

# FINANCIAL ASSISTANCE AND INCENTIVES FOR RESEARCH AND DEVELOPMENT OF NEW DRUG/BIOLOGICAL PRODUCTS

**Ronald Wilson, Director, Small Business Assistance  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration**



**Abstract:** *Small Business Assistance (SBA) is a new function of the U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research, which provides assistance to small businesses with fewer than 500 employees involved in the development of new pharmaceutical products. Through an extensive outreach program, SBA provides guidance and information to small pharmaceutical businesses through its ListServ, Q&A's, workshops, and website. The ListServ provides current information from CDER/FDA via e-mail on a biweekly basis.*

## Introduction

One of the services that Small Business Assistance provides is information on pre-approval and post-approval financial assistance and incentive programs to small businesses largely involved in the development of new pharmaceutical products. Financial programs, including those of the FDA, the National Institutes of Health (NIH), and other government agencies, are divided into three groups: financial assistance pre-approval, financial incentives post-approval, and financial assistance pre-approval and post-approval. Each of these programs and their eligibility requirements are explained on the SBA Web site ([www.fda.gov/cder/about/smallbiz/default.htm](http://www.fda.gov/cder/about/smallbiz/default.htm)), which contains Q&A documents about most of these programs. Prepared especially for small businesses, the Q&A documents use clear definitions to enable people to understand these programs.

## Financial Assistance Pre-Approval

Financial assistance pre-approval is composed of the Orphan Drug Program, the Prescription Drug User Fee Act (PDUFA), charging for investigational drugs, and FDA and NIH grants (Table 1).

### The Orphan Drug Program

The Orphan Drug Program, established in 1987, identifies orphan drug products and facilitates their development in the treatment of rare disease and conditions (rare diseases are diseases or conditions that affect less than 200,000 people in the U.S. or elsewhere in situations where cost recovery is not possible). The Orphan Drug Program has a wide array of financial benefits for clinical research, including tax credits in the pre-approval stage, annual research grants that total approximately \$15 to \$20 million, and waivers of PDUFA application and supplement fees.

**TABLE 1  
Financial Assistance Pre-Approval**

Orphan Drug Program  
Prescription Drug User Fee Act  
Charging for investigational  
drugs  
Grants (FDA and NIH)

### The Prescription Drug User Fee Act

PDUFA, enacted in 1992, authorizes the FDA to collect user fees from companies that produce certain human drug and biological products. PDUFA has played a very important role in expediting the new drug approval process and has three types of user fees: application fees, establishment fees, and product fees.

The financial provisions of PDUFA include waivers, reductions, and refunds. The application fee is waived for the first human drug application that a small business submits. Waivers of application, product, and establishment fees are available for all pharmaceutical companies that meet certain qualifying factors, including that the fee would present a significant barrier to innovation due to the business' limited resources or circumstances. Reductions or refunds of fees may be granted for an application or supplement that is refused for filing or withdrawn before or after filing.

The PDUFA Q&A contains procedures for requesting a waiver, reduction, or refund of fee. These procedures cover the qualifying factors, the information to be included in the request, the format, and where to submit the request. A written request must be submitted not later than 180 days after the fee is due.

### **Charging for Investigational Drugs**

Federal regulation 21CFR 312.7(d) permits sale of an investigational drug or biological product. The regulation contains the requirements that must be met before a company can charge for investigational drugs. The Small Business Assistance website provides a link to the regulations for Charging for Investigational Drugs.

### **Grants**

The FDA and NIH cooperate on several grant programs. NIH has a very large grant program and extensive facilities to assist grant applicants.

The FDA offers solicited and unsolicited grant applications and participates in the Small Business Innovation Research Program.

When the FDA has a program that is eligible for grants, a request for applications is published in the Federal Register and posted on FDA's Web site ([www.fda.gov/oc/ofacs/grants.default.htm](http://www.fda.gov/oc/ofacs/grants.default.htm)). The Small Business Assistance ListServ, sent every two weeks, also announces the availability of solicited grants.

