



Chiral Drugs: Current Status of the Industry and the Market

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The biological activity of chiral substances often depends upon their stereochemistry, since the living body is a highly chiral environment. A large percentage of commercial and investigational pharmaceutical compounds are enantiomers, and many of them show significant enantioselective differences in their pharmacokinetics and pharmacodynamics. The importance of chirality of drugs has been increasingly recognized, and the consequences of using them as racemates or as enantiomers has been frequently discussed in the pharmaceutical literature during recent years. Most of the chiral drugs are administered as racemates, despite the fact that the optical isomers of a racemic drug can exhibit different pharmacological profiles in living systems. These differences can be expressed in *e.g.* the affinity of the enantiomers for certain receptor subtypes or enzymes, distribution rates, their metabolism and excretion, in antagonistic actions relative to each other, or their toxicological properties. Obviously, the more chiral centres present in a (drug) molecule, the more complex the situation becomes.

The origin of the discovery of the role of stereochemistry in biochemical environments dates back to the late 1850's, when Pasteur reported the different destruction rates of *dextro* and *levo* ammonium tartrate by the mold *Penicillium glaucum*. In the conclusion of his observations, Pasteur wrote: "Most natural organic products, the essential products of life, are asymmetric and possess such asymmetry that they are not superimposable on their images." For some reason, this knowledge of racemic organic compounds and racemisation seemed to be forgotten until the question of racemic compounds was raised by Ariens in the late 1980's. He asked the question "why we in some cases have to give doses to the patient where half of the content has no effect or the opposite effect?". After this rediscovery of stereochemistry, the regulatory authorities defined more strict requirements on drug discovery and chiral compounds. Besides the ethical reasons, the therapeutic benefit (efficacy and safety) and, in several instances, extension of the life cycle of drugs have been the motivation for developing single enantiomers.

Single-enantiomer drug sales show a continuous growth worldwide and many of the topselling drugs are marketed as single enantiomers. In this context, there has been a rapid development of enantioselective synthetic methodologies, which have now reached a high degree of diversity and complexity. Simultaneously, this new trend produced a rapid increase in the demand for stereoselective separation techniques and analytical assays for precise determination of the enantiomeric purity of chiral compounds. The development of chiral stationary phases (CSPs) or chiral selectors for gas chromatography (GC), liquid chromatography (LC) and capillary electrophoresis (CE) rapidly opened a new dimension in the area of separation technologies.

The business of developing single isomer drugs came about, because the chemical production methods used for pharmaceuticals often produced racemic mixtures of two enantiomers. In the case of thalidomide, it was shown that one enantiomer was responsible for efficacy and another for side effects. Worldwide, the market for chiral fine chemicals sold as single enantiomers was \$6.63 billion in 2000 and is expected to grow at a rate of 13.2% annually, reaching \$16.0 billion in 2007. The drug industry is the driving engine for this strong growth, accounting for 81.2% of the total, equal to an overall worth of \$5.38 billion, in the year 2000. The remaining \$1.25 billion is divided among

such uses as agricultural chemicals, electronic chemicals, flavors and fragrances. The numbers look even more impressive when considered as the sale of single-enantiomer compounds made into the pharmaceutical formulations that people actually consume. The worldwide market for dosage forms of single-enantiomer drugs was \$123 billion in 2000, increasing by 7.2%, from \$115 billion in 1999. Geographically, the U.S. is the biggest consumer of enantiomeric fine chemicals, contributing to a total North American share of \$3.98 billion, making up 60% of the total. European and Asian consumption of enantiomeric fine chemicals is not expected to grow as fast, with the North American share rising to 66.9% of the market in 2007, equivalent to \$10.7 billion. Some drug companies have patented and developed a racemic drug, with the intention of patenting and developing a single enantiomer later. When the patent on the racemate expires, the company can undercut generic competition by launching the single-enantiomer. AstraZeneca, for instance, has developed esomeprazole (Nexium), a single enantiomer version of its \$6 billion anti-ulcer drug omeprazole (Prilosec), which came off patent in 2002.

The drug industry will continue to have a strong growth in chiral compounds, because of the efforts to improve drug efficacy and to cut development costs in the face of regulatory pressures. Medicinal chemists are increasingly targeting enzymes, hormones, and other compounds within patients' cells, as well as the cells of microorganisms. Additional targets are receptors on cell surfaces. These compounds and receptors are made up of chiral amino acids, carbohydrates, and lipids. Drugs that are intended to interact with them must be enantiomeric, in order to increase the chance of success.

In Iran, little attention has been paid to the importance of chiral drugs, both in the regulatory sector and in the private sector, while production of single-enantiomers especially by separation methods, is a profitable business. The API manufacturers may produce or import cheaper crude racemic mixtures of chiral drugs, and separate the active enantiomer and release it to the market. A drug molecule such as esomeprazole seems to be an ideal candidate for this business.

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