

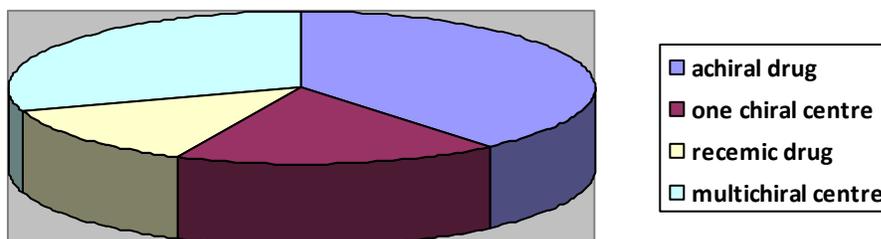
# **CHIRALITY** **(AS PREFORMULATION ASPECTS)**

## ◆ **CONTENTS**

1. INTRODUCTION
2. TERMS
3. NOMENCLATURE OF CHIRAL COMPOUND
4. IMPORTANT OF CHIRALITY
  - 4.1 STERIC ASPECTS OF PHARMACOKINETICS
    - 4.1.1 DRUG ABSORPTION
    - 4.1.2 DRUG DISTRIBUTION
    - 4.1.3 DRUG BIOTRANSFORMATION
    - 4.1.4 DRUG ELIMINATION
  - 4.2 STERIC ASPECTS OF DRUG ACTION
  - 4.3 CHIRAL IMPURITIES
  - 4.4 ADVANTAGES BY THE USE OF SINGLE ENANTIOMER AS A DRUG
5. SPECIFIC REQUIREMENTS FOR CHIRAL DRUG DEVELOPMENT
6. APPLICATION OF CHIRALITY IN FORMULATION AND DEVELOPEMENT
  - 6.1 ACCEPTANCE AND REJECTION OF API
  - 6.2 SELECTION OF ADJUVANTS
  - 6.3 IN VITRO DISSOLUTION STUDIES AND IN VIVO STUDIES
  - 6.4 STABILITY STUDY
  - 6.5 NDA/ANDA APPLICATION

## 1. INTRODUCTION

- Chiral drugs are a subgroup of drug substances that contain one or more chiral centers. More than one-half of marketed drugs are chiral.
- It is well established that the opposite enantiomer of a chiral drug often differs significantly in its pharmacological, toxicological, pharmacodynamics, and pharmacokinetic properties. Therefore from the points of view of safety and efficacy, the pure enantiomer is preferred over the racemate in many marketed dosage forms.
- However, the chiral drug is often synthesized in the racemic form, and it is frequently costly to resolve the racemic mixture into the pure enantiomer. Currently, most chiral drugs, including some “blockbuster” drugs, such as fluoxetine hydrochloride and omeprazole are still marketed as racemates.
- However, the recent trend is toward marketing more single-enantiomer drugs. In addition, a “racemic switch,” which involves the development of a pure enantiomer of a drug that is already marketed as a racemate, is actively pursued by many companies to improve its therapeutic efficacy and to extend patent protection. The decision whether to market the racemate or the enantiomer of a chiral drug is mainly based on pharmacology, toxicology, and economics.



Classification of new drug by stereochemistry

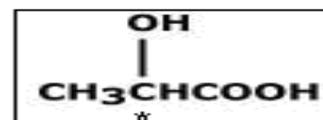
## 2. DEFINITIONS

### ⇒ CHIRAL

Molecules that are not superimposable on their mirror images are chiral. Chirality is necessary and sufficient condition for the existence of enantiomer. That is to say: a compound whose molecules are chiral can exist as enantiomer; a compound whose molecules are achiral cannot exist as enantiomer.

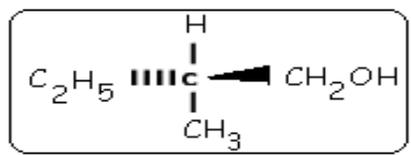
A chiral carbon is one to which four different groups are attached.

