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STEREOISOMERIC DRUGS:
FDA'S POLICY STATEMENT AND THE IMPACT ON DRUG DEVELOPMENT

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ABSTRACT

On May 1, 1992 FDA issued its long awaited policy statement concerning the development of stereoisomeric drugs. These drugs are also known as "chiral drugs." This paper will focus on the historical perspective of the stereoisomer issue, review of FDA's policy and a discussion of the potential impact of this policy on drug development including the impact on marketing exclusivity.

INTRODUCTION

The FDA Stereoisomeric Drug Policy had been in the development stage for many years and is the result of input from many scientific and regulatory bodies throughout the world including European and Japanese regulatory authorities and trade and scientific organizations such as the Pharmaceutical Manufacturers Association (PMA). It represents a subject, which since the early

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1960's has been steadily evolving, based on new information, not only in pharmacology and toxicology disciplines, but in manufacturing and processing disciplines as well. Information on the potentially differing effects of stereoisomer components has long been recognized by the pharmaceutical industry and regulatory bodies. In the past these regulatory bodies, as a whole, were content not to investigate these more fully due to the problems associated with the development of reproducible and cost effective ways of making specific individual isomers. Today, however, pharmaceutical production techniques have evolved to the point that practical manufacturing processes have been, and are continuing to be, developed that will make stereospecific drug synthesis possible on a commercially viable scale. With this, FDA has seen fit to issue their Stereoisomeric Drug Policy Statement, which will no doubt have great impact on the future development of chiral drugs.

DEFINITIONS

Before discussing the issue it would be appropriate to provide definitions for the following terms:

chiral- from the Greek word "cheir" meaning "handed." Drugs that are chiral have a structural feature that allows for an identical mirror image that cannot be superimposed.

stereoisomer- a molecule that is composed of the same atoms or groups of atoms bound in the same fashion as another but differing in three-dimensional arrangement.

enantiomer- from the Greek word "enantio" meaning opposite. One half of a stereoisomer mirror image.

eutomer- the enantiomer that exhibits a particular drug related effect.

distomer- the enantiomer that lacks the particular drug effect or exhibits it to a lesser degree.

racemate- a chiral compound that exists as an equal mixture of two enantiomers.

Cahn-Ingold-Prelog System- Absolute configurational definitions (R,S) which has generally supplanted the older d,l,(+),(-) descriptors.

A journal on chirality has recently been introduced and the reader is encouraged to select the references cited herein for more exhaustive coverage of pharmaceutical enantiomers.

HISTORICAL PERSPECTIVE

Compounds that exhibit "handedness" and therefore may exhibit varying characteristics have been recognized by scientists since the mid 19th century. In 1844 Eilhardt Mitscherlich, a German scientist, discovered that two related compounds of tartaric acid twisted a beam of light in different directions. In 1844 Louis Pasteur found that the compound paratartrate existed as two different kinds of crystals, one that bent polarized light to the right and one that bent it to the left, but when combined had no effect on polarized light. With this he realized that the light bending properties of each of the crystals canceled each other out and therefore were, in effect, mirror images of each other.[1] Since then scientists have discovered that in all living things there is a "handedness" and that different living molecules will only react with certain hands of various compounds and in fact prefer compounds with a "left handed" orientation (left handed referring to the direction to which the substance twists light).

Pfeiffer suggested more than 35 years ago that the potency of a drug is directly proportional to the activity ratio of the eutomer compared to the distomer. Pfeiffer's rule states, "The greater the difference in pharmacological effect of the optical isomers of a drug, the lower its effective dose."[2]

