Trends in the development of chiral drugs

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Drug chirality is now a major theme in the design, discovery, development, launching and marketing of new drugs [1–4]. Stereochemistry is an essential dimension in pharmacology [1]. In past decades the pharmacopoeia was dominated by racemates, but since the emergence of new technologies in the 1980s that allowed the preparation of pure enantiomers in significant quantities, the awareness and interest in the stereochemistry of drug action has increased [1–4].

The advances in stereoselective bioanalysis led to a new awareness of the importance of stereoselective pharmacodynamics and pharmacokinetics, enabling the differentiation of the relative contributions of enantiomers to overall drug action. When one enantiomer is responsible for the activity of interest, its paired enantiomer could be inactive, possess some activity of interest, be an antagonist of the active enantiomer or have a separate activity that could be desirable or undesirable [3–5]. Considering these possibilities, there appears to be major advantages in using stereochemically pure drugs, such as a reduction of the total administered dose, enhanced therapeutic window, reduction of intersubject variability and a more precise estimation of dose–response relationships [3,4]. These factors have led to an increasing preference for single enantiomers in both industry and regulatory authorities. Regulatory control of chiral drugs began in the US with the publication in 1992 of formal guidelines on the development of chiral drugs in a document entitled *Policy Statement for the Development of New Stereoisomeric Drugs* [6] and was followed in the European Union (EU) in 1994 by *Investigation of Chiral Active Substances* [7]. Applicants must recognize the occurrence of chirality in new drugs, attempt to separate the stereoisomers, assess the contribution of the various stereoisomers to the activity of interest and make a rational selection of the stereoisomeric form that is proposed for marketing [4].

Worldwide sales of chiral drugs in single-enantiomer forms continue to grow. The market share of single-enantiomer dosage form drugs increased annually from 27% (US $74.4 billion) in 1996, 29% (1997), 30% (1998), 32% (1999), 34% (2000), 38% (2001) to an estimate of 39% (US $151.9 billion) in 2002 [8–13].

The top ten single enantiomer blockbuster drugs (>US $1 billion sales per year) are: Atorvastatin calcium [Pfizer; http://www.pfizer.com] (cardiovascular); Simvastatin [Merck; http://www.merck.com] (cardiovascular); Pravastatin sodium [Bristol-Myers Squibb; http://www.bms.com] (cardiovascular); Paroxetine hydrochloride [GlaxoSmithKline; http://www.gsk.com] (CNS); Clopidogrel bisulfate [Sanofi-Synthelabo/Bristol-Myers Squibb; http://www.sanofi-synthelabo.com] (hematology); Sertraline hydrochloride [Pfizer] (CNS); Fluticasone propionate and salmeterol xinafoate [GlaxoSmithKline] (respiratory); Esomeprazole magnesium [AstraZeneca; http://www.astrazeneca.com] (gastrointestinal); Amoxicillin and potassium clavulanate [GlaxoSmithKline] (antibiotic); and Valsartan [Novartis; http://www.novartis.com] (cardiovascular) (Source: Technology Catalysts International) [13].

The previously reported surveys of chiral and achiral drugs have been limited in scope, each covering only short periods and a single jurisdiction. Examples include an informal analysis of the 95 submissions of new chemical entities (NCEs) assessed by the UK Medicines Control Agency [MCA; now Medicines and Healthcare products Regulatory Agency (MHRA)] in 1996–2000 [14], and an analysis of the new molecular entities (NMEs) approved by the FDA in 1998–2001 (http://www.fda.gov/cder/rdmt/) [15].

In this article we evaluate and provide an insight into the development of chiral and achiral drugs and examine the impact of this on industrial drug development and drug regulation worldwide.

