Introduction
Where a drug has an optically active centre in a part of the molecule important for its therapeutic activity or receptor binding, it is usually only one of the enantiomers (eutomer) that has the desired therapeutic activity. At best, the other isomer (the distomer) or isomers consist of ballast or impurity. However, the distomer may compete for the receptor at the site of activity or on the serum protein, and it may have an inhibitory or a synergistic effect. Perhaps the most famous example is thalidomide, marketed as a sedative throughout most of the world in the 1950s, but administered as a racemic mixture. The R-enantiomer is a safe, effective sedative, whereas the S-isomer is a very potent teratogen.

The first separation of racemic isomers was carried out in 1849 by the French chemist/microbiologist Louis Pasteur on tartrates. However, although some of the science has been known for many years, it is only in the last 20 years that any real emphasis has been given to the development of single enantiomers. What are the current regulatory requirements in Europe (the E.E.C. and E.F.T.A. countries) and how will they develop over the next few years?

Current E.C. regulatory requirements: the 1989 ‘Notice to Applicants’
The current regulatory situation is set out in the section on ‘Evaluation’ in the Pharmaceutical Expert Report (pp. 73–74) of the 1989 (2nd edn.) of the ‘Notice to Applicants’ (vol. II of ‘The Rules Governing Medicinal Products in the European Community’) [1].

It lays down in this section on stereoisomerism that, when a new active substance (NAS) contains one or more chiral centres, it must be specified whether specific isomers or a mixture of stereoisomers have been used in the animal and human studies, and also information given as to the form of the active ingredient to be used in the final marketed product.

The ‘Notice to Applicants’ does not currently require isomers to be separated and single enantiomers to be marketed. It does, however, require the possible problems in relation to stereoisomerism to be discussed in: (i) the Pharmaceutical Expert Report; (ii) the Pharmacological/Toxicological Expert Report; and (iii) the Clinical Expert Report, and cross-referenced to each other. The issues to be discussed include: the toxicological issues; the pharmacological aspects (including evidence as to which stereoisomer has the desired pharmacological properties; pharmacokinetics (including information on the relative metabolism of the stereoisomers); extrapolation of the pre-clinical data (paying particular attention to species differences in the handling of stereoisomers); and the significant clinical issues.

Thus, at the moment it is still possible to make a successful marketing authorization application for a racemic mixture, provided that information is available on the activity of the enantiomers, and that enantio-selective methods of analysis are used in both the animal toxicology studies and the pharmacokinetic and metabolic studies in man.
However, for the future, as more emphasis is given to this requirement, it is clear that it is likely to become cheaper to decide at the 'discovery chemistry' stage which is the active enantiomer, to find a method of manufacturing it and then to concentrate all the subsequent development and testing on the eutomer.

Definition of an NAS: regulatory implications now and after 1992
The 1989 'Notice to Applicants' states that where a mixture of stereoisomers has previously been marketed and it is now proposed to market a product containing only one isomer, full data on this isomer should be provided. This means that the single isomer is effectively being treated as an NAS.

This may have regulatory implications both now and in the future. At present, it may be economic for a second company to develop and test a product containing one isomer, even though the racemate is a well-established one and even out of patent. The 10 year 'second applicant' protection (the 10 years during which a second application cannot be made without the full pharmacology/toxicology data and clinical trials data being supplied to the authorities) will apply to this single enantiomer.

In the future, under the proposed post-1992 'future system', there will be an option for companies to apply, either through a 'centralized procedure' directly to a new European Medicines Agency (EMA), or through a 'decentralized procedure' (to one Member State first and then to others) for an NAS. It seems likely that this option will also apply to the eutomer of an existing racemate.

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Other European guidance
The Swiss Agency [the Interkantonal Kontroletelle (IKS) fur Heilmittel] has issued a note on its evaluation practice in its monthly bulletin [2]. It gives the following 'fundamental reflections' on the evaluation practice of the IKS and its expert committees:

1. It would be preferable if only pure isomers were used in medicines.
2. Stereochemical problems should be discussed in a separate section for any new chemical entity. This should state the exact configuration, and however, in any case specify the centres of asymmetry and the relative quantity of isomers. An important issue is the consistency of the isomer composition during the different phases of the clinical trials.

