Journal of Pharmaceutical & Biomedical Analysis
Vol. 11, No. 11/12, pp. 1167–1172, 1993
Printed in Great Britain

0731–7085/93 $6.00 + 0.00
Pergamon Press Ltd

Chiral drugs: the FDA perspective on manufacturing and control*

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Abstract: On 27 May 1992, the FDA announced the availability of a policy statement on the development of stereoisomeric drugs. This statement has significant implications for the chemist who is working on the development and validation of analytical controls for chiral drug substances and products. The testing of the bulk drug, the manufacturing of the finished product, the design of stability testing protocols, and the labelling of the drug must all take the chirality of the active ingredient into consideration.

Keywords: *Stereochemistry; chiral drugs; identity tests; assays; stability; chiral HPLC; polarimetry; enantiomers; racemates.*

Chirality

The word 'chirality', derived from the Greek, *chiros* (χειρ or χειρὸζ, meaning 'hand'), describes the nature of an object which is not superimposable on its mirror image. The word itself seems to be contrary to any concept of harmonization. Yet, in the world of drug development and regulation, the harmonization of regulations is an issue which is being confronted. The reality of the international marketplace today is that a manufacturer cannot survive if his product cannot be sold in all major markets in a substantially identical form. This is the driving force behind efforts at regulatory harmonization, regardless of the industry involved.

Our focus in this paper is on a particular part of drug development, manufacture and marketing. This is, of course, the role played by the analytical chemist. Whether the samples being analysed originate from a synthetic organic chemist or a clinical pharmacologist, the chirality of a drug influences the analyst's approach. To be more correct, it is often the approach of the regulatory scientist to the chirality of the drug which influences the analyst.

The scientific background which provides a common foundation for both research and regulatory science will be discussed first. Second, brief consideration will be given to what constitutes the 'state of the art' with regard to the regulatory analytical chemistry of chiral drugs. Lastly, the regulatory basis for the FDA's policy on the development of stereoisomeric drugs [1] will be discussed. This will focus on issues of nomenclature and analytical controls. Special attention will be given to those areas which appear to present the greatest challenges to achieving true harmonization in the regulations for the analysis of chiral drugs.

Scientific Background

Within reasonable limits, these considerations are restricted to those issues directly related to the applications of analytical chemistry to pharmaceutical and biomedical problems. The challenge of the stereospecific synthesis of organic compounds, while interesting, is beyond the scope of this paper. Also, the stereochemical characterization of a chiral compound will be bypassed. As crucial as these questions are to drug development, they are not analytical chemistry questions.

Similarly, the larger issues of pharmacology and clinical testing will not be addressed, with a single exception. Without considering any questions of specific study design, or the extent

*Presented at the 'Fourth International Symposium on Pharmaceutical and Biomedical Analysis', April 1993, Baltimore, MD, USA.

of testing on the unwanted stereoisomeric form that should support the marketing approval of a chiral drug, the importance of analytical chemistry is apparent from the significance that the Center for Drug Evaluation and Research gives to stereospecific assays. From the beginning of the development of a chiral drug, it is essential that a stereospecific assay be used [2]. Therefore, the laboratory development of such an assay should not be deferred for any chiral drug, whether racemic or enantiopure.

Before any attempt at harmonization can be made, the positions that are to be harmonized must be defined as well as thoroughly understood. A living system sees the chiral drug as the left- and right-handed optical antipodes. However, in the manufacturing and control of chiral drugs, the antipodes are not the *R*- and *S*-molecules, but bulk amounts of the racemic drug and the bulk drug which is enantiomerically pure — more or less. Distinguishing between the former may be among the easiest tasks in the analytical laboratory, while the latter problem may be both more challenging and more essential. Let us briefly recall the background from which these concepts arose [3–6].

Few students of chemistry have forgotten the fascinating story of Pasteur's physical resolution of dextro- and levo-rotatory tartaric acid through his observation of the hemihedral faces of the crystals of sodium ammonium tartrate in May of 1848. The importance of Pasteur's interest in mineralogy to his discovery is somewhat less well known. His interest in the polarization of light resulting from double refraction by Iceland spar led him to the work of the French mineralogist Biot, who had studied the rotation of polarized light by quartz plates. Biot had also found that certain organic compounds, such as camphor, behaved similarly in solution.

Biot's work, in turn, stimulated Pasteur to study the effect of solutions of organic compounds on polarized light. Thus, when he observed hemihedry in the crystals of sodium ammonium tartrate, as he had both in other organic crystals and quartz, the next step was clearly to sort the crystals into two parts, and then study the solutions with polarized light. This work resulted in the finding that there were not only the dextro- and levo-rotatory forms of the acid, but two forms which did not rotate polarized light — 'racemic' or 'paratartaric' acid, and 'mesotartaric' acid.