TABLE 1

RECENT STUDIES ON CHIRAL DRUGS MARKETED AS RACEMATES

propranolol-	(S)-propranolol has been found to be as effective a beta blocker in half the dose as the currently used racemate. It did not effect the conversion of thyroxine to triiodothyronine and can be used without disturbance of thyroid function.[7,8]
labetalol-	(R,R)-labetalol is responsible for the beta blocker properties while (S,R)-labetalol is an alpha-antagonist. Studies are now being conducted to determine if the (R,R) isomer alone does not produce peripheral vascular problems common with beta blockers.[9]
mianserin-	In vitro studies have shown that toxic reactions are mainly due to (R)-mianserin. If clinically confirmed, there would be a strong case for single (S)-mianserin development.[9,10]
hexobarbital-	In elderly subjects, reduced oral clearance of (S)-hexobarbital but not (R)-hexobarbital was found.[10]
etodolac-	Anti-inflammatory activity is mainly due to the (S)-enantiomer. The decrease in synovial fluid PGE_2 and PGF_2 has been found to correlate with the free (S)-etodolac concentration in synovial fluid.[11]
verapamil-	Only (S)-verapamil has cardiovascular effects. (R)-verapamil has shown efficacy in overcoming multiple-drug resistance in cancer therapy.[12] Evaluation of both immediate and controlled release formulations established that R/S ratios were formulation dependent.[13]

TABLE 1 Continued

hydroxychloroquine-	Blood concentrations of the (R) enantiomer exceeded that of (S)-hydroxychloroquine following both oral and intravenous doses in all patients studied. The renal clearance and metabolism but not absorption was stereoselective.[14]
flurbiprofen-	(S)-flurbiprofen has been shown to be responsible for the analgesic and anti-inflammatory activity in rodents.[13]
atenolol-	(S)-atenolol has been observed to account for all the negative chronotropic and inotropic responses of the racemic drug.[10,14]

The importance of chiral compounds in the pharmaceutical industry came to be realized in the early 1960's in connection with the drug thalidomide. This molecule was developed as a racemic mixture, a 50/50 mixture of two enantiomers, and was being marketed in Europe as a sedative while awaiting approval in the U.S. During the U.S. approval process it was discovered that the drug caused birth defects. Upon investigation of this compound it was later postulated that one of the enantiomers was responsible for the sedative properties (eutomer), while the other (distomer) was responsible for the teratogenic effects.[3] If the single eutomer was developed it may have been possible to avoid the unwanted effects. Similarly, the R,R-enantiomer of the tuberculostatic ethambutol can cause blindness and the lethal side effects of benoxaprofen might have been avoided had the drug been sold as the pure enantiomer.[4]

It is estimated that today approximately one-half of the 700 most prescribed drugs contain at least one chiral center[5] and that 90% of these chiral drugs are marketed as racemic mixtures.[6] Some

TABLE 2

MARKETED DRUGS EXHIBITING ENANTIOSELECTIVITY

ABSORPTION ENANTIOSELECTIVITY[15]

L-dopa methotrexate

D enantiomers of beta lactam antibiotics

METABOLIC ENANTIOSELECTIVITY[12]

mephobarbital	warfarin	amphetamines
ifosfamide	mephenytoin	

DISTRIBUTION AND PROTEIN BINDING ENANTIOSELECTIVITY[15]

verapamil	warfarin	
pentobarbital	methadone	moxalactam
disopyramide	verapamil	chloroquine

ELIMINATION ENANTIOSELECTIVITY[15]

pentobarbital	verapamil	warfarin
tocainide	benoxaprofen	

of these more common drugs include; ibuprofen, in which the left handed twin (S enantiomer) is four times more potent than the right handed and Darvon, in which one enantiomer is a sedative and the other, called Novrad (Darvon backwards) is a cough suppressant. There have been many recent studies on chiral drugs marketed as racemic mixtures (Table 1) and examples of drugs marketed as racemates which exhibit enantioselectivity are plentiful (Table 2). However, some drugs, such as the ACE inhibitors, are marketed as single enantiomers (Table 3).

As a result of advances in the area of stereochemistry and its effect on pharmacology and toxicology, regulatory bodies have

TABLE 3

DRUGS MARKETED AS SINGLE ENANTIOMERS[16]

D-penicillamine	dextroamphetamine	naproxen
L-dopa	methotrexate	diltiazem
ACE inhibitors	L-thyroxine	timolol
dextromethorphan		

become more concerned with the possible effects of these compounds on the chemical, and biological systems of humans, as well as their potential differing clinical effects. To help ascertain answers to these questions and establish standards for the systemic development and review of such compounds these bodies have established policies relating to chiral compound development. In 1987 the Japanese were the first to establish rational requirements for racemic mixtures.[17] They require full pharmacology and toxicology characterization for each of the enantiomers. They have been followed by the European Community and the Nordic countries in the establishment of guidelines.[18] In the U.S. the FDA as early as the 1980's had included in their New Drug Application (NDA) guidelines for the submission of data on the drug substance[19], requirements for the full characterization of stereoisomers from the chemical point of view as well as information on the toxicology and pharmacology of each enantiomer. However, these requirements were applied on a case by case basis.