Methods of surveying approved drugs according to chirality character

To survey the chirality character of worldwide approved drugs, drugs were classified as being achiral, single enantiomer or racemate. Racemates also include diastereomeric mixtures

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Box 1. FDA classification of investigational new drug applications (INDs) and new drug applications (NDAs) according to Chemical Type (CHE)

Chemical Type (CHE)

1 New Molecular Entity (NME): an active ingredient that has never been marketed in the US.
2 New derivative: a chemical derived from an active ingredient already marketed (a 'parent' drug).
3 New formulation: a new dosage form or new formulation of an active ingredient already on the market.
4 New combination: a drug that contains two or more compounds, the combination of which has not been marketed together in a product.
5 Already marketed drug product, but a new manufacture: a product that duplicates another firm's already marketed drug product (same active ingredient, formulation or combination).
6 Already marketed drug product, but a new use: a new use for a drug product already marketed by a different firm.
7 A drug that is already legally marketed without an approved NDA.

for the purpose of this survey. It should be noted that racemates are considered to be chiral drugs. The present analysis does not include new biological entities (NBEs).

The following two databases of approved drugs were surveyed according to the chirality character of the drugs: (i) *To Market, To Market* in Annual Reports in Medicinal Chemistry, in the years 1983–2002 [16]. This database lists all the new drugs launched each year in worldwide markets; and (ii) new molecular entities (NMEs) also termed by the FDA as new chemical entities (NCEs), approved by the FDA in the years 1991–2002 (http://www.fda.gov/cder/da/da.htm). This database lists all new drugs classified as Chemical Type 1 (NME). NMEs are defined as active ingredients that have never been manufactured in the US. The FDA classifies investigational new drug applications (INDs) and new drug applications (NDAs) to assign review priority on the basis of the Chemical Type (CHE) of the drug and potential benefit (Box 1). According to the FDA a chiral switch [4] is not classified as a NME as it already contains a previously approved active moiety.

Chiral switches are drugs that have already been claimed, approved and/or marketed as racemates or as mixtures of diastereomers, but have since been redeveloped as single enantiomers [4,17]. The essential criterion of a chiral switch is a change in the status of chirality [4]. Thus, the chiral switches, esomeprazole magnesium (Nexium) (CHE 2), levobupivacaine hydrochloride [Chirocaine; AstraZeneca/Celltech (http://www.celltechgroup.com)] (CHE 2), dexfenfluramine [Redux; Indevus/Wyeth (http://www.indevus.com and http://www.wyeth.com)] (CHE 3; withdrawn), levofloxacin [Levaquin; Daiichi/Aventis/Ortho-McNeil (http://www.daiichius.com; http://www.aventis.com; and http://www.ortho-mcneil.com] (CHE 3), levalbuterol [Xopenex; Sepracor (http://www.sepracor.com)] (CHE 3), dexmethylphenidate [Focalin; Novartis/Cellgene (http://www.celgene.com)] (CHE 3), levocetirizine hydrochloride [Xyzal, Xusal; Sepracor/UCB Farchim SA (http://www.ucbpharma.com)] (CHE 3) and escitalopram oxalate