Biot challenged Pasteur to reproduce his work in Biot's own laboratory, using his own materials. Pasteur was successful at this, leading Biot to tell him, 'My dear boy, I have loved Science so much during my life, that this touches my very heart.' This is likely one of the earliest examples of analytical methods validation. It is, however, even less known that, over the next few years, Pasteur assumed a role not unlike that of an FDA inspector. He visited manufacturing sites for tartaric acid, especially those which were known to produce 'racemic acid'. His systematic search for the manufacturing variations which caused the production of racemic acid would surely have been easier if our GMP regulations had been in effect then!

Pasteur realized the role of luck in his discovery. He was fond of saying that 'chance only favours the mind which is prepared'. Yet his luck involved more than the mental preparedness which led him to recognize the hemihedral faces on the crystals. It was established some years later that sodium ammonium tartrate crystallizes in an entirely different structure above 26°C, and not only does not exhibit the hemihedral faces, but crystallizes as a racemic compound! It has been speculated that a part of Pasteur's luck was his choice to work in the cooler climate of Paris [4].

To bring this brief tale of chemical detective work to a conclusion, Pasteur ultimately succeeded in racemizing optically active tartaric acid by maintaining its salt with cinchonine at a high temperature for several hours. After this, he was able to isolate both the *dextro*- and *levo*-tartaric acids, as well as mesotartaric acid, from the solution. Though his studies of fermentation continued for many years, this appears to have brought his work on the resolution of tartaric acid salts by crystallization to a close.

In his subsequent work, Pasteur found that fermentation processes used only *dextro*-tartaric acid as a substrate. This finding was soon generalized to other biological processes, leading to the concept, so effectively propounded by Ariëns in recent years, that one molecule of an enantiomeric pair is inactive, and thus constitutes 'isomeric ballast' which has no physiological effect [7, 8].

If this concept were universally true for chiral drugs, then there would be little need for harmonization. Developing a chiral drug would require only that the stereoisomer in

which the desired activity resided be identified. The most safe and effective drug formulation would then contain only this stereoisomer in appropriate purity.

However, the real worlds of chemistry and pharmacology are not that simple. The methods of analytical chemistry have given the chemist the chromatographic tools necessary to accurately quantitate one enantiomer in the presence of another, often without an intermediate derivatization. The beginnings of direct resolutions by chiral chromatography were in the mid-1960s, when gas chromatography was applied to this problem by Gil-Av [9]. Such separations were extended to liquid chromatography in the 70s [10]. Direct resolutions of enantiomers became more common with the development of synthetic multiple-interaction chiral stationary phases, mainly by Pirkle at Illinois [11, 12].

Regulatory Analytical Chemistry

Today the direct resolution of enantiomers is a relatively common technology, supported by the development of a wide variety of chiral stationary phases. While it is not yet clear whether an analytical separation capable of baseline resolution can be developed for *any* chiral analyte, it is clear that this accomplishment is no longer a remarkable event. Indeed, it appears that, for most chiral drugs, quantitation of one enantiomer in the presence of the other to a precision suitable for regulatory purposes is within reach. It is, of course, true that, as of today, there are few, if any, marketed products for which a stereoselective assay using chiral liquid chromatography has been proposed. None is published in the United States Pharmacopeia as a compendial monograph. The only rationale for this lack of regulatory and compendial recognition seems to be that the drugs approved today were manufactured and controlled using the analytical technology commonly accepted five years ago. Even the most prudent manufacturer may understandably be hesitant to propose a novel regulatory method when it may delay the approval of its newest drug product.

The compendial applications of polarimetry to the establishment of identity, purity and stability have been discussed by Chafetz [13]. Despite its classical significance, the practice of relying on the rotation at the sodium D wavelength (589 nm) often leads to measurements which are less precise than those which may be obtained at shorter wavelengths using a photoelectric polarimeter. Similarly, the relatively wide limits often found in compendial monographs make optical rotation a less appropriate measure of purity than the usual chromatographic assay. There appears to be significant potential for a conclusion based on such data to be of limited technical and regulatory use.

Just as the synthetic organic chemist can now determine how stereoselective a reaction is, the pharmacologist can now assess the ratio of any given activity between the more active and the less active enantiomer. An exhaustive survey of the literature reveals that determinations of this ratio may be used to divide chiral drugs into four groups. There are those for which the enantiomers are essentially equally effective, those where all or most of the desired activity is associated with one enantiomer, those where the therapeutic effectiveness is greater for the racemate than for either pure enantiomer, and those where the enantiomers have distinct pharmacological activities [14]. It is not the author's objective to give examples of members of these groups. Instead, let me emphasize that the regulatory scientist relies on the information provided him by the laboratory analyst to place the drug in one of these groups.

