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The predicated demise of racemic new molecular entities is an exaggeration

Israel Agranat, Silvya R. Wainschtein and Enav Z. Zusman

Since 2003, *Nature Reviews Drug Discovery* has consistently published reports of annual new drug approvals by the US Food and Drug Administration (FDA) (2011 FDA drug approvals. *Nature Rev. Drug Discov.* **11**, 91–94 (2012))[1]. These informative summaries provide an opportunity for us to introduce drug chirality in the analysis of the trends in the development of new drugs.

The chirality of drugs has become a major theme in the design, discovery, development, patenting and marketing of new drugs[2,3]. For many years the pharmacopoeias were dominated by racemates. However, this trend was inverted owing to the emergence of new technologies in the 1980s that allowed the preparation of single enantiomers in substantial quantities; it was also inverted as a result of E. J. Arien's effective rediscovery and outspoken advocacy of the significance of stereochemistry in therapeutic action and his preference for single-enantiomer drugs over racemic drugs[4]. It has been accepted since the early 1980s that most of the biological activity observed for a racemate often resides within a single enantiomer.

In 1986, a turning point was reached when C. Kumkumian, a senior FDA official, sent a message to the large audience of a major international scientific meeting: the FDA wanted racemic drugs to be resolved and their enantiomers characterized (this was recently reported in a patent litigation case)[5]. By making these remarks, the FDA was providing information about its future direction. This direction, grafted in the FDA's 1987 'Guideline for submitting supporting documentation in drug applications for the manufacture of drug substances', would eventually crystallize and become the authoritative 1992 FDA policy statement for the development of new stereoisomeric drugs[5,6]. Since the turn of the century, it has been predicated that the proportion of racemic new molecular entities (NMEs) will vanish. For example, the 2006 book entitled *Chirality in Drug Research* claimed that "new racemic drugs are highly unlikely to appear"[7]. The 2012 book entitled *Pharmaceutical Lifecycle Management* argues that "it has become increasingly difficult for a company to obtain regular approval of a racemic mixture"[8].

Here, we report the results of two surveys that determine the proportion of racemic drugs from all NME approvals by the FDA and worldwide (defined as every county in the world that had an NME approved; each NME is only counted once in the worldwide data). The FDA's definition of an NME is as follows: an active ingredient that has never before been marketed in the United States in any form. The European Medicines Agency (EMA) uses the term 'new active substance' (NAS) instead of NME. This is primarily defined as a chemical, biological or radiochemical substance that has not been previously authorized as a medicinal product in the European Union.

For our surveys we used the following reports: reports from the US Center for Drug Evaluation and Research (CDER) entitled 'CDER New Molecular Entity (NME) & New Biologic License Application (BLA) Calendar Year Approvals' from 2002 to 2011 (used for FDA approvals); and the annual reports entitled 'To Market, to Market' from 2001 to 2010, published in *Annual Reports in Medicinal Chemistry*.

We analysed the list of annual NME approvals to determine the distributions of drug chirality: that is, racemate, single enantiomer and achiral. Drugs that were the subject of biologics license applications (and other biologics) were excluded from our surveys, whereas the classification of racemates also included mixtures of diastereomers. FIGURE 1a shows the annual distributions of FDA-approved NMEs according to the chirality of the NME for the 2002–2011 period, whereas FIG. 1b shows the annual distributions of worldwide-approved NMEs according to the chirality of the NME for the 2001–2010 period.

It was not unexpected that in accordance with previous trends in the development of chiral drugs[3,9], out of 195 NMEs approved by the FDA and 205 NMEs approved worldwide during the past decade, single enantiomers were the major component, representing 108