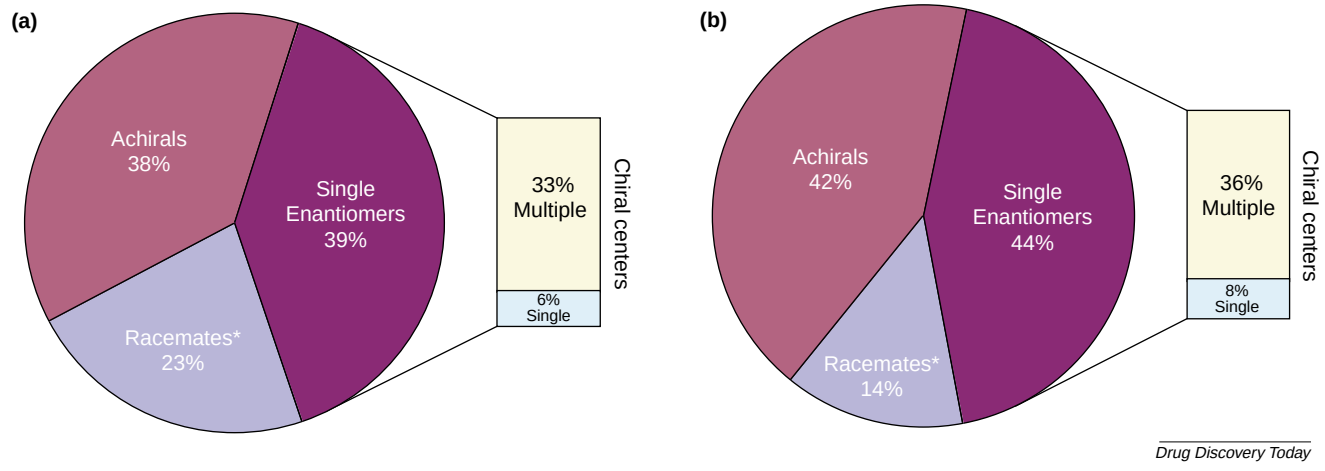

Figure 1. **(a)** Distribution of worldwide-approved drugs according to chirality character in the period 1983–2002 **(b)** Distribution of FDA approved drugs (NMEs) according to chirality character in the period 1991–2002. *Including diastereomeric mixtures.

[Cipralex/Lexapro; H. Lundbeck/Forest Laboratories (http://www.lundbeck.com and http://www.frx.com)] (CHE 3) are not included among the NMEs (CHE 1). Most of the chiral switches appear in the database of worldwide-approved drugs [16].

It should be noted that most (>90%) of the FDA-approved drugs in 1991–2002 were also included in the database of worldwide approved drugs, although not necessarily in the same year.

Figure 1a illustrates the total worldwide distribution of 730 approved drugs in 1983–2002 (including 382 in 1991–2002) and the US distribution of 304 FDA approved drugs (NMEs) in 1991–2002 according to their chirality character. Table 1 and Figures 2–5 describe the annual distributions of worldwide approved drugs in the period 1983–2002 and of the FDA-approved drugs (NMEs) in the period 1991–2002 and the corresponding four year (worldwide) and three year (FDA) range distributions.

Table 1. Annual distribution of worldwide and FDA-approved drugs (NMEs) according to chirality character in the period 1983–2002

Year	Racemates[a]		Single enantiomers		Achiral	
	Worldwide (%)	FDA (%)	Worldwide (%)	FDA (%)	Worldwide (%)	FDA (%)
1983	37	na	26	na	37	na
1984	28	na	26	na	46	na
1985	38	na	22	na	40	na
1986	26	na	26	na	48	na
1987	18	na	49	na	33	na
1988	26	na	39	na	35	na
1989	29	na	26	na	45	na
1990	33	na	35	na	32	na
1991	20	9	40	65	40	26
1992	21	33	44	42	35	25
1993	16	17	45	29	39	54
1994	38	5	38	57	24	38
1995	21	37	46	30	33	33
1996	9	14	41	43	50	43
1997	24	8	30	38	46	54
1998	15	9	50	41	35	50
1999	13	4	52	46	35	50
2000	9	19	62	37	29	44
2001	0	0	68	60	32	40
2002	6	0	55	53	39	47

[a]Including diastereomeric mixtures; Abbreviations: na, not applicable

Distribution of worldwide approved drugs, according to chirality character*

1983–2002

An overall look at the 20-year period from 1983–2002 (Figure 1a) indicates that single-enantiomers surpassed achirals whereas racemates represented the minority category at 23% of worldwide approved drugs. The preponderance of single-enantiomers was probably driven by the tide of approved single-enantiomer drugs that occurred since 1998. In the four-year period from 1983–1986 (Figure 3), more racemic drugs (32%) were approved compared with single enantiomer drugs and achiral drugs exceeded both categories of chiral drugs. However, even in this early time span of the 1980s, single enantiomers were not a minor component of approved drugs and of approved chiral drugs. In subsequent years the percentage of achiral drugs decreased gradually from 43 to 34% of all approved drugs. The achirals:chirals ratios were 43:57 (1983–1986), 36:64 (1987–1990), 34:66 (1991–1994), 41:59 (1995–1998) and 34:66 (1999–2002) (Figure 3). The percentage of racemates dropped dramatically in the period 1999–2002 to 8% compared with the earlier gradual decreases. In 2001 there were no racemates approved whereas two racemic drugs were approved in 2002 (in Japan and in South Korea). Single enantiomers reached 50% of all approved drugs for the first time in 1998, rising to >60% between 2000–2001.

These trends were probably influenced considerably by the guidelines of the regulatory agencies in the major jurisdictions, which favored and encouraged, but did not force, the development of single-enantiomer drugs over racemates [6,7], thus accounting for the dramatic shift of pharmaceutical company interest in manufacturing the safer single enantiomer and achiral drugs over the problematic racemic drugs.