FDA Policy

In contrast with our colleagues in the laboratory, the work of the regulatory scientist is not governed solely by technical considerations. In this environment, the regulatory scientist cannot personally do the experiment; reliance must be upon reports of the experimental observations and conclusions of others. Since the analytical controls on a manufacturing process that may be performed thousands of times in the future must be evaluated *in advance*, the control methods should be adequate to demonstrate *after the fact* that the process was performed correctly.

The beacons that guide regulatory efforts are the laws, regulations, and guidelines which have been published. These are words, and no more, though they are based on laboratory observations which are presumed to be technically sound. Therefore, let us turn first to questions of nomenclature. In saying this, I am not referring to the systematic nomenclature of

chemistry. These issues have been and are both well-defined and subject to little controversy. I refer instead to more general questions of the terminology of stereochemistry — first in the area of regulations.

Our responsibilities as chemists at the Food and Drug Administration rest primarily on two parts of the Food, Drug and Cosmetic Act. The first requires us to refuse to approve a New Drug Application (NDA) if: '. . . the methods used in, and the controls used for, the manufacture, processing, and packaging of such drug are inadequate to preserve its identity, strength, quality, and purity . . .' [15]. The second addresses the practical implementation of these methods and controls by deeming a drug: '. . . to be adulterated . . . if . . . the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated in conformity with current good manufacturing practice . . .' [16].

Clearly, there is not much about chirality here, nor should there be. The law is quoted primarily to show where the FDA begins, and where it may be assumed that regulatory scientists in other countries also begin. The exact words may vary, but the intent is shared.

Next, consider the regulations which implement Good Manufacturing Practices (GMPs). The manufacturer is required to test each lot of each component of a drug, with the proviso that a supplier's certificate of analysis may be accepted under certain conditions. These require that the manufacturer of the drug 'conduct at least one specific identity test' on each component, and that the supplier's results be validated at appropriate intervals [17]. This requirement begins to touch on chirality, for how can an identity test for a chiral drug be specific if it does not discriminate between enantiomers, as well as between either enantiomer and the racemate?

This question will be discussed further in conjunction with identity tests and assays. But now let us turn to two additional questions of harmonization in the area of the terminology of stereochemistry.

We have heard about the various names for tartaric acid that were known to Louis Pasteur. The fact is that the original name, 'racemic acid' has long been forgotten as it applied to a specific compound. It is well established as an adjective to describe a mixture of equal amounts of two enantiomeric molecules. Upon further consideration, it is found that this word is used in quite different ways. A 'racemic mixture' refers to a 50:50 mixture in general. A 'racemic conglomerate' refers to the 50:50 mixtures of crystals, each individual of which is either left- or right-handed. And a 'racemic compound' refers to crystalline material in which the crystal structure contains a centre of symmetry, so that each unit cell of the crystal contains exactly equal numbers of the left- and right-handed molecules.

Over the past couple of years, there has been extensive debate over such general stereochemical terminology. While there appears to be general agreement about what is meant by a 'racemate' and an 'enantiomer', there is less agreement about what lies between. Since the technical capability now exists to quantitate one enantiomer in the presence of the other, how far can a racemic mixture deviate from 50:50 before it is no longer a 'racemate'? What level of enantiomeric purity is required for a drug to be called 'enantiopure'? 'Enantiomerically enriched' may seem appropriate for a 60:40 or 70:30 mixture, but where does it become a 'pure enantiomer'? What use, if any, should be allowed or encouraged for such newly coined terms as 'homochiral' or 'scalemic'?

Such issues as these are not merely the concern of regulators in their efforts to achieve international harmonization. Indeed, the International Union for Pure and Applied Chemistry is currently working to develop standards for the terminology of stereochemistry. The author implores all analytical chemists to address these questions through their professional societies, for the efforts to harmonize regulations will depend upon the clarity of the technical terminology which is used.

A second area of concern with the nomenclature of stereochemistry is that of established or nonproprietary names. Although these are often called 'generic names', I shall avoid this usage to keep the issue clearly separate from that of the manufacturing and control of generic drugs.

The use of nonproprietary names as an aid to the health care professional is well-established. An established name, as published by the United States Adopted Names Council, or USAN, is required to appear on the labelling of drugs marketed in the USA. The World Health Organization (WHO) is empowered to

recommend names (identified as International Nonproprietary Names, or INN) to its member states.

The rules for coining a USAN do not routinely include specification of the chirality of the molecule in the nonproprietary name for a new chemical entity [18]. The primary presentation of this information is found in the systematic chemical name. Subsequent USAN's for the racemate or another enantiomer should add appropriate prefixes, such as rac-, dextro-, etc.