Example, Lactic acid



⇒ **STEREISOMER**

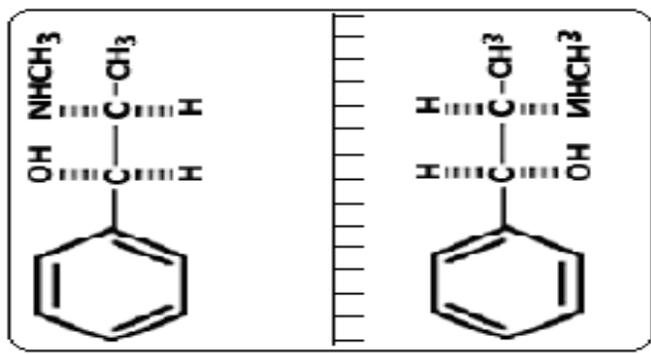
It is three dimensional arrangement of atom around the chiral center. The particular types of isomer that differ from each other only in the way the atoms are oriented in space are called as stereoisomers.



2-METHYL-1-BUTANOL

⇒ **ENANTIOMER**

Enantiomers are pairs of configurational isomers that are mirror images of each other and yet are not superimposable. Each enantiomer is *homochiral*, meaning that all the molecules have exactly the same configuration.



Ephedrine (-) Ephedrine (+)

⇒ **DISTEREOISOMER**

Diastereomers are pairs of compounds that contain more than one chiral center, not all of which are superimposable and are not mirror images.

⇒ **MESO COMPOUND**

A compound whose molecules are superimposable on their mirror images even though they contain chiral centres.

⇒ **RACEMATE**

A mixture of equimolar amount of enantiomers, and is *heterochira* meaning that the molecules have different chiralities.

⇒ **EUTOMERS**

Refers to enantiomers with higher pharmacological affinity or activity.

⇒ **DISTOMER**

Refers to enantiomers with higher pharmacological affinity or activity.

⇒ **EUDISMIC INDEX (EI)**

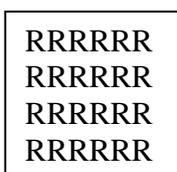
The logarithm of ratio of activity of eutomer to distomer.

⇒ **RACEMIZATIONS**

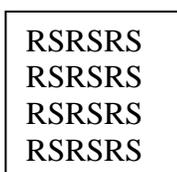
Conversion of enantiomer in to its racemate.

⇒ **CHIRAL INVERSION**

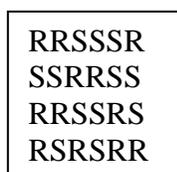
Conversion one enantiomer into its mirror image.



a. enantiomer  
(homochiral)



b. racemate  
(heterochiral)



c. pseudoracemate

They can be differentiated by spectroscopic method, X-ray diffraction and melting phase diagram (hot stage microscopy or DSC).

### **3. NOMENCLATURE OF CHIRAL COMPOUND**

Chiral substances can be classified as follows:

⇒ **OPTICAL ROTATION:** On basis of plane polarized light:

DEXTRO (d) or (+) and LEVO (l) or (-).

This method is based upon a physical property of the molecule but does not provide information about absolute configuration.

⇒ **CIRCULAR DICHROISM:** differential absorption of left and right circularly polarized rotation.

There are differences in absorption of the left and right handed components of circularly polarized light by a non racemic sample.

**Example:** Chloramphenicol has two chiral centers so four possible

stereoisomers. i.e, ( + ) chloramphenicol solublise in ethanol and  
( - ) chloramphenicol solublise in ethyl acetate.

⇒ **BY FISHER AND ROSANOFF:** Nomenclature of carbohydrate was on  
of D ( + ) or L ( - ) Glyceraldehyde and same for amino acids as D ( + )  
or L ( - ) Serine.

- But this system inconvenient for molecules containing more than one chiral center.

⇒ **R AND S NOMENCLATURE:** In 1956 cahn, Ingold and Pregold devised a system for stereoisomers  
referred as the Sequence Rule System (CIP system).

- In this system chiral center are ranked according to their atomic number.  
R: CLOCKWISE and S: ANTICLOCK WISE.