Since 1989, FDA has had in place an internal Center for Drug Evaluation and Research (CDER) Stereoisomer Committee charged with determining what requirements, if any, should be imposed upon a sponsor developing a stereoisomeric compound.[20] It was the work of this committee and other factors (Table 4) that formed the

TABLE 4

RATIONALE FOR ISSUANCE OF FDA'S POLICY STATEMENT FOR THE DEVELOPMENT OF NEW STEREOISOMERIC DRUGS[20,21,23]

o Commercially viable technological advances in isomer separation.

o Actions of other regulatory bodies on similar issues.

o Realization that some adverse reactions are attributable to an unnecessary isomer.

o Realization that for some drugs (especially those with steep dose-response curves) use of single enantiomers may increase selectivity of drug action, reduce total drug exposure, and simplify dose-response relationships.

o FDC Act and regulations that pertain to Investigational New Drug (IND)/New Drug (NDA) applications do not adequately address the situation concerning drug molecules containing stereoisomers.

o A desire to design and discover drugs through rational processes.

o Requests from sponsors for guidance.

rationale for the issuance of the FDA's stereoisomeric drugs policy statement. Also in 1989, the Pharmaceutical Manufacturer's Association formed its own committee which articulated an industry position on the development of chiral drugs via a position paper.[21] In Canada, the Health Protection Branch has established a working group on drug stereochemistry to develop a guideline for chiral drugs.[22]

FDA'S POLICY

The document addressing FDA's position on stereoisomers is entitled "FDA POLICY STATEMENT FOR THE DEVELOPMENT OF NEW STEREOISOMERIC DRUGS"[24]. It is a six page document which spells out in detail FDA's expectations of sponsors in the development of "new" chiral drugs. Although limited to new stereochemical drugs, i.e. those for which new NDA's are filed, it also covers the development of single enantiomer drugs from currently marketed racemic mixtures.In the policy FDA makes it clear that although they would prefer the development of only one enantiomer form of a chiral drug, the development of a racemic mixture may continue to be appropriate in certain situations. CDER now believes there are no compelling legal or scientific reasons for terminating the approval of a drug solely because it is a racemate.[15]

The FDA has divided enantiomers into three distinct categories as follows:

1) Both enantiomers have similar desirable activities which could be identical or each enantiomer could differ in the magnitude of effects (e.g. ibuprofen, promethazine).[12]

2) One enantiomer is pharmacologically active and the other is inactive (e.g. terbutaline), and

3) Each enantiomer has a completely different activity (e.g. propranolol).

Certainly, in case #1 the development of a racemic mixture would be justified. The appropriateness of a racemic mixture in either case

2 or 3 is less clear and would require significant justification based on any number of factors including toxicological profile, pharmacologic profile and pharmacokinetic profile. FDA further indicates that development of a racemic mixture would be appropriate in cases where the drug exhibits in vivo interconversion (instances where the enantiomer racemizes in plasma) and the differences between isomers, in terms of activity and disposition, are small. In order to generate the data needed to make determinations based on the above, a significant amount of time and resources would be required up front and this FDA policy helps sponsors to identify the scope and type of data needed to make such determinations.

FDA's policy is broken down into two major sections: one dealing with the general aspects of stereochemical drug development and the other dealing with the specific issues relating to chemistry, pharmacology/toxicology and clinical/biopharmaceutical aspects. Each section will be addressed in detail.

In general terms the policy calls for the development of quantitative assays for individual isomers in in vivo samples in order to properly evaluate the pharmacokinetics of enantiomers. These assays should be established early on in the drug development process to allow for the evaluation of interconversion potential and the absorption, distribution, biotransformation and excretion profile of each enantiomer. The policy also states that 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. This would call for laboratory data showing the activity of each enantiomer in terms of its intended drug use.