Distribution of FDA approved drugs, according to chirality character

1991–2002

The distribution of FDA approved NMEs according to chirality character covers

*The annual distribution in 1989–2000 and 1989–2001, and for five-year distributions in the period 1983–2002 have recently been reported [4, 17, 20]

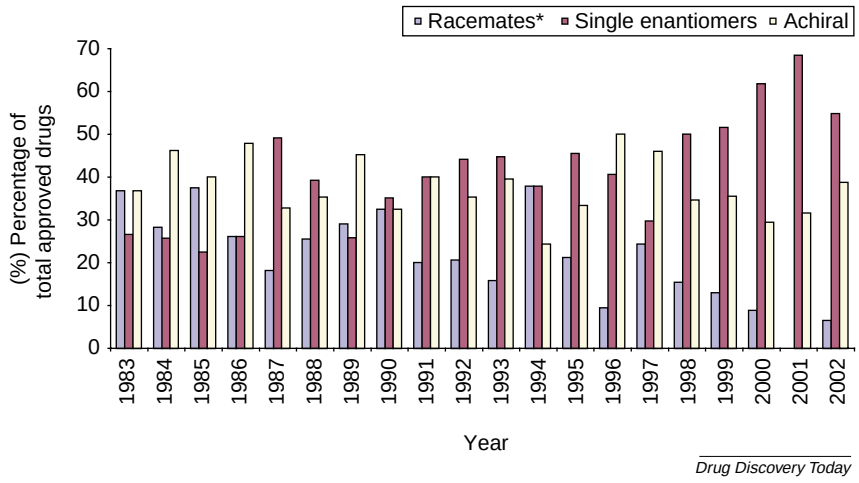

Figure 2. Annual distribution of worldwide-approved drugs according to chirality in the period 1983–2002. * Including diastereomeric mixtures

only 12 years (1991–2002) (Figure 1b). It does not include the decade before the publication of the FDA guidelines [6]. The distribution of FDA approved drugs for the whole 12-year period bears some similarity to the worldwide distribution, in that 44% were single enantiomers, 42% achiral drugs and a minority (14%) were racemic drugs.

In the three-year range distribution (Figure 5) the dominance of single-enantiomer drugs is obvious, starting with 45% between 1991–1993. This figure varied only slightly in the period of 1991–2002 whereas racemates dropped significantly in the same period. Achirals fluctuated from 35% in 1991–1993 to 52% in 1997–1999 and then dropped slightly to represent 44% of FDA-approved drugs in 2000–2001. Single enantiomers took over as the leading category in 2001 (60%) compared with achirals (40%) and racemates (0%).

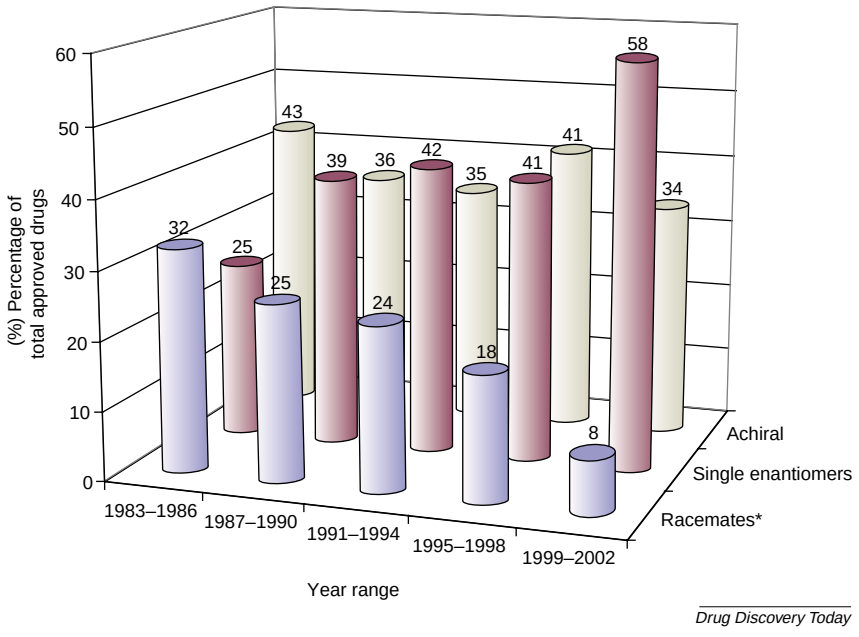

Figure 3. Distribution of worldwide-approved drugs according to chirality character in four-year ranges. *Including diastereomeric mixtures