⇒ **Z AND E ISOMERS:** According to that in double bonded compounds the substituents can be  
oriented on the same side or opposite sides of the double bond.

- Substituents are, on same side than Z-isomer or on opposite side than E-isomer.

#### **4. IMPORTANT OF CHIRALITY**

##### **4.1 STERIC ASPECTS OF PHARMACOKINETICS**

The macromolecules (proteins) of body can distinguish between isomers leading to stereoselective difference in absorption, tissue and protein binding, biotransformation and renal excretion. Slight spatial differences in stereoisomers can have marked effects on the degree of association and interaction with protein and enzyme and enzyme system.

##### **4.1.1 Drug absorption**

The passive gastrointestinal absorption of enantiomeric drugs would be expected to be similar since the physical properties of partitioning and solubility of enantiomers are the same. Drugs that interact with and are absorbed by carrier transport system have a potential for stereoisomeric effects on the rate of enantiomer absorption.

Stereoisomers with structural similarities to endogenous entities and nutrients display differences in permeability rates across the g.i. membrane and hence in bioavailability. L-dopa, which is absorbed by an amino acid transport system, passes the g.i. wall at a rate 4 to 5 times that of D-enantiomer.

The L-methotrexate is absorbed by active processes in the g.i. tract and the d-isomer is reportedly absorbed by passive absorption.

The crystalline form of racemates may not be the same as the crystal structures of the individual stereoisomers and may be a source of differences in rates of dissolution between racemic and single enantiomeric dosage forms.

#### 4.1.2 Drug distribution

The interaction of enantiomer with a plasma protein yields a diastereomeric association. (+)-Oxazepam hemisuccinate has 30 to 50 higher association constants for albumin than its (-) isomer. The S isomer of warfarin is bound to a greater extent to albumin than R isomer. A1 acid glycoprotein binds S-propranolol (87.3 %) to a slightly higher degree than R-propranolol (83.8%) where as human albumin binds R-propranolol more strongly than S-form.

#### 4.1.3 Drug biotransformation

The intrinsic hepatic clearance of S-warfarin is reported to be approximately two fold greater than that of R-warfarin and reflects differences in metabolic pathways of the two stereoisomers.

A novel method for assessing inhibition of ibuprofen chiral inversion and its application in drug discovery\*. The ibuprofen is a phenyl acetic acid derivative undergoes chiral inversion in body from R(-) isomer to S(+) isomer and its interesting to know that only S(+) isomer is responsible for anti inflammatory activity rather than R(-) isomer.

#### 4.1.4 Drug elimination

The tubular secretory contribution to drug renal clearance has the potential of producing stereoselective renal elimination in the handling of stereoisomers.

The renal clearance of S-prenylamine is approximately 2.4 times higher than that of the R isomer. L-disopyramide has a renal clearance of 29 to 86% higher than that of D-isomer.

The analgesic activity of propoxyphene is due mainly to the d enantiomer. However, the racemate is more potent than an equimolar dose of d-propoxyphene due to a reduced clearance of the latter caused by the presence of l enantiomer in the racemate.

### 4.2 STERIC ASPECTS OF DRUG ACTION

The following possibilities exist for the distribution of pharmacological activity between enantiomers of a chiral drug molecule.

- Equipotent enantiomer. eg. flecainide and cyclophosphamide
- All pharmacologic activity resides in one enantiomer with the other stereoisomer being inactive (*stereospecificity*).

A classical example is  **$\alpha$ -methyldopa** in which all the desired antihypertensive activity is confined to the **S isomer**. This basis of stereospecificity of action has been related to the prodrug nature of  $\alpha$ -methyldopa, which is bioactivated stereoselectively in vivo to (1R, 2S)- $\alpha$ -methylnorepinephrine, a presynaptic  $\alpha_1$  sympathomimetic involved in the anti-hypertensive effect.

- Both enantiomers have similar qualitative pharmacological activity but they exhibit significant quantitative (e.g. potency) differences (*stereoselectivity*).

The pharmacologic behavior of warfarin is classical example of stereoselectivity of drug action. The anticoagulant potency of **S-warfarin** in vivo is from two-to five fold higher than that of its R enantiomer.

