Pharmaceutical Substances: Syntheses, Patents, Applications. By A. Kleemann, J. Engel, B. Kutschner, D. Reichert. Thieme: Stuttgart, New York, **2001**, hardback, € 499, ISBN 3-13-558403-8, 2488 pp. CD-ROM, € 798, ISBN 3-13-115134-X.

Pharmaceutical Substances: Syntheses, Patents, Applications is the new revised and expended fourth edition of *Pharmazeutische Wirkstoffe*, in English. The second edition and its supplemental volume were published in 1983 and 1988, respectively, in German. The third edition of *Pharmaceutical Substances* (*PS3*) was published in 1999 in English and was, in many respects, not just an upgrade, but a new product. *Pharmaceutical Substances*, fourth edition (*PS4*) contains a collection of 2267 active pharmaceutical ingredients (APIs) of interest to the pharmaceutical and chemical industry, academia and government agencies. It is available both in print and in CD-ROM. About 100 new drug monographs were added to *PS4*. According to the authors, *PS3* was more or less sold out in less than 18 months. *Pharmaceutical Substance PS4*, similarly to *PS3*, is designed to be a complete reference guide to every pharmaceutical compound of significance and an essential, first point of reference to specialists in drug chemistry and anyone involved in the synthesis and use of pharmaceuticals. The purpose and objective of this book, according to its authors, are to establish a link between International Nonpropriety Names (INNs), structures, syntheses and production processes, patent (and literature) scenarios, medical uses and trade names of important pharmaceuticals.

The description of each compound in *PS4* follows the same pattern as in *PS3*. It includes the following components: Chemical structure; molecular formula; molecular weight; graphical representation of the synthetic route, including intermediates; Nomenclature: INN and other Generic Names (e.g., BAN, DCF, USAN), trivial names, synonyms, Chemical Abstract name; Trade Names; CAS Registry Number; EINES number; Anatomic Therapeutic Chemical (ATC) Code Number; medical application/therapeutic category; pharmaceutical dosage forms; toxicological data; patent numbers, origin, holder application, priority and expiry dates; bibliographical information. The book includes, in addition to the alphabetical list of drug monographs, ATC classification, and Drug Monographs, four indexes: Trade Names; Intermediates; Enzymes, Microorganisms, Plants, Animal Tissue; Substance Classes.

The main advantage of *PS3* was the integration of the multiple components of each pharmaceutical ingredient. *PS4* follows this tradition. An important feature of this reference book is the special emphasis given to patents, Trade Names and synthetic schemes. In many respects it is complementary to the *Dictionary of Pharmaceutical Agents* (Chapman & Hall/CRC Press, print version published 1997, CD-ROM version updated biannually). Although *PS4* has a distinct chemical character, its pharmacological characteristics are pronounced. Unfortunately, *Pharmaceutical Substances PS4* has not been comprehensively updated, especially with new drugs, bearing in mind that this edition of the Reference Book was published in 2001 and the authors' Preface is dated Autumn 2000. According to the *Annual Reports in Medicinal Chemistry* (Volumes 35 and 36, Academic Press), in 1999 and 2000, the numbers of new therapeutic chemical entities (NCEs) introduced into the world market for the first time were 36 and 35, respectively, including new biological entities (NBEs). *PS4* contains 15 (42%) of the 1999 new drugs and only 2 (6%) of the 2001 new drugs. Conspicuously missing from *PS4* is Esomeprazole magnesium (Nexium), the single enantiomer chiral switch of the blockbuster drug Omeprazole (Losec, Prilosec), the leading gastric proton pump inhibitor (PPI). Esomeprazole has been approved in the EU (2000) and in the US (2/2001). However, the introduction in the U.S. of the racemic antiulcer PPI, pantoprazole sodium (Protonix) has been added. The absence of the potent antimalarial Arteether (Artemotil), introduced in the Netherlands in 2000, for the treatment of severe malaria infections in children and adolescents, is also noted. Arteether is an ether derivative of the naturally occurring Artemisinin (Chinese: Qinghaosu), the active component of Qinghao, the Chinese traditional herbal medicine. The monograph on Sildenafil citrate (Viagra) still lists the WO patent claiming the use of this drug for the treatment of male erectile dysfunction, with GB priority date of 9/6/1993. The authors have overlooked the revocation of the corresponding European Patent (UK) for obviousness, both by the High Court in England (11/2000) and by the Opposition Department of the EPO (7/2001). It is gratifying that the racemic drug Thalidomide, which had a profound impact on the development of drugs in general and on the regulatory environment of drugs in particular, has been included in *PS4*. Thalidomide, a human teratogen, was originally marketed as a sedative outside the US from the 1950s until the early 1960s when it was linked with severe birth defects and withdrawn. In 1998, the US FDA cleared Thalidomide for marketing as a treatment for erythema nodosum leprosum (ENL), a serious inflammatory condition in patients with Hansen's disease (Leprosy), while at the same time imposing unprecedented restrictions on its distribution.

The treatment of Stereochemistry in *PS4* should be improved. For example, the structure of the antidiabetic alpha-glucosidase inhibitor Miglitor (Diastabol, Glyset), launched in 1998, lacks the absolute configurations of the four stereogenic centers of its piperidine ring. The characterization of Thalidomide as a racemate is also missing. The authors should be complimented for introducing the acronym (wfm) whenever a drug has been withdrawn from the market. In this connection, the withdrawals from

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the markets in 2001 of the important HMG-CoA-reductase inhibitor antihypercholesterolemic agent, Cerivastatin sodium (Lipobay, Baycol), due to severe side-effects, have been overlooked. The antiobesity drugs Fenfluramine (Pondimin) and Dexfenflurmanine (Redux), withdrawn from the US market in 1997, following significant, unfavorable side-effects, are still listed in *PS4* without the wfm label in USA.

The decision to publish *PS4* in two volumes was wise, rendering it a more friendly reference book. The presentation of a colored 3D picture of a successful drug in the front cover of the book is very attractive. In *PS4*, the cover of each volume carries the 3D picture of the HMG-CoA-reductase inhibitor antihyperlipidemic cholesterol synthesis inhibitor, HMG-CoA-reductase inhibitor, Simvastatin (Zocor). Hopefully, the success of the lipid-lowering statins in primary prevention of coronary heart disease will not be hampered by the recent withdrawal of Cerivastatin.

In conclusion, *Pharmaceutical Substances PS4* has maintained its high quality. It is an excellent, indispensable source of information and reference guide of drugs, which should be present in all libraries of pharmaceutical companies, departments of Medicinal Chemistry and institutes of Pharmaceutical Chemistry, colleges of Pharmacy, patent attorneys, and government agencies (including regulatory and patent agencies) involved in the design, discovery, development and evaluation of drugs, world wide.

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