Perhaps the most important general consideration of the policy deals with the toxicological aspects of the stereochemistry issue. FDA states in the policy that "A relatively benign toxicological profile using the racemate would ordinarily support further

development without separate toxicological evaluation of the individual isomers"[24]. This, however, changes in instances where there are significant toxicological findings that are not extensions of the pharmacologic actions of the drug. If these toxicological findings are unusual or occur near the effective dose planned for human exposure, FDA would expect full toxicological evaluation of each enantiomer in the same type of study where the toxicity was detected. This would require repeating the study in which the toxicity was observed with each of the isomers and would no doubt add significantly to the development costs and timing for that drug's development.

In terms of specific requirements the policy sets forth criteria for the chemical evaluation of isomers in regard to methods and specifications for the drug substance (bulk active ingredient) and drug product (finished formulation) and for stability and labeling. For both the drug substance and drug product the policy states that stereochemical specific identity tests and/or stereochemical selective assay methods be provided for in the NDA. The choice of these control methods is up to the manufacturer and should be based on the method of manufacture of the substance and its stability characteristics. Stability protocols for enantiomeric drug substances and drug products should include a method capable of assessing the stereochemical integrity of each. The labeling of an enantiomeric drug (one enantiomer of a chiral drug) should include a unique established name and a chemical name with an appropriate stereochemical descriptor. By this statement FDA is accepting the premise that an enantiomer of a chiral drug can be considered a new entity, which may have a significant impact on its approval status as well as its potential marketing exclusivity.

Concerning pharmacology and toxicology, the FDA policy provides some very specific guidance in relation to pharmacology,

pharmacokinetics, toxicology, impurity limits and the development of a single stereoisomer after the racemate is studied. Each of these will be covered in more detail.

The policy states that the pharmacologic activity of the individual enantiomers should be characterized for the principal pharmacologic effect. It is left up to the sponsor to decide if this characterization needs to be performed in vitro or in vivo or in animals or in man. Obviously, the development stage which the drug is in would dictate the appropriate models. For pharmacokinetics, the pharmacokinetic profile of each enantiomer should be characterized in animals and compared to the clinical pharmacokinetic profile obtained in man from Phase 1 studies. This will serve to monitor potential in vivo interconversion and disposition. Enzymatic metabolism and protein binding can show a high degree of stereoselectivity. For example, we now know that the biotransformation of chiral compounds by cytochrome P450 systems may exhibit enantioselectivity.[14] When multiple isomers and multiple metabolites exist completely answering all of these questions represents an extensive undertaking compared with developing one molecule with one isomer and no metabolism.[20]

Many examples of stereoselective absorption and release from formulation may be found in the literature. Many pharmaceutical excipients are chiral (e.g. cyclodextrins and cellulose derivatives) and can interact preferentially with one of the enantiomers. The dissolution rate of the individual enantiomers from a formulation containing a racemate and a chiral excipient may differ significantly. In assessing bioequivalence, stereospecific assays provide more meaningful information because changes in the pattern of absorption may result in stereoselective metabolism.[25] For example, a stereospecific flurbiprofen assay showed a small (~ 8%) but statistically significant difference in AUC between different flurbiprofen products.[25] Despite this, little attention

has been directed toward the stereochemical implications of bioequivalence.

From the toxicological point of view it would ordinarily be appropriate to carry out toxicity studies on the racemic mixture. However, in the case of significant toxicity FDA will expect to see these studies repeated utilizing each of the individual enantiomers. This will ascertain whether the toxicity can be attributed to any of the single enantiomers. In the policy FDA invites sponsors to discuss with the agency "any cases where questions exist regarding the definition of 'significant toxicity'."[24]

In terms of impurity limits FDA indicates that it is essential to determine and define limits for all isomeric components, including impurities and contaminants and that they be known for the compound that is to be tested in the clinic. FDA is recommending that the allowable level of impurities in stereoisomeric drugs utilized in clinical trials not exceed the levels present in the material that was studied in the preclinical toxicity studies. Therefore, much if not all of this information needs to be defined in the preclinical stage and will no doubt be required for the IND before clinical studies can commence.