- Enantiomers of a chiral drug differ in their therapeutic and toxicologic profiles. The therapeutic antiparkinson effects of **DOPA** reside in the L-isomer, while the D isomer shows granulocytopenic effects.

The S enantiomers of the profen derivatives (e.g. naproxen) possess significantly greater intrinsic anti-inflammatory potency, but evidence suggests that the R-profens are more toxic by production of xenobiotic lipids.

- Enantiomers possess different pharmacological properties but mutually beneficial actions form the therapeutic standpoint. In the sulindac the Z isomer is the more potent anti-inflammatory agent and is used in pharmaceutical formulations. Although not available commercially, E-sulindac has greater theoretical utility for the treatment of preeclampsia because of its selective effects on NAD-linked prostaglandin dehydrogenase, which conceivably could lead to a more favorable balance of vasoconstrictive and vasodilatory metabolites of arachidonic acid.

### 4.3 CHIRAL IMPURITIES

Chiral impurities during pharmaceutical processing include:

- The opposite enantiomer in a single isomer
- Excess enantiomer in a racemic compound
- A diastereomer in a chiral or a racemic crystal.

The presence of small amounts of opposite enantiomer may significantly reduce the apparent solubility of the enantiomer, because the racemic compound will form in the solution and may precipitate from the solution. For example, the solubility of (p)- dexclamol hydrochloride is five times that of (l)-dexclamol hydrochloride.

In ephedrine and pseudoephedrine studies demonstrated that traces (as low as 0.0025 mole fraction) of the enantiomeric impurity might cause significant changes in the physicochemical properties of the pure enantiomer. Similarly incorporation of excess enantiomers (1.5 to 3 mole fraction) resulted in significant changes in the thermodynamic property and gave rise large variations (27%) of IDR (intrinsic dissolution rate) of the racemic compound.

### 4.4 ADVANTAGES BY THE USE OF SINGLE ENANTIOMER AS A DRUG

- Separating unwanted pharmacodynamic side effects from toxic effects if these reside exclusively in one enantiomer.
- Expose the patient to less body load and thus reduce metabolic/renal/hepatic drug load.
- Easier assessment of physiology, disease, and drug co-administration effects.
- Reduce drug interactions.

- Avoid enantiomer–enantiomer drug interactions.
- Avoid bioinversion.
- Easier assessment of efficacy and toxicity through pharmacokinetic or pharmacodynamic monitoring of the stereochemically pure active enantiomer.

## **5. SPECIFIC REQUIREMENTS FOR CHIRAL DRUG DEVELOPMENT**

- ❖ Development of enantiomeric assay.
- ❖ Synthesis of individual enantiomer.
- ❖ Safety evaluation of the individual enantiomer.
- ❖ Pharmacokinetic of individual enantiomers.
- ❖ Resolution of the individual enantiomer.
- ❖ Bulk drug: enantiomeric purity
- ❖ Chiral conversion

In pharmaceutical development, the relevant expansion of the specification of a chiral drug substances is its stereochemistry in terms of optical purity, batch-to-batch variations and the confirmation of enantiomeric stability in formulation both on storage and in vivo.

The decision to develop a single enantiomer is made only if it gives genuine therapeutic benefit and becomes economically feasible.

In other cases, a 'racemate switch' from a single enantiomer may extend a patent on a chiral drug initially marketed as a racemate, because a stereochemically pure compound derived from the available racemate will be treated as a new drug.

## **6. APPLICATION OF CHIRALITY IN FORMULATION AND DEVELOPMENT**

F & D scientists now have to focus their attention on chirality. The applications of chirality from the viewpoint of F & D are as follows.