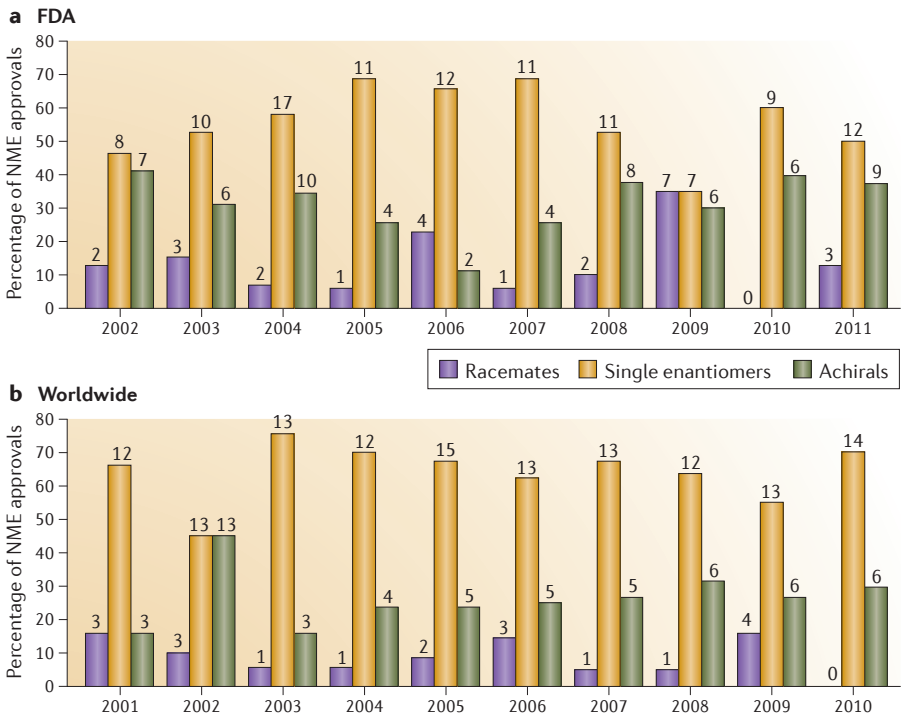

Figure 1 | **The chirality of NMEs. a** | The percentage (shown on the *y*-axis) and number (shown above the bars) of US Food and Drug Administration (FDA)-approved new molecular entities (NMEs) according to the chirality of the NME are shown for the years 2002 to 2011. **b** | The percentage (shown on the *y*-axis) and number (shown above the bars) of worldwide-approved NMEs according to the chirality of the NME are shown for the 2001–2010 period.

(55%) of the NMEs approved by the FDA and 130 of the NMEs (63%) approved worldwide. Achirals reached second place, amounting to 62 of the NMEs (32%) approved by the FDA and 56 of the NMEs (27%) approved worldwide. Surprisingly, however, racemates have not disappeared from the list of NME approvals, amounting to 25 of the NMEs (13%) approved by the FDA and 19 of the NMEs (9%) approved worldwide. These numbers equate to an annual average of 2.5 and 1.9 NMEs, respectively. Strikingly, in 2009, the FDA approved seven racemates (35%) out of 20 NME approvals, whereas four racemates (17%) out of 23 NMEs were approved worldwide. There were no approvals of racemic NMEs in 2010 (by the FDA and worldwide), and in 2011 there were three approved (by the FDA).

So although the factors that have been present since the 1980s to favour the development of single-enantiomer drugs have been reflected in a substantial decline in the percentage of racemic NMEs approved since circa the mid-1990s[3], the data reported here show that the development and approval of racemic compounds continues to be viable. The rationale for developing racemic NMEs may be based on commercial and strategic considerations, such as avoiding resolutions (that is, the separation of a racemic mixture into component enantiomers) and asymmetric syntheses during the large-scale synthesis of new drugs, which could reduce costs as well as the time taken to develop viable manufacturing processes, thus potentially facilitating earlier regulatory approval. In addition, there may be cases in which there is no rationale for developing a single-enantiomer drug; for example, if the single enantiomer is converted into a racemate *in vivo*. An example of such a compound is thalidomide, which the FDA approved as an NME in 1998.

There may also be a lower risk of challenges to the validity of basic patents versus enantiomer patents. An enantiomer patent is a patent that claims a single enantiomer of a chiral compound that has been claimed previously in the corresponding basic patent as a racemate or as a mixture of diastereomers[10]. Enantiomer patents are especially susceptible (or exposed) to challenges on the grounds of obviousness, including the 'obvious to try' test[10].

Finally, it should be noted that the continuing approval of racemic NMEs could have implications for the persistence of the 'chiral-switch strategy'[2], in which a single enantiomer of a racemic NME is developed in the anticipation that it may have superior therapeutic properties — well above the expected 2:1 ratio[10] — compared to the racemic NME, which could provide the basis for a patent that claims the enantiomer alone. This has been viewed as a life cycle management measure[8], and it has been recently proposed that it is "bound to lose its importance in the coming years"[8]. However, this may not be the case if racemic NMEs continue to be approved, as indicated by the data here, and if the difference in therapeutic properties between a single enantiomer of a racemic NME and the racemate is sufficiently substantial to justify subsequent development and patenting of the enantiomer.

Overall, drawing inspiration from Mark Twain's 1897 quote — "the report of my death was an exaggeration" — we believe that the death of racemic NMEs is an exaggeration[11].

Israel Agranat is at the Institute of Chemistry, The Hebrew University of Jerusalem, Philadelphia Bldg 201/205, Edmond J. Safra Campus, Jerusalem 91904, Israel.

Silvya R. Wainschtein was previously at the Institute of Chemistry, The Hebrew University of Jerusalem, Philadelphia Bldg 201/205, Edmond J. Safra Campus, Jerusalem 91904, Israel. Present address: School of Chemistry, Tel Aviv University, Tel Aviv 69978, Israel.

Enav Z. Zusman is at the Department of Life and Medical Sciences, Tel Aviv University, Tel Aviv 69978, Israel.

Correspondence to I.A.
e-mail: isri.agranat@mail.huji.ac.il
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Competing interests statement
The authors declare no competing financial interests.