DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 98N–0517]

Development of Antimicrobial Drug Products; Development and Use of FDA Guidance Documents; Request for Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for comments.

SUMMARY: The Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER), Office of Drug Evaluation IV (ODE IV), is providing notice to drug manufacturers regarding its current plans for revising existing guidance documents and preparing new guidance documents on the development of antimicrobial drug products for the treatment of infections. ODE IV is reviewing, updating, consolidating, and revising its existing guidance documents and identifying topics for future guidance. The agency is requesting public comment on topics for future guidance development.

DATES: Written comments may be submitted by October 19, 1998. General comments on agency guidance documents are welcome at any time.

ADDRESSES: Copies of agency guidance documents can be obtained on the Internet at ''http://www.fda.gov/cder/guidance/index.htm''. Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville MD 20852. Comments are to be identified with the docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: Renata Albrecht, Center for Drug Evaluation and Research (HFD–590), Food and Drug Administration, 9201 Corporate Blvd., Rockville, MD 20850, 301–827–2336.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of February 27, 1997 (62 FR 8961), FDA published a notice explaining its policy for guidance document development, issuance, and use. The notice included an agency document entitled ''Good Guidance Practices'' (GGP's), which sets forth agency policies and procedures for developing, issuing, and using guidance documents. The GGP's emphasize the importance of gaining public input early in the guidance development process.

Since the 1970's the agency has issued guidance in a variety of forms to the pharmaceutical industry to facilitate the development of antimicrobial drug products. In addition to advice and guidance provided verbally during various industry and FDA meetings and other interactions between the regulated industry and FDA, or in individual letters written to sponsors, general written guidance has also been provided. In 1977, the agency issued guidance on the development of antimicrobial drug products entitled ''Clinical Evaluation of Anti-Infective Drugs (Systemic).'' In fulfillment of a contract from FDA, in November 1992, the Infectious Disease Society of America (IDSA) published its ''Guidelines for the Evaluation of Anti-Infective Drug Products'' in the supplement of ''Clinical Infectious Disease'' (formerly, ''Reviews of Infectious Diseases''). That same month, FDA's Division of Anti-Infective Drug Products issued ''Points to Consider: Clinical Development and Labeling of Anti-Infective Drug Products'' (1992) on issues related to evaluating new drug applications for anti-infective drug products. All of these documents contain information helpful for designing clinical trial protocols for evaluating the safety and effectiveness of new therapies to treat infections and gaining approval for supplemental indications.

In 1996, in an attempt to outline in more detail the elements the agency considers important when evaluating clinical studies, the agency initiated efforts to develop guidance that would provide investigators, academia, and industry with insight on those elements (often referred to as ''evaluability criteria'') considered important during the evaluation of clinical studies for antimicrobial drug products. In March 1997, an early draft guidance, entitled ''Evaluating Clinical Studies of Antimicrobials in the Division of Anti-Infective Drug Products,'' was discussed at an Anti-Infective Drug Products Advisory Committee meeting. That early draft contained an introduction and individual sections addressing 12 specific indications. Space was reserved to provide guidance at some later date on approximately 15 additional indications.

Since the 1997 advisory committee meeting, several events have occurred that affect how clinical trials are designed, conducted, evaluated, and reported and that are relevant to the revision and development of guidance on antimicrobial drug products. ODE IV, which includes the Division of Anti-Infective Drug Products, the Division of Special Pathogens and Immunologic Drug Products, and the Division of Anti-Viral Drug Products, reviewed all of its guidance documents and determined that certain revisions were necessary. In November 1997, the Food and Drug Administration Modernization Act of 1997 (Modernization Act) was enacted (Pub. L. 105–115); it contains several provisions related to drug development and will lead to additional agency guidance documents on a variety of subjects relating to clinical trial design and evaluation. For example, section 119 of the Modernization Act addresses meetings and agreements concerning the design and size of clinical trials. In addition, in May 1998, the agency published a guidance for industry entitled ''Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products'' (63 FR 27093, May 15, 1998) that fulfills certain requirements in section 403(b) of the Modernization Act and that also has implications for antimicrobial drug products.

ODE IV is continuing its efforts to develop comprehensive guidance on evaluability criteria by reviewing, updating, consolidating, and revising its existing guidance documents, taking into account these broader agency initiatives. Specifically, the office is deciding which elements of current guidance documents remain applicable, which elements need to be removed, which elements need to be updated, and which elements need to be added. In the process, all guidances are being developed consistent with the agency's GGP's.

Throughout the 1990's, ODE IV has approached the development of guidance in an open forum as part of its advisory committee process. It wishes to continue this public and transparent process for guidance document development. ODE IV generally expects to include advisory committee review as part of the process of reviewing and developing guidance for industry on antimicrobial drug development.