An interesting concept brought up in the FDA policy is that of "bridging studies." These are defined as abbreviated, appropriate pharmacology/toxicology evaluations conducted to allow the existing knowledge of the racemate to be applied to the enantiomer for purposes of approval of the single enantiomer. These bridging studies will be important in instances where a sponsor seeks to develop a single enantiomer from a racemate that has already been studied clinically or is in fact an approved product. The scope and type of bridging studies required would depend in large part on the existing data base for that product. The policy indicates that

these bridging studies would usually include repeating the longest repeat-dose toxicology study (up to three months) and repeating a reproductive segment II toxicity study in the most sensitive species. The policy points out that these studies should include a positive control group consisting of the racemate and if no differences are found no further studies would be needed. In the case where the single enantiomer is more toxic a full explanation would need to be provided which would take into account all the other factors previously discussed.

From the clinical and biopharmaceutical point of view FDA's position as stated in the policy is very simple, development of a single enantiomer should be considered when both enantiomers are pharmacologically active but differ significantly in potency, specificity, or maximum effect. When one enantiomer is essentially inert, as evidenced by the appropriate data the racemate may continue to be clinically developed. Also, when the effects of both enantiomers are not stereoselective, the use of the racemate may be entirely justifiable.

The policy is silent with regard to labeling issues. For example, should the labeling describe actions or side effects attributable to another stereoisomer where only one stereoisomer is proposed for marketing? Now that this policy is issued, it is up to the individual manufacturers to determine how best to deal with it and in some instances how to utilize it to their advantage. Questions regarding marketing are left up to the sponsor (Table 5) Although it appears that this policy will serve to add only time and cost to an already time consuming and costly endeavor, the drug approval process, it may ultimately prove to be very beneficial to both industry and the public.

IMPACT ON THE DRUG APPROVAL PROCESS

At this point in time it is estimated that the drug approval process for a New Chemical Entity (NCE) takes approximately 12

TABLE 5

UNANSWERED MARKETING QUESTIONS[26]

- How much information should be included in the brand and generic names?
- What specifications and controls are needed to ensure stereochemical identity and purity?
- What information about stereoisomers should appear in the description section of the package insert?
- Will further Post-Marketing Surveillance studies be required for drugs marketed as racemates in order to identify stereospecificity of adverse drug reactions?
- As more stereoisomers are developed, what changes will be needed to simplify or clarify the nomenclature to reflect the fact that the agents are enantiomers?

years and costs approximately 231 million dollars.[27] Certainly, any new policy that would impose additional time and cost onto this would have to be questioned from the standpoint of its adding value to the end product, and also whether or not it is truly serving the public. The question becomes one of whether or not FDA's stereoisomeric drug policy does in fact add to the time and cost burden of the approval process. Some have postulated that the effect of this policy would be to diminish, overall, the drug discovery process. That far fewer drug entities would be researched and that fewer innovative medicines would reach the market.[27]

In the past, the separation of isomers was difficult and expensive. Although new processes for the synthetization of enantiomerically pure substances are continuing to be developed, the development of commercially feasible processes are lagging behind. Improvements in the technology include the development of enantioselective catalysts based on metal complexes.[8] This method can produce chiral multiplication. Under the right conditions, thousands of chiral product molecules can be produced by one molecule of catalyst.[8] The biotechnology industry is currently using, biocatalysis, a breakthrough process that uses microbes or microbial enzymes to produce high-purity chiral compounds.[28] New techniques to assess the optical purity of chiral drugs have been developed. It is evident that, compared with just a few short years ago, an abundance of methods are available for the analysis of enantiomers. For example, chiral capillary electrophoresis is highly efficient, easier to construct, less expensive and more conducive to mathematical models than chromatographic methods.[29]

It is clear that pursuing a single enantiomeric form of a stereoisomer would add additional time and cost up front, in terms of synthesis and determination of the appropriate development candidate, via pharmacologic and toxicologic screening; but it may, in the end, prove to be a more cost effective and timely route. If at the early stages of development problems of potential unwanted toxicity can be effectively dealt with, it could greatly increase the speed with which new drugs could be approved. Often in the past, studies of individual isomers have been initiated after-the-fact when clinical investigations show a serious adverse reaction. Since, through reading of the policy, the main impetus for it stems from questions of toxicity, improving the toxicological profile of the drug candidate will no doubt speed FDA's review of the application. Even if a single enantiomer is not pursued, data generated at the early stages justifying development of the

racemate will answer the questions FDA will no doubt raise, and as such will preclude drug sponsors from having to go "backwards" to generate data to justify racemate development.