Unsolicited grants, awarded occasionally, are those that are not submitted in response to a published request for applications. Funds for unsolicited grants come from the Center for Drug Evaluation and Research, and thus, are limited. FDA works with NIH on unsolicited grants, which should be submitted to NIH's Center for Scientific Review. NIH reviews these grants for FDA because it has extensive facilities for this process.

NIH participates in the Small Business Technology Transfer Program and the Small Business Innovation Research Program, and offers grants and funding opportunities. The Small Business Assistance Web site has more information, including contact information for an NIH grant manager.

Small Business Innovation Research Programs are required by law for federal agencies with extramural budgets of more than \$100 million. These programs are designed to enable small businesses to engage in federal research and development (R&D) projects that have the potential for commercialization and public benefit. Agencies must set aside 2.5% of their budget for these grants. NIH reviews FDA grant applications for this program. In fiscal year 2002, the FDA provided \$2 million and NIH \$500 million in health research grants through the Small Business Innovation Research Program.

NIH also has a Small Business Technology Transfer Program, which is required by law for federal agencies with extramural budgets of more than \$1 billion. The objective of the Small Business Technology Transfer Program is similar to that of the Small Business Innovation Research Program. Its unique feature is the requirement that the small business applicant formally collaborate with a research institution. At least 40% of the project must be conducted by the small business and at least 30% must be conducted by the research institution. NIH must set aside 0.3% of its budget for this program. In fiscal year 2002, NIH awarded \$30 million in Small Business Technology Transfer Program grants.

The Small Business Innovation Research Program and the Small Business Technology Transfer Program each have three phases. Phase 1 provides a grant to establish the technical merit and feasibility of the proposed R&D effort. Phase 2 continues the R&D effort with additional support. In phase 3, the small business must pursue the commercialization of objectives resulting from phase 1 and 2 without grant funding from these programs.

Every June, NIH has an annual Small Business Innovation Research Program/ Small Business Technology Transfer Program conference in Bethesda, Maryland. This conference, usually two days, provides extensive information about these programs and how to qualify and apply for them. NIH invites all federal agencies that have these programs to attend and have one-on-one sessions with participants. The FDA sends representatives of Small Business Assistance and the grant program. This conference is announced on the Small Business Assistance ListServ.

NIH's Web site includes links to NIH funding (<http://grants1.nih.gov/grants/index.cfm>). It includes a grants page, research contracts, the NIH Guide for Grants and Contracts document, and research training opportunities.

### Financial Incentives Post-Approval

Financial incentives post-approval revolve around the concept of exclusivity except for patent term extension (Table 2). Exclusivity generally bars FDA approval or acceptance of certain applications for competing drugs. It begins from the date of approval. Exclusivity is available in periods of six months, or three, five, or seven years. Post-approval incentives are: orphan drug exclusivity, Hatch/ Waxman five-year exclusivity, Hatch/ Waxman three-year exclusivity, 180-day generic drug exclusivity, patent term extension, and pediatric exclusivity. Most of these incentives have been established through law since 1987.

**TABLE 2**  
**Financial Incentives**  
**Post-Approval**

Orphan drug products exclusivity  
Hatch/Waxman five-year  
exclusivity  
Hatch/Waxman three-year  
exclusivity  
Pediatric exclusivity  
180-day generic drug exclusivity  
Patent term extension

### Orphan Drug Program

The Orphan Drug Program also offers post-approval exclusivity, providing seven years of exclusivity, the most generous exclusivity of all programs. This generally pertains to drugs and biologics, and applies only to designated and approved orphan indications. Orphan drug

exclusivity blocks approval of another application, including a full New Drug Application.

### Hatch/Waxman Five-and-Three Year Exclusivity

The Hatch/Waxman Act enacted many new programs, including five- and three-year exclusivity, patent term extension, and the 180-day generic drug exclusivity.