The lack of unequivocal information about the stereochemistry of a drug in its nonproprietary name has led to recommendations for a system which has been given the acronym 'SIGNS' (for Stereochemically Informative Generic Name System) [19]. This proposal has received extensive support in both Canada and Europe. Its clarity of definition should, however, be considered along with potential ambiguities.

For example, when a USAN has been adopted which is fully stereospecific (e.g. ibuprofen, which is defined as a racemate), what is the technical and legal significance of labelling its dextro-rotatory isomer as *dextro*-ibuprofen? Suppose that conditions of solvent, concentration, and wavelength are found that render this latter material levo-rotary? This is not unknown, for the closely-related naproxen is dextro-rotatory as the acid and levo-rotatory as the sodium salt [20]. There is no provision, either in the USAN rules or in FDA's regulations, for treating a relative stereochemical descriptor as a separable prefix. The established name, as well as the systematic chemical name, is a single entity.

Let us turn now to questions of analytical controls. A New Drug Application is required to contain, for the drug substance, full information about its physical and chemical characteristics, as well as specifications and analytical methods which are sufficient to assure its identity, strength, quality and purity [21]. For the drug substance, FDA's recently released policy statement requires the submission of either or both a stereochemically specific identity test and a stereochemically selective assay method [1]. Both may be needed, depending upon the nature of the drug substance and the method of manufacture.

The validity of such methods should be demonstrated. This necessitates the preparation and characterization of laboratory scale samples of both the racemate and at least one enantiomer. Physical properties, such as IR spectra and melting range, can then be measured for both. These measurements will support the validation of the identity tests.

Now, let us return briefly to the GMP questions raised above, to see why such measurements are needed. If an identity test is to be a specific identity test for GMP purposes, it must distinguish between enantiomers, or between an enantiomer and the racemate. The regulations require that it be performed by the manufacturer on every lot of the component received from the supplier. Racemic chiral drugs are often manufactured by a method which is 'known' to lack stereoselectivity. 'Pure enantiomers' often may be obtained from natural sources, and thus 'known' to be optically pure. While, as chemists, we do not question this knowledge, as regulators, we ask for verification of the results of the manufacturing process through the GMP process.

As with the bulk drug substances, FDA regulations require specifications and analytical methods which are sufficient to assure the identity, strength, quality and purity of the drug product, as well as its bioavailability [22]. As with drug substances, the FDA's policy statement calls for drug products with a chiral active ingredient, whether enantiomeric or racemic, to include either or both a stereochemically specific identity test for the active ingredient in the formulation and a stereochemically selective assay method.

For the drug product, the rationale for such controls is different. For those products which are non-racemic, whether this means enantiomerically enriched or enantiomerically pure, this will be stated on the label. In turn, the analytical controls used to release the product must show that it conforms to the label claim. Thus the FDA's policy expresses a concern that an enantiopure active may be partially racemized in manufacture, and asks that this be investigated. It is, of course, possible that such racemization does not occur under the conditions of manufacture, packaging, distribution and storage through expiration. In such an event, the implication of the policy statement would be rebuttable by laboratory data.

A second implication of FDA policy focuses more on products manufactured from racemic active ingredients. If such a product contains a chiral inactive ingredient, then it seems

reasonable to investigate its effect on the drug product. For example, cyclodextrin is commonly used both to enhance the solubility of a slightly soluble drug and as a resolving agent in chiral liquid chromatography. The availability of a stereoselective assay for a racemic drug would permit evaluation of the relative concentrations of both enantiomers in dissolution studies. Whether such data would lead to enantiomeric ratios as part of dissolution specifications cannot be said at this time, but the question should be asked in the drug development process.

Similarly, the development of a stereoselective assay provides essential support for bioavailability studies. The important point to remember is that such studies depend absolutely on the availability of a valid stereoselective assay method.

As with the analytical controls on the bulk drug substance, there appear to be few, if any, areas of significant difference between the various national regulatory agencies. What differences exist are more in the nature and number of studies which must be done to show that a chiral drug product is safe and effective. The fact that such studies are needed is not in dispute, as far as is known today. Thus stereoselective analytical methods will continue to be an essential part of drug development.

FDA's announcement of a policy statement on the development of stereoisomeric drugs has significant implications. These are not limited to clinical, pharmacological, or toxicological issues. They extend also to the chemist involved in the development and validation of analytical controls for chiral drug substances and products. The prudent chemist can no longer assume that a steroselective reaction yields a pure stereoisomer. The prudent drug developer can no longer assume that all activity is found in one enantiomer. These 'assumptions' must now be stated as hypotheses which we now have the laboratory tools to test experimentally.

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[*Received for review 16 June 1993*]