The case of the racemic drug thalidomide is worthy of comment. The thalidomide tragedy of 1961 was a landmark in drug regulation [4,18]. Thalidomide was marketed outside the US in the late 1950s and early 1960s as a sleeping pill and a treatment for morning sickness during pregnancy. This treatment resulted in the birth of deformed babies. At that time thalidomide had not been approved by the FDA. However, in 1998 the FDA-approved racemic thalidomide [Thalomid (Celgene)] for the acute treatment of the cutaneous manifestations of moderate to severe erythema nodosum leprosum (ENL) and as maintenance therapy for the prevention and suppression of the cutaneous manifestations of ENL recurrences. It was awarded orphan drug status and was classified as a NME (CHE 1). The proposal that the thalidomide tragedy could have been avoided if the single enantiomer had been used is misleading [4].

Conclusions

- In the 1980s single enantiomers were a significant and important component of approved drugs even before changes in guidelines by regulatory agencies encouraged (but did not force) the development and marketing of enantiomerically pure drugs.
- The regulatory guidelines did not affect significantly the chiral (single enantiomers + racemates) to achiral ratio. However, the guidelines did have a major impact within the chiral drug category, resulting in the dramatic decline in the development of racemates in recent years.
- Changes in the attitudes of the regulatory agencies over the past

decade with respect to chiral drugs have affected the number of submissions of single enantiomers.

- Of the single-enantiomer approved drugs, the overwhelming majority contain multiple chiral centers (84% worldwide and 82% FDA) compared with those containing only one chiral center (16% worldwide, 18% FDA).
- The available data for 15 FDA approved drugs in the period January–August 2003 indicate the following distribution: 64% single enantiomers, 14% racemates and 22% achirals (http://www.fda.gov/cder/rdmt/NMECY2003.htm).
- In spite of the absence of any FDA-approved racemates in 2001 and 2002 and only two approved racemates in 2002 (worldwide), racemic drugs should not be declared a dead option. It remains to be seen whether or not racemates will disappear from the drug approval scene.
- The present study might shed light on aspects of intellectual property in chiral switch scenarios [4,19], such as that relating to the pending litigation in the US challenging the patents covering the oral anti-platelet chiral drug Plavix (clopidogrel bisulphate) [20].
- Finally, the data reported here verifies the conclusion that the debate about the relative merits of racemates and single enantiomers has been resolved emphatically in favor of single enantiomer drugs [4].

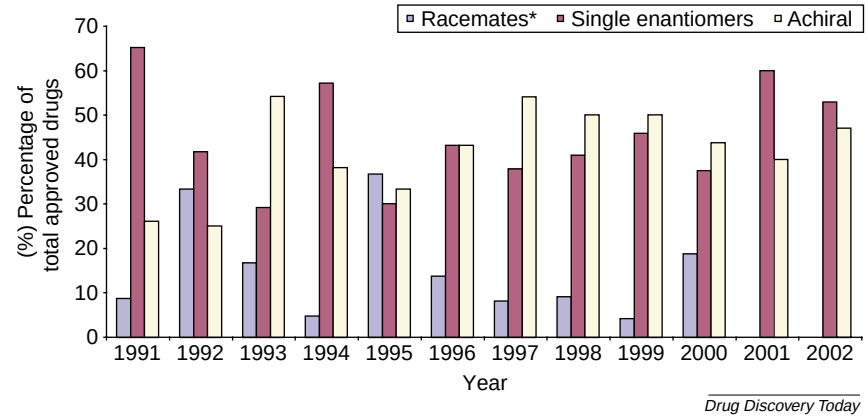

Figure 4. Annual distribution of FDA-approved drugs (NMEs) according to chirality in the period 1991–2002. * Including diastereomeric mixtures.