Under Hatch/Waxman, manufacturers can receive five years of exclusivity for new chemical entities (NCEs), which by definition are innovative. Applications under 505(b)(1) and 505(b)(2) can receive 5 years of exclusivity. Three years of exclusivity is granted for significant changes as a change in dosage form or strength. Other examples of changes are new indications or routes of administration. Approval of three-year exclusivity requires new clinical investigations (other than bioavailability studies). For three years, FDA may not approve an Abbreviated New Drug Application (ANDA) 505(j) or 505(b)(2) for the protected change.

### 180-Day Generic Drug Exclusivity

180-Day Generic Drug Exclusivity is not involved in new drug development, but it is useful to know about it to avoid confusion. The first ANDA applicant to challenge the listed patent is granted 180 days of exclusivity. Generic drug exclusivity has been very controversial and has resulted in a great deal of litigation. Additional information on 180-Day Generic Drug Exclusivity is available on the Small Business Assistance website.

### Patent Term Extension

Patent term extension is another program enacted by the Hatch/ Waxman Act in 1984. The purpose of the program is to stimulate product innovation by extending

patent life up to five years, which compensates patent holders for marketing time lost while developing the product and awaiting government approval. Most products regulated by the FDA, including drugs and biologics, are eligible for patent extension. Patent term extension is only granted for the first commercial marketing or use of the product under the provision of law for which such regulatory review occurred. The FDA assists the Patent Trademark Office in determining a product's eligibility for patent extension. The Patent Trademark Office determines the period of patent extension.

### Pediatric Exclusivity

Pediatric exclusivity provides six months of exclusivity as an incentive to sponsors to conduct more studies of the use of drugs in pediatric populations. This attaches to an exclusivity period or a patent extension. Only drug products subject to section 505(b) are eligible for pediatric exclusivity.

### Financial Assistance Pre-Approval and Post-Approval

Table 3 outlines financial assistance pre-approval and post-approval.

**TABLE 3**  
**Financial Assistance**  
**Pre-Approval and Post-Approval**

Small Business Administration  
federal grant resources  
(<http://www.sba.gov/expandinggrants.html>)  
Bioshield (treatments for bioterror agents)  
Catalogue of Federal Domestic Assistance  
(<http://www.cfda.gov/default.htm>)

These programs include Small Business Administration federal grant resources, Bioshield, and the Catalogue of Federal Domestic Assistance. As more resources become available, they will be added to the Small Business Assistance Website.

As of July 2003, Bioshield was pending in Congress. When it is passed, there will be a great deal of money for the development of treatments for bioterror agents. The Small Business Assistance ListServ will announce developments with Bioshield. The Catalogue of Federal Domestic Assistance provides online information on federal assistance that is available through all federal agencies.

#### **Small Business Assistance**

The Small Business Assistance Website covers all of the major programs within the Center for Drug Evaluation and Research (Table 4). It includes clear descriptions of programs, links to the offices that handle each program, and contact information.

The Small Business Assistance ListServ, sent via e-mail every two weeks, covers news for small pharmaceutical businesses. The ListServ includes notification of new information such as Federal Register notices, guidances, workshops, presentations by the commissioner, and so forth. People can subscribe to the ListServ by completing the form on the Small Business Assistance Website.

**TABLE 4**  
**Small Business Assistance**

#### **Small Business Assistance Web site**

**[www.fda.gov/cder/about/smallbiz/default.htm](http://www.fda.gov/cder/about/smallbiz/default.htm)**

- Information for clinical investigators
- New drug development and review process
- Orphan drug program
- Generic drug review process
- Over-the-counter drug product review process
- Post-drug approval activities
- Drug registration and listing
- Organization, contact, and meeting information
- FDA-related laws, regulations, and guidance
- Economic assistance and incentives for drug development
- Economic assistance pre-approval
- Economic incentives post-approval
- Economic assistance pre-approval and post-approval

#### **Small Business Assistance ListServ**

- E-mail notification of new information every two weeks
- Subscribe by completing the ListServ form on the Small Business Assistance Website