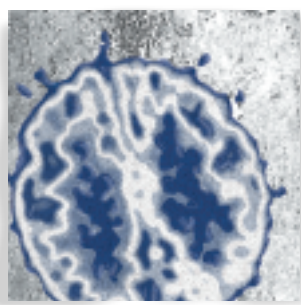


# Basic research

## *FDA relations during drug development*

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*Working closely and cooperatively with regulatory authorities during drug development is vital to successful drug development programs. In the United States, the drug development team includes not only members of the key disciplines of drug discovery, clinical research, regulatory affairs, marketing, chemistry, toxicology, and legal aspects, but also the Food and Drug Administration (FDA). New regulations encourage meetings at the pre-investigational new drug (pre-IND), end-of-phase-2, and pre-new drug application (pre-NDA) submission phases. Appropriate informal discussions via fax and telephone are also encouraged. By proactively interacting with the FDA, the pharmaceutical industry increases the probability of a successful drug development program.*

**I**n order for a drug to reach the market, three general elements must be satisfied. The first is for the product to have a solid scientific rationale based on the concept of “good science.” If possible, the mechanism of action should be understood and potential adverse events anticipated. These concepts can be approached theoretically as well as in nonclinical pharmacological studies. While efficacy and safety in humans cannot be

assured by studies in animals, some comfort level can be achieved by the use of animal models of toxicology. The second element is for the program to be run with solid medical principles, or “good medicine.” The main principle is to do no harm. No clinical program should knowingly put any clinical trial subject at risk of harm. Proper clinical trial designs should be based on acceptable methods with a profound understanding of the disease under study. When adverse events appear, a conscientious evaluation of their significance to the individual patient as well as to the population at large, must be performed. The third element in drug development is to assure compliance with regulatory requirements, or “good regulations.” Fulfillment of regulatory requirements is in addition to fulfillment of the requirements of “good science” and “good medicine.” The regulations ensure that regulatory bodies such as the Food and Drug Administration (FDA) can properly review and evaluate a drug development program in a standardized manner.

### The team

The drug development team includes a diverse group of individuals with different philosophies and approaches to the development process. All team members must work closely together to ensure that a drug is both safe and efficacious.

### Discovery/development

The discovery and development groups are comprised of the basic scientists and chemists who created the new molecule. This group synthesizes drug substances for “drug-screening,” pharmacology, and toxicology studies, and also prepares clinical supplies.

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## Selected abbreviations and acronyms

<b>CBER</b>	<i>Center for Biologics Evaluation and Research</i>
<b>CDER</b>	<i>Center for Drug Evaluation and Research</i>
<b>CDRH</b>	<i>Center for Devices and Radiological Health</i>
<b>CFR</b>	<i>Code of Federal Regulations</i>
<b>CFSAN</b>	<i>Center for Food Safety and Applied Nutrition</i>
<b>CRO</b>	<i>contract research organization</i>
<b>FDCA</b>	<i>Federal Food, Drug, and Cosmetic Act</i>
<b>FTC</b>	<i>Federal Trade Commission</i>
<b>IND</b>	<i>investigational new drug</i>
<b>NDA</b>	<i>new drug application</i>

## Nonclinical pharmacology and toxicology

This group studies the drug product in animal models of efficacy and safety in order to identify potential efficacy and safety issues in humans. It is critical for the clinical and development groups to work closely with the toxicologists in the design of animal studies to ensure their relevance to the clinical environment.

## Clinical research

Clinical research has the ultimate responsibility for testing drug products in humans: the monitoring of drug safety rests squarely on the shoulders of clinical research. Clinical trials must be science-based with proper statistical methodologies and have clinically relevant end points. Clinical research interacts directly with the FDA and is responsible for the generation of study reports with input from biostatisticians and regulatory affairs. Clinical research can also generate the publications necessary for the marketing of any drug product.

## Regulatory affairs

The regulatory affairs department is the interface with the FDA. It is their responsibility to ensure compliance with the rules and regulations established by the Federal Food Drug and Cosmetic Act (FDCA)<sup>1</sup> and its amendments.

## Marketing

The marketing group has the ultimate responsibility for marketing and selling the drug. As a result, they need product labeling that differentiates their drug from those already marketed. Marketing has to provide creative concepts for the prescribing physician, the patient, and the company's senior management. They also have to make sure that budget goals are met. It is not uncommon for the marketing group to have differences of opinion from both the clinical and regulatory groups within their own company, as well as with the FDA.

## Legal

In order for a drug to be financially successful, patent protection is a key element. The legal group must submit patents at the appropriate time and do all in its power to avoid lawsuits from potential competitors. The legal group also ensures that neither the FDA nor the Federal Trade Commission (FTC) will challenge advertising and promotional materials.

## Food and Drug Administration

The FDA's primary mission is to protect public health by regulating the food supply, drugs, devices, and cosmetics. The FDA regulates through the FDCA, Title 21 of the Code of Federal Regulations (CFR),<sup>2</sup> and publications in the Federal Register,<sup>3</sup> and by issuing guidance and other regulatory documents.

## Development philosophy

### Don't waste time: time is money

Time is a key factor in drug development. With finite patent lives, the quicker a drug gets to the market, the longer the revenue stream will be free of generic competition. Therefore, in order to minimize the development time, the team should:

- Plan carefully.
- Execute meticulously.
- Replan when necessary.
- Do only what is needed.
- Hire people who want to get the job done.
- Have pride in their product.

