Drugs

Development of New Stereoisomeric Drugs

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I. INTRODUCTION AND BACKGROUND

Stereoisomers are molecules that are identical in atomic constitution and bonding, but differ in the three-dimensional arrangement of the atoms. For the purpose of this document, the stereoisomeric pairs of greatest interest are those with one or more asymmetric (chiral) centers whose enantiomers (individual stereoisomers) are mirror images. They have essentially identical physical (except for optical rotatory) and chemical (except in a chiral environment) properties.

This document focuses on issues relating to the study and pharmaceutical development of individual enantiomers and racemates. Such stereoisomers usually require specialized chiral techniques for their correct identification, characterization, separation and measurement. They are often readily distinguished by biological systems, however, and may have different pharmacokinetic properties (absorption; distribution, biotransformation. and excretion) and quantitatively or qualitatively different pharmacologic or toxicologic effects.

When stereoisomers are biologically distinguishable, they might seem to be different drugs, yet it has been past practice to develop racemates (i.e., compounds with 50:50 proportion of enantiomers). The properties of the individual enantiomers have not generally been well studied or characterized. Whether separated enantiomers should be developed was largely an academic question because commercial separation of racemates was difficult. Now that technological advances (large scale chiral separation procedures or asymmetric syntheses) permit production of many single enantiomers on a commercial scale, it is appropriate to consider what FDA's policy with respect to stereoisomeric mixtures should be. Development of racemates raises issues of acceptable manufacturing control of synthesis and impurities, adequate pharmacologic and toxicologic assessment, proper characterization of metabolism and distribution, and appropriate clinical evaluation.

It should be noted that the term "stereoisomers" is a general one for all isomers that differ only in the orientation of the atoms in space. Stereoisomers include not only the mirror image enantiomers, but also geometric (cis/trans) isomers and diastereoisomers (isomers of drugs with more than one chiral center that are not mirror images of one another). Diastereoisomers and geometric isomers are both chemically distinct and pharmacologically different (unless they are interconverted *in vivo*) and are generally readily separated without chiral techniques. Geometric isomers and diastereoisomers therefore should, with the rare exception of cases where in vivo interconversion occurs, be treated as separate drugs and developed accordingly. There is no reason to consider developing mixtures of geometric isomers or diastereoisomers unless they fortuitously represent a reasonable fixed dose combination (see 21 CFR 300.50). Even in that case, whether the optimal ratio of the two isomers is the ratio produced by an undirected or unmodified synthesis should be critically examined. In general, geometric isomers have been developed as single isomers. Practice with respect to diastereoisomers has been variable. These categories of stereoisomers will not be considered further in this document. Examination of cases in which the properties of enantiomers have been evaluated reveals instances in which both members had similar desirable activities:

- both enantiomers of dobutamine are positive inotropes;
- both ibuprofen enantiomers are anti-inflammatory agents;
- both enantiomers of warfarin and phenprocoumon are anticoagulants;
- the enantiomers of bupivicaine both produce local anesthesia;
- the enantiomers of the quinolones and the b-lactam antibiotics are all antibacterial instances in which one member of a pair was pharmacologically active and the other inactive (l-propranolol is a b-blocker; d-propranolol is not),
- the enantiomers had completely different activities (d-sotalol is a type 3 antiarrhythmic while l-sotalol is a b-blocker) or
- had different concentration-response relationships for a given property.

While inactivity of one member of a pair might be considered trivial, there are instances in which toxicity has been linked to one member of a pair of stereoisomers, not necessarily the active isomer (granulocytopenia is related to the d-isomer of levodopa; vomiting is caused by the d-isomer of levamisole; and myasthenia gravis symptoms were no longer observed when the d-isomer was removed from d,lcarnitine), and there are examples of an effect on the disposition of one member of a pair by the other. In addition, there are many cases in which enantiomers have been shown to have different pharmacokinetic behavior. Differences in pharmacokinetic behavior may not pose a major therapeutic problem although it can make non-chiral blood level assays difficult

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to interpret with respect to activity and confuse interpretation of non-clinical data if the pharmacokinetic properties of the isomers in animals differ from those in humans.

