/or clinical studies on all three forms before making a final determination. However, it is clear that economics enters into this decision. As a result, the decision to select a racemate or a stereoisomer for product development may be made well before clinical trials are begun.

The major effort to characterize the differences between enantiomers in a racemic drug, therefore, takes place during its investigational phases, and possibly even earlier. Suppose, as an illustration, that a racemic investigational drug is being prepared for an NDA submission, and that data are needed to support this decision. In addition to physical, chemical, and pharmacological studies, clinical studies to compare the safety and efficacy of the racemate with the enantiomers may be needed. Such trials, in contrast to the case for a drug already marketed as a racemate, can be carried out under the existing IND for the racemate, as long as appropriate chemistry, manufacturing, and control data are submitted for the optical isomers.

How has the FDA approached review of such decisions? Consideration of questions of *either* safety *or* efficacy, in isolation from others, leads to the trivial and obvious conclusion that one of the three possibilities—two enantiomers and one racemate—must be "best," or else the three must be essentially equal. Whether the decision is to market a racemate in preference to a pure enantiomer, or the reverse, it should be justified by the submission of appropriate data. Let us examine the situations encountered in the past to see where our policy may be headed.

Until recently, the studies necessary to provide data about the relative safety and efficacy of enantiomers were difficult, expensive, or even technically impossible to carry out. As an example of such a case, consider the tragedy of thalidomide in the early 1960's. Ultimately this led to the passage of the Kefauver–Harris Amendments.

Thalidomide contains a chiral carbon, and thus exhibits optical isomerism. It was synthesized as a racemate, although stereospecific syntheses were developed later. Considering that the routine resolution of racemates was not feasible at that time, it is not surprising that its developers did not carry out studies of the physiological effects of the pure enantiomers. As a result, it is understandable that, in addressing these issues, the Kefauver–Harris Drug Amendments of 1962 did not contain a specific requirement that the clinical effectiveness of a racemic drug be evaluated relative to the pure stereoisomers of which the mixture is composed. It should be kept in mind that, even if thalidomide had been subjected to resolution and thorough clinical testing, there is no proof that the catastrophe would have been avoided.

Although thalidomide was never marketed in the United States, it entered commerce in Europe with no apparent consideration of the relation between its biological activity and its stereochemistry. It was initially described as a sedative that was alleged to be nontoxic. Within a few months of its first use, its terrible side-effects were seen. It was found to be irreversibly neurotoxic, causing peripheral neuritis that remained after the drug was discontinued. Then it was found to be teratogenic, causing a variety of fetal abnormalities. The greatest attention was attracted by a birth defect known as phocomelia, in which the hands or feet are attached to the shoulder or hip by a single, small, irregularly shaped bone. Unfortunately, because of its supposed safety, the sedative and antinausea properties of thalidomide led physicians to prescribe it for morning sickness in early pregnancy. The tragedy of its teratogenicity stimulated research into this problem for many years afterward.[7]

The developmental research for thalidomide took place without the modern technological tool of chiral HPLC. The initial point of attack to understand its hazards was its synthesis. Even though a stereospecific synthesis for thalidomide was ultimately developed by Casini and Ferappi in 1964,[8] the racemate was obtained by the synthetic methods used at the time of its initial use in Germany.[9] The stereospecific synthesis starts from glutamic acid or one of its derivatives. No step in the reaction sequence involves the chiral center, so the absolute configuration of the product is known.[10,11]

Dextrorotatory thalidomide has the D absolute configuration, which corresponds to R using the Cahn, Ingold, and Prelog nomenclature.[12] Resolution of clinically useful supplies of the pure enantiomers from a batch of the racemate does not appear to have been described in the open literature. However, the racemate has been chromatographically resolved by Blaschke et al.[13] using an HPLC chiral stationary phase.

Several investigations of the safety and efficacy of the stereoisomers of thalidomide have been published. All of them were carried out after the fact of the tragedy. The results of these studies suggest that the enantiomers of thalidomide differ significantly in their biological activity. This has, in turn, led others to conclude that the teratogenic effect of thalidomide is found in only one enantiomer, and to speculate that the tragedy could

have been avoided if the other had been marketed.[14] Let us briefly review these experimental data.

The earliest reported investigation of stereoisomerism and biological activity in thalidomide was by Fabro et al.[15] They found that the LD_{50} in SAS ICI albino mice was greater by a factor of approximately 20 for the racemate relative to either of the pure stereoisomers. They also found no difference in teratogenic action, either between enantiomers or between an enantiomer and the racemate, at an oral dose of 150 mg/kg from the seventh to twelfth days of pregnancy, inclusive, in New Zealand white rabbits. No stereochemical differences were noted in the hypnotic effect.

Some years later, in a review article, Simonyi pointed out an observation that the original authors had overlooked.[16] The ratio of malformed to normal fetuses for either enantiomer was less than half that found for the racemate. It should also be noted that both the pure enantiomers and the racemate were administered at the same dose. If, as has been hypothesized, only one enantiomer is teratogenic, then a comparison between the effect of an enantiomer with that of the racemate is being made between a drug administered at one dose in one group and half the dose in the other.

A later study by Blaschke et al.[17] showed significant differences between the enantiomers, with the teratogenic activity appearing to be concentrated in the (−)-S isomer. Unfortunately, this latter study used SWS mice and Natal rats, rather than the New Zealand white rabbits that were known to be the most sensitive to teratogenic effects. A different route of administration was also used.

An investigation of the effects of thalidomide on the graft-versus-host reaction in chick embryos reported that both (−)-S and *rac*-thalidomide had a significant immunosuppressant action, whereas (+)-R-thalidomide had none.[18] However, the authors seriously compromised the potential significance of their work by failing to provide any evidence of the stereochemical identity of the drugs used.