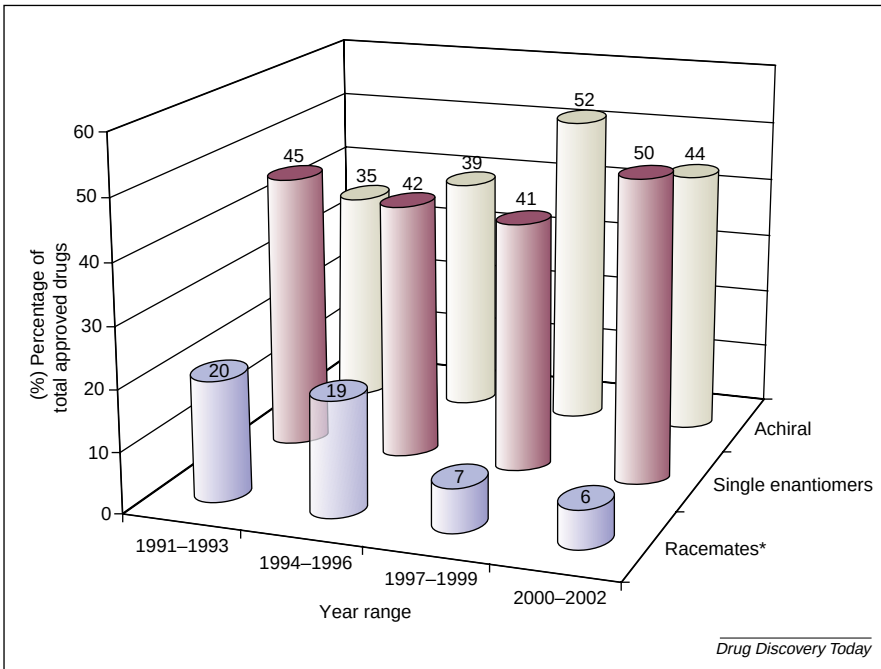

Figure 5. Distribution of FDA-approved drugs (NMEs) according to chirality character in three-year ranges. *Including diastereomeric mixtures

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Advancing in the face of conventional wisdom

In recent issues of *Drug Discovery Today* [1,2], Jurgen Drews and David Cavalla discussed the future productivity of drug discovery. Although they made many insightful and valid comments, I would like to add some points to the overall discussion.

My first point is that most small biotechnology companies are not funded enough to enter a Phase III clinical study. Often, it is not even in their business strategy to enter Phase III development without a major partner on board. Therefore, it might be that the lack of funding and increased discretion of the major pharmaceutical companies play the more important roles in determining which products enter Phase III drug development. This would explain many of David Cavalla's observations, including why there has been an increase in Phase I and II investigations, with a 71% increase in the time taken in Phase II between 1997 and 2001 (Ref. [2] and references therein).

My second point is that drug discovery could blossom if we recognized the need both for more accurate descriptions of drug–receptor interactions and for safer drugs. I believe that most readers would agree with these two points, although when it comes to Drews' and Cavalla's point that '…without the conviction based on scientific rectitude to advance into uncharted areas in the face of conventional commercial wisdom, medicine will advance little, and the future for the pharmaceutical industry is lacklustre.' [2], we enter a rather strange realm in which we should promote the unusual and more creative scientific ideas to develop better drugs. However, the drug discovery process is not constructed to do this in a way that encourages the funding of the more creative young biotechnology companies or entrepreneurs. Much investor money is risk adverse, so this job is handed over to the well-funded pharmaceutical or biotechnology companies, or to the universities and National Institutes of Health. This is slightly better, although they are all invested in the conventional wisdom (which is often shaped by money and power) and, therefore, have no desire to upset it.

Often, there are rather large egos involved in promoting and keeping scientific theories and ideas in press for possible prestige and potential fame. Yet some of the areas of most need are left wanting for the necessary cutting-edge research. Many diseases have only palliative treatments and many of the drug therapies have serious side effects that have increased morbidity and mortality. Much has been made of the Institute of Medicine report suggesting that from 44 000 to 98 000 deaths occur annually in the USA because of medical errors [3]. However, the side effects of drugs and drug combinations increase each year, despite increased vigilance from the health care community. Certainly, some of the reported medical errors are due to the improper use of drugs. For the most part, the Food and Drug Administration

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