II. Guidance Development Plan

ODE IV has reviewed all existing, relevant documents. Within the next few months, ODE IV expects to issue a general draft guidance that addresses issues common to all indications and a series of companion draft guidances that address the following individual indications:

1. Uncomplicated urinary tract infections,
2. Uncomplicated skin and superficial skin structure infections,
3. Complicated skin and soft tissue infections,
4. Community-acquired pneumonia,
5. Nosocomial pneumonia,

6. Acute bacterial exacerbation of chronic bronchitis,
7. Secondary bacterial infection of acute bronchitis,
8. Acute otitis media,
9. Acute uncomplicated gonorrhea,
10. Acute sinusitus,
11. Complicated urinary tract infections and pyelonephritis,
12. Bacterial prostatitis,
13. Early Lyme disease,
14. Empiric therapy of febrile neutropenia,
15. Vulvovaginal candidiasis,
16. Streptococcal pharyngitis and tonsillitis,
17. Bacterial meningitis, and
18. Bacterial vaginosis.

Key aspects of these draft guidances will be discussed in a July 1998 advisory committee meeting. After the meeting, ODE IV will work toward finalizing these guidances.

The next step will involve developing draft guidance documents for the following proposed indications:
1. Nongonoccocal urethritis/cervicitis,
2. Endocarditis,
3. Uncomplicated intra-abdominal infections,
4. Complicated intra-abdominal infections,
5. Gynecologic infections (except sexually transmitted disease and pelvic inflammatory disease),
6. Pelvic inflammatory disease,
7. Osteomyelitis (acute and chronic),
8. Acute bacterial arthritis, and
9. Helicobacter pylori infections.

Once developed, the agency expects that it will release the guidances in draft for review and comment, with key elements discussed before the advisory committee.

ODE IV also is considering developing guidance during the next few years for the following agents:
1. Agents to treat opportunistic infections related to AIDS;
2. Antimycobacterial agents;
3. Antifungal agents;
4. Antiparasitic agents;
5. Immunologic/transplant agents;
6. Antiviral agents;
7. Dermatologic surgical scrubs, etc.;
8. Agents to treat sepsis/septic shock; and
9. Agents used in surgical prophylaxis.

As with the other guidances, it is expected that these guidances will first be issued in draft for review and comment and discussed before the advisory committee.

III. Comments

ODE IV is seeking suggestions and recommendations for future guidance development. Interested persons may submit comments to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: July 13, 1998.

William K. Hubbard,

Associate Commissioner for Policy Coordination.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 97E–0358]

Determination of Regulatory Review Period for Purposes of Patent Extension; Flowmax™

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) has determined the regulatory review period for Flowmax™ and is publishing this notice of that determination as required by law. FDA has made the determination because of the submission of an application to the Commissioner of Patents and Trademarks, Department of Commerce, for the extension of a patent which claims that human drug product.

ADDRESSES: Written comments and petitions should be directed to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Brian J. Malkin, Office of Health Affairs (HFY–20), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–6620.

SUPPLEMENTARY INFORMATION: The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98–417) and the Generic Animal Drug and Patent Term Restoration Act (Pub. L. 100–670) generally provide that a patent may be extended for a period of up to 5 years so long as the patented item (human drug product, animal drug product, medical device, food additive, or color additive) was subject to regulatory review by FDA before the item was marketed. Under these acts, a product's regulatory review period forms the basis for determining the amount of extension an applicant may receive.

A regulatory review period consists of two periods of time: a testing phase and an approval phase. For human drug products, the testing phase begins when the exemption to permit the clinical investigations of the drug becomes effective and runs until the approval phase begins. The approval phase starts with the initial submission of an application to market the human drug product and continues until FDA grants permission to market the drug product. Although only a portion of a regulatory review period may count toward the actual amount of extension that the Commissioner of Patents and Trademarks may award (for example, half the testing phase must be subtracted as well as any time that may have occurred before the patent was issued), FDA's determination of the length of a regulatory review period for a human drug product will include all of the testing phase and approval phase as specified in 35 U.S.C. 156(g)(1)(B).

FDA recently approved for marketing the human drug product Flowmax™ (tamsulosin hydrochloride). Flowmax™ is indicated for the treatment of the signs and symptoms of benign prostatic hyperplasia (BPH). Subsequent to this approval, the Patent and Trademark Office received a patent term restoration application for Flowmax™ (U.S. Patent No. 4,703,063) from Yamanouchi Pharmaceutical Co., Ltd., and the Patent and Trademark Office requested FDA's assistance in determining this patent's eligibility for patent term restoration. In a letter dated November 7, 1997, FDA advised the Patent and Trademark Office that this human drug product had undergone a regulatory review period and that the approval of Flowmax™ represented the first permitted commercial marketing or use of the product. Shortly thereafter, the Patent and Trademark Office requested that the FDA determine the product's regulatory review period.

FDA has determined that the applicable regulatory review period for Flowmax™ is 3,529 days. Of this time, 3,163 days occurred during the testing phase of the regulatory review period, 366 days occurred during the approval phase. These periods of time were derived from the following dates:

1. *The date an exemption under section 505 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 355) became effective*: August 19, 1987. FDA has verified the applicant's claim that the date the investigational new drug application became effective was on on August 19, 1987.