While some enantiomeric pairs have had interesting and useful therapeutic properties (e.g., dl-sotalol, dl-dobutamine), there is no reason to expect the optimum ratio of the components to be the 1:1 ratio of a racemate (i.e., the dose response curves would not usually be expected to be congruent).

Despite the problems identified with some racemates, the common practice of developing racemates has resulted in few recognized adverse consequences. Although it is now technologically feasible to prepare purified enantiomers, development of racemates may continue to be appropriate. However, currently available information suggests that the following should be considered in product development:

1. Appropriate manufacturing and control procedures should be used to assure stereoisomeric composition of a product, with respect to identity, strength, quality and purity. Manufacturers should notify compendia of these specifications and tests.
2. Pharmacokinetic evaluations that do not use a chiral assay will be misleading if the disposition of the enantiomers is different. Therefore, techniques to quantify individual stereoisomers in pharmacokinetic samples should be available early. If the pharmacokinetics of the enantiomers are demonstrated to be the some or to exist as a fixed-ratio in the target population, an achiral assay or an assay that monitors one of the enantiomers may be used, subsequently.

II. POLICY IN GENERAL

The stereoisomeric composition of a drug with a chiral center should be known and the quantitative isomeric composition of the material used in pharmacologic, toxicologic, and clinical studies known. Specifications for the final product should assure identity; strength, quality, and purity from a stereochemical viewpoint.

To evaluate the pharmacokinetics of a single enantiomer or mixture of enantiomers, manufacturers should develop quantitative assays for individual enantiomers in *in vivo* samples early in drug development. This will allow assessment of the potential for interconversion and the absorption, distribution, biotransformation, and excretion (ADBE) profile of the individual isomers. When the drug product is a racemate and the pharmacokinetic profiles of the isomers are different, manufacturers should monitor the enantiomers individually to determine such properties as dose linearity and the effects of altered metabolic or excretory function and drug-drug interactions. If the pharmacokinetic profile is the same for both isomers or a fixed ratio between the plasma levels of enantiomers is demonstrated in the target population, an achiral assay or an assay that monitors one of the stereoisomers should suffice for later evaluation. In vivo measurement of individual enantiomers should be available to help assess toxicologic findings, but if this cannot be achieved, it would be sufficient in some cases to establish the kinetics of the isomers in humans.

Unless it proves particularly difficult, the main pharmacologic activities of the isomers should be compared in *in vitro* systems, in animals and/or in humans.A relatively benign toxicologic profile using the racemate would ordinarily support further development without separate toxicologic evaluation of the individual enantiomers. If, however, there are toxic findings other than those that are natural extensions of the pharmacologic effects of the drug, and especially if they are unusual or occur near the effective dose inanimals or near the planned human exposure, toxicologic evaluation of the individual isomers in the study where the toxicity was detected should be undertaken.

FDA invites discussion with sponsors concerning whether to pursue development of the racemate or the individual enantiomer. All information developed by the sponsor or available from the literature that is relevant to the chemistry, pharmacology, toxicology, or clinical actions of the stereoisomers should be included in the IND and NDA submissions.

III. CHEMISTRY, MANUFACTURING AND CONTROLS

The chemistry section of the application should contain the requisite information to assure the identity, quality, purity and strength of the drug substance and drug product. In addition, the following considerations should be taken into account when dealing with chiral drug substances and drug products.

Methods and Specifications

Drug Substance

Applications for enantiomeric and racemic drug substances should include a stereochemically specific identity test and/or a stereochemically selective assay method The choice of the controls should be based upon the substance's method of manufacture and stability characteristics.

Drug Product

Applications for drug products that contain an enantiomer or racemic drug substance should include a stereochemically specific identity test and/or a stereochemically selective assay method. The choice of the controls should be based upon the product's composition, method of manufacture and stability characteristics.