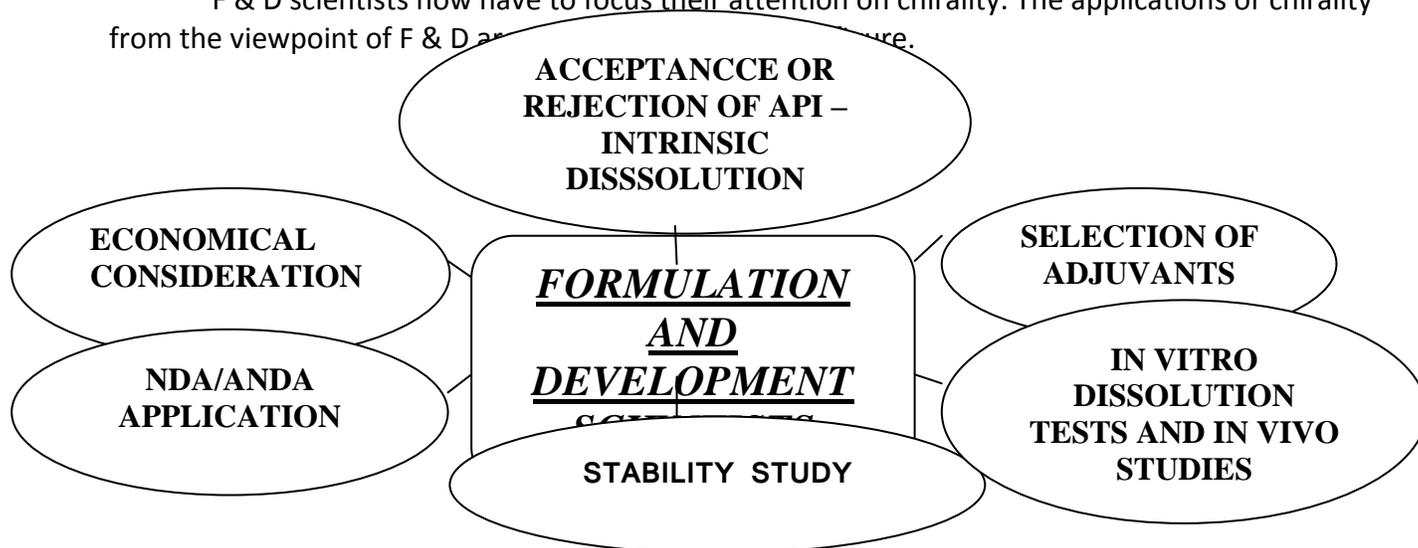


Figure 1, Application of chirality in formulation and development

## 6.1 ACCEPTANCE AND REJECTION OF API

The Chiral pure drugs should be quantitatively analyzed for the presence of absence of chiral impurities besides the routine determination of related impurities.

Tao and Cooks recently reported that quantitative chiral analysis could be done by tandem MS. The method is rapid and requires very little sample. Lou recently reported that it would be useful to determine enantiomers and other structurally similar drug impurities using one rather than two analytical methods.

The pharmaceutical companies should accept or reject a sample of API based on the ratio of the active/inactive enantiomers in the non-racemic mixtures. This ratio may change from one vendor to another. Most pharmaceutical companies do not consider this fact at the time of purchase/ the success or failure of the formulation and development team may depend upon this ratio.

The in vitro dissolution test and in-vitro/in-vivo correlation (IVIVC) are the two major areas where the differences may be observed if an eye is not kept on Chirality when API is purchased.

The intrinsic dissolution rate of chirally pure API may prove to be a useful quality control parameter.

## 6.2 SELECTION OF ADJUVANTS

Formulation and development scientists add a number of adjuvants with diversified purposes in pharmaceutical formulations. Adjuvants are added to facilitate manufacturing, for functionality improvement, and to improve appearance and stability. The adjuvants may be either chiral or non-chiral in nature. The type and amount of the adjuvant may determine the functionality of the dosage form, especially the drug release rate.

The characteristics of adjuvant such as solubility, compressibility, surface area, porosity, etc/ are considered today in F & D. However, very little attention is given to the nature of adjuvant from the viewpoint of Chirality.

A few references are cited below to show the effect of adjuvant type on drug release.

- Solinis et al. studied the release of salbutamol and ketoprofen enantiomers from hydroxypropylmethylcellulose (HPMC) K100M matrices containing two types of

cellulose derivatives. The authors concluded that stereoselectivity is dependent on the amount of chiral excipients in the formulation.