In terms of already marketed racemates this new policy could be quite advantageous to a sponsor in that it could allow for the approval of a new, safer and perhaps more effective version of the drug with additional marketing exclusivity. An example is S-fluoxetine, a pure isomer form of Prozac which is currently under study for efficacy and safety. The FDA does not consider racemates to be fixed combination drugs unless specific claims for individual enantiomer actions is made.[21] It could be argued that certain racemic drugs are fixed combinations and should be regulated as such. However, the FDA policy is not to be applied retroactively to previously approved racemate drugs. CDER now believes there are no compelling legal or scientific reasons for terminating the approval of a drug solely because it is a racemate.[15]

ENANTIOMER EXCLUSIVITY

The question of whether or not an enantiomeric form of an already approved racemic mixture would be eligible for additional exclusivity, is one which has been widely considered, even before the FDA policy was issued. Based on a review of the FDC Act particularly Section 502 (b)[30], it is clear that enantiomeric forms of already approved racemic mixtures would be entitled to additional exclusivity. Pursuant to the FDC Act, as amended by the Waxman-Hatch Act, a new form of an already approved drug could be eligible for either 3 or 5 years additional marketing exclusivity depending on the circumstances. Three year exclusivity is applicable to previously approved products which incorporate changes for which "new" and "essential" clinical studies were required for approval. Although mainly used in instances where a new indication is sought for an approved drug it could be applied

to the case of a single enantiomer form of an already approved racemate. The sponsor would no doubt have to perform "bridging studies" for the safety aspects of the submission as well as additional clinical efficacy studies. Five year exclusivity is available to products in which "no active ingredient (including any salt or ester of the active ingredient) of which" has been approved in another NDA.[31] A strong case can be made that an enantiomer is not "approved" in the NDA for the racemate even though it is part of the racemate, and, therefore qualifies for five years of exclusivity. The single enantiomer would be entitled to five years of exclusivity since no data would have been previously submitted regarding the activity of the enantiomer alone. Data in the racemic mixture would only apply to that mixture and could not necessarily be applied to the enantiomer. FDA recognizes this to some degree in that the policy does require "bridging studies" in order to extrapolate toxicity data to the enantiomer.

In either event, 3 or 5 year exclusivity, the potential for acquiring additional marketing exclusivity should be incentive enough for sponsors to examine the stereochemical aspects of various approved racemates with the idea of gaining approval for improved versions.

The FDA policy specifically deals with new stereoisomeric drugs. For generic versions of racemic drugs with approved NDAs, the Office of Generic Drugs does not impose a requirement for enantiomer specific assays in the absence of compelling reasons to do so. The primary reason for this policy is because differences in rate and extent of absorption from the gut to the systemic circulation should effect both enantiomers equally.[15] Documentation that the racemate rate and extent of absorption is comparable between the innovator and generic formulation satisfies the in vivo bioequivalence requirement.[15] However, the Office of Generic Drugs encourages Abbreviated New Drug Application and Abbreviated

Antibiotic Application (ANDA/AADA) applicants to discuss bioequivalence requirements of racemate drugs exhibiting nonlinear or unusual pharmacokinetics prior to actual study of bioequivalence.[15]

CONCLUSIONS

With the issuance of the policy, FDA will no doubt take a harder look at new drugs which are presented to them as racemic mixtures. A mixture of stereoisomers in a medicine will need to be justified in just the same way as any other combination of compounds. Sponsors need to recognize this and begin to work with FDA in determining the appropriate type of work that will be needed to develop and approve racemic drug products in the future.

Any policy that would serve to improve the safety and efficacy of new drug candidates, as this policy is intended to do, would no doubt greatly benefit the public health. It would also benefit the sponsors from the standpoint of bringing to market the best possible compounds in terms of safety and efficacy. From the economic point of view, it would benefit both industry and the public by providing a more cost effective dosage form, alleviating the so called "isomeric ballast"[1], perhaps translating into reduced cost for the consumer. Even though at first glance this policy would seem to impose greater cost and timing requirements on the approval process, early and appropriate consideration of the stereochemistry of a particular compound could result in speedier approval, allowing a product to get to the market sooner, providing financial benefit to the sponsor and consumer, as well as a greater public health benefit.

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[1] Ariens has referred to the component with limited activity (i.e. distomer) as the "isomeric ballast."[32]

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