3. For isomer mixtures, data should be available for each component as regards pharmacodynamics, metabolism and pharmacokinetics. For drugs containing pure isomers, the presence of another isomer is to be regarded as an impurity. The tolerance limits for such impurities depends on their pharmacological (efficacy/toxicity) and pharmacokinetic (potential for cumulation) properties.

4. The possible clinical implications regarding efficacy and toxicity should be discussed for each isomer.

5. Pharmacokinetic data based on non-specific methods for evaluation of isomers should be assessed very critically.

6. A new application of a pure isomer of a substance which is already registered as a racemate will be treated by the IKS as a New Chemical Entity (NCE) application.

7. Similar reflections apply to generic products, where the proportion of isomers should be indicated and compared with the original preparation. A modified release preparation may affect the relative proportion of the bioavailable isomers.

8. Data regarding the relative proportion of each isomer and its pharmacokinetics, should be included in the information for the medical profession.

A future C.P.M.P. guideline
In view of the considerable interest in this subject in the industry and the national authorities, a guideline is being developed in the Working Parties of the E.C. Committee for Proprietary Medicinal Products (C.P.M.P.). It is likely that such a guideline will be issued to the industry and the national authorities for consultation in 1991 and then adopted in late 1991. It will probably include the following headings:

- 'Definitions' (of isomers, stereoisomers, enantiomers, diastereoisomers, etc.)
- 'Nomenclature' (with descriptions of the absolute configuration)
- 'Manufacture of Enantiomerically Pure Drugs' (use of chiral synthons, resolution, etc.)
- 'Requirements for Pharmacodynamics, Pharmacokinetics and Toxicology Studies' (the consequences of enantioselectivity in the animal studies)
- 'Clinical Implications'.

As pointed out by Cartwright [3], guidelines are intended to be: (i) complementary to the E.E.C.
Directive (75.318/EEC) legal requirements; (ii) in accord with the current consensus of scientific opinion; (iii) approved by the national authorities in the E.C. Member States, who all agree to see that they are observed and will follow them when assessing applications for marketing authorizations; and (iv) a published statement of the views of the European authorities on the subject.

C.P.M.P. Working Parties include representatives from all the E.C. Member States, the Nordic countries and E.F.T.A. The E.C. guidelines are then published and accepted by these countries [4].

Conclusions
There is growing interest in the subject of chiral active ingredients. The cost of providing full information on the two or more isomers in a mixture is likely to be prohibitive and companies are likely, in future, to determine at an early stage which is the eutomer and only develop and test that material.

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**Regulatory implications: a company’s perspective**

C. M. Macdonald


The Pharmaceutical Industry is experiencing an unprecedented period of change and challenge. Not only are new therapeutic breakthroughs less easy and more costly to find, but the political climate under which the industry operates has also become increasingly difficult. In many countries, concern about the spiralling cost of health care has led to considerable governmental pressure for reductions in their national drugs bills. In its various guises this may involve lower reimbursement, indicative budgets, restricted lists or generic substitution. Public perception of the industry has also changed with issues such as profit motive, over-prescribing, 'me-too' products, the environment and animal rights now being more critically questioned. Somewhat at odds with this, is the demand for new medicines which combine both high efficacy with low or zero risk.

Increased regulatory requirements have also had a significant influence on the financial risk to companies by increasing the cost of the drug development programme and by the de facto reduction in patent life to the point where new products have only a few years of protected life. It is estimated that perhaps as few as one in five new products fully recovers its developmental costs.

An added dilemma for companies is the difficulty in predicting what the market will be like some 10–12 years after key development decisions have to be made. For example, will there be treatment changes, or will new therapies be discovered which will render a product clinically obsolete before it can be marketed? It is also important to keep abreast of competitor activities, since the financial penalties of late arrival on the market can be considerable.

On top of this now comes new hurdles such as the question of stereoisomers. It has been estimated that about 50% of all drugs marketed have chiral centres. Of these, some three-quarters have been developed as racemates and one-quarter as an optically pure isomer. By the year 2000, it is predicted that this may change to the point where as many as 50% of all new products could be marketed as pure isomers.

Most of the major regulatory authorities throughout the world are presently considering their positions on stereoisomerism. This has led to concern in the industry that new regulations will be introduced which will make it difficult to market racemic drugs in the future. In response to this, companies are having to review their strategies. Some, which feel uncomfortable because they cannot predict what the outcome will be, may be tempted to avoid chiral compounds altogether.

Abbreviation used: ADME, Absorption, distribution, metabolism and excretion.