- Srichana and Suedee examined the in vitro dissolution of salbutamol from matrix tablets containing various chiral excipients such as gamma cyclodextrin, heptakis (2,6 di-o-methyl)-beta cyclodextrin, sulfobutyl –beta-cyclodextrin, HPMC and egg albumin. The formulation containing gamma cyclodextrin provided significant stereoselectivity throughout the dissolution profile. The release of eutomer R-salbutamol was higher than that of the distomer S-salbutamol from the gamma cyclodextrin tablets.
- Suedee et al. monitored enantioselective in vitro release of propranolol. The influence of the method of polymer synthesis, drug to polymer ratio, pH, and temperature on the release of eutomer can be controlled via means of formulation. The distomer was retained in the dosage form.
- Stereoselective interaction of ibuprofen was evaluated with chiral excipients such as HP-beta-cyclodextrin, tartaric acid, sucrose, HPMC, methylcellulose and a non-chiral excipients citric acid. The co precipitates showed higher dissolution rate. The presence of chiral excipients did not cause stereoselective release of the drug.

The objective may be achieved by preparing a bi-layer tablet. Applications of interaction between API and chiral excipients may be explored in the areas of sustained release buccal dosage form and colon drug delivery system.

Teamwork between an expert analyst in chiral science and an F &D scientist may open up many avenues in formulation development work.

### 6.3 IN VITRO DISSOLUTION STUDIES AND VIVO STUDY

Crystals of both enantiomer & racemic compound are having different molecular arrangement. Due to the difference between the crystal lattice of both forms, *the solubility of pure enantiomers may be different from the racemic compound.*

It was proved by the experiment that the initial dissolution rate of racemic propranolol HCl was three times greater than that of enantiomers in distilled water.

While performing dissolution testing for stereo-selective drugs,

- (I) we must concerned about the amount of a particular enantiomer released from the dosage form
- (II) We should not see the surplus amount of drug (R form + S form) release from the dosage form.

Now a days, it is possible to do this because of the development of analytical tools like... capillary electrophoresis\*, simulated moving bed chromatography etc. Comparative study of chiral separation of ofloxacin enantiomer by capillary

electrophoresis using neutral cyclodextrin.

**(\*Ref: C.A. 147(8) AUG; 2007; 173958a)**

For the drugs where only one of the forms (R or S) is active, the use of a stereo selective dissolution test is recommended for the calculation of t50 or Q30. A single point dissolution specification such as t50 (time required for 50% API dissolution) or Q30 (amount of API dissolved in 30 min) is routinely employed as a quality control release test.

After establishing the similarity of in vitro dissolution testing between a reference and a test product in different dissolution media, in vivo testing in man (bioequivalence testing) is ordered. It is a hard fact that many experimental formulations fail to establish an IVIVC.

Table 1-Extension of Biopharmaceutics Drug Classification System

Biopharmaceutics classification system (BCS) guidance of US FDA classifies the drugs in four classes considering the solubility and permeability of drugs. Once the drug meant for oral use dissolves in gastro-intestinal fluid and subsequently permeates through the membrane, it enters into general circulation.

One should remember that some drugs might undergo chiral conversion in blood. In such cases, the pharmacological action will depend upon the amount of unchanged active enantiomers reaching the receptor. Enantioselective analysis should be adopted in cases where there is the possibility of chiral conversion in blood.

The third dimension can be added to BCS, i.e. chiral conversion for the drugs where only one form (R or S) is active and the other form is inactive (table 1). The drugs that fall under class 1B will show superior action as compared to class 1A. Polli reported that one intent of in vitro- in vivo relationship (IVIVR) is to learn about the relative contribution of dissolution to a product's overall absorption kinetics. Here also, chiral-specific dissolution can be used.