Stability

The stability protocol for enantiomeric drug substances and drug products should include a method or methods capable of assessing the stereochemical integrity of the drug substance and drug product. However, once it has been demonstrated that stereochemical conversion does not occur, stereoselective tests might not be needed.

Labeling

The labeling should include a unique established name and a chemical name with the appropriate stereochemical descriptors.

Pharmacology/Toxicology

Pharmacology

The pharmacologic activity of the individual enantiomers should be characterized for the principal pharmacologic effect and any other important pharmacological effect, with respect to potency, specificity, maximum effect, etc.

Pharmacokinetic Profile

To monitor in vivo interconversion and disposition, the pharmacokinetic profile of each isomer should be characterized in animals and later compared to the clinical pharmacokinetic profile obtained in phase 1.

Toxicology

It is ordinarily sufficient to carry out toxicity studies on the racemate. If toxicity other than that predicted from the pharmacologic properties of the drug occurs at relatively low multiples of the exposure planned for clinical trials, the toxicity study where the unexpected toxicity occurred should be repeated with the individual isomers to ascertain whether only one enantiomer was responsible for the toxicity. If toxicity of significant concern can be eliminated by development of single isomer with the desired pharmacologic effect, it would in general be desirable to do so. The agency would be pleased to discuss any cases where questions exist regarding the definition of "significant toxicity."

Impurity Limits

It is essential to determine the concentration of each isomer and define limits for all isomeric components, impurities, and contaminants on the compound tested preclinically that is intended for use in clinical trials. The maximum allowable level of impurity in a stereoisomeric product employed in clinical trials should not exceed that present in the material evaluated in nonclinical toxicity studies.

IV. Developing a Single Stereoisomer After the Racemate is Studied

To develop a single stereoisomer from a mixture that has already been studied non-clinically, an abbreviated, appropriate pharmacology/toxicology evaluation could be conducted to allow the existing knowledge of the racemate available to the sponsor to be applied to the pure stereoisomer. Ongoing studies would usually include the longest repeat-dose toxicity study conducted (up to 3 months), and the reproductive toxicity segment II study in the most sensitive species, using the single enantiomer. These studies should include a positive control group consisting of the racemate. If there is no difference between the toxicological profile of the single stereoisomeric product and the racemate, no further studies would be needed. If the single enantiomer is more toxic, the explanation should be sought and the implications for human dosing considered.

Clinical and Biopharmaceutical:

Where little difference is observed in activity and disposition of the enantiomers, racemates may be developed. In some situations, development of a single enantiomer is particularly desirable (e.g., where one enantiomer has a toxic or undesirable pharmacologic effect and the other does not). A signal that should trigger further investigation of the properties of the individual enantiomers and their active metabolites is the occurrence at clinical doses of toxicity with the racemate that is not clearly expected from the pharmacology of the drug or the occurrence of any other unexpected pharmacologic effect with the racemate. These signals might be explored in animals but human testing may be essential.

It should be appreciated that toxicity or unusual pharmacologic properties might reside not in the parent isomer, but in an isomer-specific metabolite.In general, it is more important to evaluate both enantiomers clinically and consider developing only one when both enantiomers are pharmacologically active but differ significantly in potency, specificity, or maximum effect, than when one isomer is essentially inert. Where both enantiomers are fortuitously found to carry desirable but different properties, development of a mixture of the two, not necessarily the racemate, as a fixed combination might be reasonable.

If a racemate is studied, the pharmacokinetics of the two isomers should be studied in Phase 1. Potential interconversion should also be examined. Based on Phase 1 or 2 pharmacokinetic data in the target population, it should be possible to determine whether an achiral assay or monitoring of just one enantiomer where a fixed ratio is confirmed will be sufficient for pharmacokinetic evaluation.

If a racemate has been marketed and the sponsor wishes to develop the single enantiomer, evaluation should include determination of whether there is significant conversion to the other isomer, and whether the pharmacokinetics of the single isomer are the same as they were for that isomer as part of the racemate.

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