The evidence that seems to be most indicative of the teratogenic action being restricted to (−)-S-thalidomide comes from a series of studies on its hydrolysis products.[19–23] However, this conclusion should be accepted with caution, since the mechanism of teratogenic action in thalidomide remains uncertain.

None of the published studies has succeeded in answering the questions without ambiguity. The definitive experiment does not yet appear to have been done. The published investigations have focused on stereochemical aspects of the hypnotic and teratogenic effects of thalidomide, to the neglect of its neurotoxicity, which is also an undesirable side-effect. Finally, although it may be an oversimplification to assume that desirable and undesirable actions must be separable between enantiomers, it should be realized that it may be necessary to test such an hypothesis using the pure enantiomers.

It is clear that, within the body, a drug exists in a chiral environment in which its release, absorption, transport, action, degradation, and elimination may involve interactions with enzymes, cell surfaces, etc.[24] Thus, it is expected that two enantiomeric molecules will be acted on differently by the body. The factors that differ between enantiomers are not limited to pharmacological effects. Pharmacokinetic models for racemic drugs are not necessarily valid if they assume that such processes involve only a single component changing with time.[25]

A primary example of such effects is the family of nonsteroidal antiinflammatory drugs. With a single exception (naproxen and its sodium salt), all of the drugs in this family that have been approved for marketing in the United States are marketed as racemates. Hutt and Caldwell,[26–28] as well as many other investigators,[29] have shown that the enantiomers of 2-arylpropionic acids frequently show stereoselectivity in their disposition kinetics. Furthermore, metabolic inversion of the inactive R enantiomer to the active S form has been demonstrated for many members of this family of drugs. Tiaprofenic acid is an exception,[30] and, of course, there may be others.

The different pharmacokinetic behavior of enantiomers appears to have been a contributor to the adverse reactions that led to the withdrawal of benoxaprofen from the market in 1982.[31] Inversion of (−)-R-benoxaprofen to its (+)-S-enantiomer in humans following oral administration of either the racemate or the pure R enantiomer has been demonstrated.[32] Subsequent in vitro studies suggest that the inversion occurs as the drug passes through the intestinal wall.[33] The contribution of this inversion to the decreased rate of metabolism and excretion in some elderly patients, which led to the hepatotoxicity that prompted the suspension of marketing of the drug, does not appear to have been established. As in the case of thalidomide, it is interesting to speculate about the possibility that this unfortunate incident would not have occurred if the pure stereoisomer had been developed for the market.

Disopyramide is another drug that shows stereoselective pharmacokinetics.[34] Its binding to plasma protein has been shown to be both stereoselective and concentration dependent. This combination of kinetic factors leads to pharmacokinetic data that cannot be explained by a model that assumes that the drug is a single component. Such an assumption, unfortunately, appears to be common practice.

In at least one case (for a drug not yet marketed in the United States), the enantiomeric ratio has been varied to improve therapeutic effects. Indacrinone is a relatively long-acting, high-ceiling diuretic. Although both enantiomers have uricosuric activity, the (−) enantiomer is more potent as a natriuretic agent. A balance between the natriuretic and uricosuric effects was found for a 4:1 ratio of plus and minus enantiomers.[35]

A thorough understanding of the pharmacokinetics of any drug is essential for the determination of a safe and effective dosage regimen. In the case of a racemic drug, therefore, this implies knowledge of the in vivo behavior of the pure stereoisomers. Indeed, given adequate information about the kinetic behavior of both enantiomers of a drug, it is tempting to speculate as to the extent to which its pharmacokinetics might be able to be varied by the use of partially, rather than fully, resolved drug.

The use of combinations of drugs to improve therapeutic efficacy is not unusual. FDA's regulations require that, in such a combination,

> each component makes a contribution to the claimed effects and the dosage of each component . . . is such that the combination is safe and effective.[36]

The potential for application of such a regulation to racemates seems obvious, though not explicitly stated in the CFR. Our guideline notes,

> even in racemates, . . . enantiomers may be considered as impurities.[37]

A formal extension of the combination drug policy to racemates has not yet been proposed.

U.S. regulatory requirements include a requirement that the bioavailability of the drug be demonstrated.[38] When pharmacokinetic models differ between enantiomers, it seems obvious that establishing the bioavailability of the drug from a racemate is a much more complex task, which cannot be accomplished without separation of the enantiomers and investigation of their pharmacokinetics as individual molecular entities.

For most of the years since Pasteur's discovery, it was beyond practicality to ask about the detailed implications of stereochemistry for drug action. As scientists, we did not want to spend our time designing an experiment that could not be done. As regulators, we did not ask questions for which the answers could not be provided. And, all too often, the resulting ignorance was part of a decision.

Good science requires that our conclusions be based on experimental evidence that is derived from well-planned experiments. Such a level of planning should not neglect the potential for differences in properties for enantiomers of a chiral molecule in a chiral environment. Thus, not only is it desirable to recognize the implications of stereochemistry for drug action, but it is also desirable that they be investigated. Either the enantiomers should be separated, or they should be synthesized.

Good sense requires that the hazards associated with the use of any substance, or its components, be identified. It is expected that the toxicity of impurities, degradation products, and residues from manufacturing processes will be investigated as the development of a drug is pursued. The same standards should, therefore, be applied to the enantiomeric molecules in a racemate.

Whenever a drug can be obtained in a variety of chemically equivalent forms (such as enantiomers), it is both good science and good sense to explore the potential for in vivo differences between these forms.

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