## 6.4 STABILITY STUDY

In the FDA's policy statement for the development of new stereomeric drugs, it is

Class	Solubility	Permeability	Chiral inversion*	
			A	High
I	High	High	A	High
			B	Low
II	Low	High	A	High
			B	Low
III	High	Low	A	High
			B	Low
IV	Low	Low	A	High
			B	Low

that the protocol drug and drug a method capable of

mentioned stability for enantiomeric substances products should include or methods 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. The stability study program must address the issue of chiral inversion and racemization. Thalidomide undergoes facile base-catalysed chemical racemization in aqueous media.

Shelf life of pharmaceutical formulation is fixed after considering 90% or 95% drug degradation under stated conditions of drug storage. This could be the amount of inactive enantiomers (R or S) degraded. We should not be surprised if the FDA starts assigning shelf life on the basis of degradation of active enantiomers since that seems to be more realistic.

## 6.5 NDA/ANDA APPLICATION

The current applicable guidance documents shall be kept in mind while preparing the applications. We should also keep in mind that increasing the desired activity should not be accompanied by a rise in the untoward effect. FDA requires toxicology testing on the racemate. The data of stereoselective dissolution testing should be submitted for the enantiomers that exhibit different action (e.g, Methyl phenyl propyl barbituric acid). There are endless opportunities and it is difficult to address all relevant issues in this communication. The current guidance documents should be consulted at the time of submitting an application.

## 6.6 ECONOMICAL CONSIDERATION

The significant expenses associated with the development and manufacture of Stereochemically pure drugs will add to their cost and there may be economic justifications for acceptance or rejection of a new therapeutic entity. It may not be economically feasible to pay an increased amount for only slightly increased efficacy.

▪ LIST OFFICIAL CHIRAL DRUGS

Sr. no	Drugs	Official in	Sr. no	Drugs	Official in
1.	Dextroamphetamine	USP	21.	Levomenthol	MartindaleEP, BP
2.	Dextromethorphan	USP, BP	22.	Levompropazine	MartindaleEP, BP
3.	Dextromoramide	MartindaleEP	23.	Levomethadone	MartindaleEP
4.	Dextropropoxyphene	MartindaleEP, BP	24.	Livamisol	IP, BP
5.	Esmoprazole		25.	Levonantradol	MartindaleEP
6.	Levobunolol Hcl	MartindaleEP	26.	Levonordefin	MartindaleEP
7.	Levobupivacaine		27.	Levonorgesterol	MartindaleEP, IP, BP
8.	Levocabastine	MartindaleEP	28.	Levoorphanol	MartindaleEP, BP
9.	Levocalamine	MartindaleEP	29.	Levophan	MartindaleEP
10.	Levocarit	MartindaleEP	30.	Levophed barbiturate	MartindaleEP
11.	Levocarnil	MartindaleEP	31.	Levoprolactine	MartindaleEP
12.	Levocarnitine	MartindaleEP	32.	levopropizine	MartindaleEP
13.	Levodiphenopyrine	MartindaleEP	33.	Levopropoxyphene	MartindaleEP
14.	Levodopa	MartindaleEP, IP, BP	34.	Levopropylhexidine	MartindaleEP
15.	Levodopum	MartindaleEP	35.	Levorenin	MartindaleEP
16.	Levodromaran	MartindaleEP	36.	Levoresin	MartindaleEP
17.	Levofloxacin	MartindaleEP	37.	Levorterenol	IP
18.	Levoglutamine	MartindaleEP	38.	Levoterenol	BP
19.	Levomaprolool	MartindaleEP	39.	Levothoid	MartindaleEP
20.	Levomenol	MartindaleEP	40.	Levothyroxin	MartindaleEP, IP, BP

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▪ STUDY QUESTIONS:

1. Application of chirality in F & D. Sept, 2006/2007
2. Define chiral and enlist such product. Discuss application of Chirality from F & D viewpoint giving suitable example. March 2006 (1st Int.)
3. Describe steric aspects of drug action.
4. Describe steric aspects of pharmacokinetics.
5. Enlist the chiral impurities during pharmaceutical processing and how they can affect the performance of the drug with an example.
6. Write a novel method for assessing inhibition of ibuprofen chiral inversion and its application in drug discovery.