## Working with the FDA

### Structure of the FDA

There are four FDA centers that have the potential to interact in drug development. These are the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH), and Center for Food Safety and Applied Nutrition (CFSAN). With the advent of drug-delivery devices and dietary supplements that can sometimes appear to be drugs, the boundaries between the centers can at times be unclear. As a result, it is always a good idea to know which center will review a particular product.

### Sources of information

There are several sources from which information can be obtained about the FDA. Through the Freedom of Information Act,<sup>4</sup> the United States government has established a mechanism to obtain information directly from the FDA, which is otherwise not easily accessible through publicly available information. The FDA can be contacted via letter or fax. The FDA also has research services and can provide, on a fee-for-service basis, specific information located within their archives. Commercial companies also provide information services. With the creation of the Internet, public information is more readily available than ever before. The FDA has a web site for each of its divisions with a sophisticated search engine and document services (<http://www.fda.gov/>).

### How are regulatory requirements determined?

Sometimes it is obvious where a product will be reviewed. A small molecule that will be used to treat depression or schizophrenia will be reviewed in the Division of Neurological Drug Products. If the designation is not clear, in order to determine which center and which group within that center will have primary product review, it may be appropriate to ask the FDA for clarification. Another alternative is to submit a Request for Designation.<sup>5</sup> In the Request for Designation, the sponsoring company may suggest what the primary reviewing center should be. Since an original investigational new drug (IND) is submitted to the Document Control Room

at FDA, the FDA will designate the primary reviewing center and division if the sponsor does nothing. The latter strategy is rarely adopted: it is almost always a good idea to meet with FDA prior to an IND submission.

## Contacting the FDA

### What should be the initial exposure to FDA rules and regulations?

It is a good idea to be very familiar with the regulations. The formal source of regulations is Title 21 of the CFR. FDA guidance documents for specific issues are also available. Consultants, including regulatory attorneys, are available for consultations. Companies such as contract research organizations (CROs) may also have regulatory specialists as part of their services.

### How are specific toxicological, chemical, and clinical requirements determined?

There are publications available in the Federal Register as well as online at the FDA web site. It is a good idea to review these publications, and then have access to experts who are knowledgeable with specific requirements. It is important to distinguish those vendors who provide services such as toxicology and manufacturing programs. Just because a site can perform services, does not mean that they know how to design a development program.

### What should be the initial contact with the FDA and how should it be carried out?

After completing the above background tasks, make an initial call to the division of interest and briefly introduce yourself. Discuss the project and its status and discuss the option of an initial meeting. If a meeting is decided upon, establish action items, plan meeting dates, send in the briefing document with an agenda, and prepare for the meeting. Find out how many copies the FDA needs. Put in proposed meeting dates and blackout dates, let the FDA know when the briefing document has been sent, and confirm receipt over the phone.

### Preparation for the initial FDA meeting

In general, it is usually a good idea to assign one person to organize and champion the meeting. It is critical to

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prepare a well-thought-out document containing the meeting agenda; attendees; rationale for the product; chemical characteristics of the drug and how it is made; nonclinical pharmacology results; toxicology development plan; clinical data, if available; clinical protocol outline; reprints; and any specific questions to be addressed. The document should be fully paginated, and reproduced accurately so everything is legible, with a clear table of contents.

## How should an FDA meeting be conducted?

The most important aspects of an FDA meeting are to be prepared and to get the FDA to share their position as to how your drug should be developed. Remember, the FDA has already seen your presentation, so there is no need to spend a lot of time telling them what they already know. We have participated in many FDA meetings with no presentations. Bring to the meeting one experienced scientist and one experienced clinician expert as partici-

pants. A clinical expert in the indication under study is a major plus. If at all possible, the expert should have prior FDA experience. If not, the expert must be coached as to the goal of the meeting, and how to act and respond to questions. Sometimes it is recommended to bring administrative and marketing executives so they can better appreciate the regulatory process. Make sure each person knows his/her role. If a presentation is decided upon, limit the presentation to 10 to 15 minutes. During the meeting, if possible, have two people take copious notes for the generation of meeting minutes. Make sure that all of your issues are addressed at the meeting and, if possible, chat informally with the FDA after the meeting.

## Conclusion

Bring the FDA in as part of the development team and share ideas, set milestones, share data, maintain a dialogue, and keep no secrets. Remember: the FDA is part of the team whether you like it or not. □

### *Relaciones con la FDA durante el desarrollo de nuevos fármacos*

*Para que los programas de desarrollo de nuevos fármacos resulten exitosos es imprescindible un trabajo estrecho y de colaboración con las autoridades regulatorias. En los EEUU el equipo de desarrollo de fármacos está integrado por miembros de las disciplinas claves en el descubrimiento de una nueva molécula (como investigadores clínicos, especialistas en aspectos regulatorios, legales y de marketing, químicos y toxicólogos) como también por representantes de la Food and Drug Administration (FDA). Los nuevos sistemas de regulación promueven reuniones en distintas etapas del proceso; previo a la investigación propiamente tal (pre INV), al final de la fase II, y antes de las propuestas preliminares para la aplicación de la nueva molécula (pre APL). También se fomentan las discusiones informales vía fax o por teléfono cuando se requiera. A través de una interacción proactiva con la FDA la industria farmacéutica aumenta la probabilidad de obtener buenos resultados durante el programa de desarrollo de nuevos fármacos.*

### *Les relations avec la FDA au cours du développement d'un médicament*

*Le succès des programmes de développement des médicaments est essentiellement lié à une collaboration étroite avec les autorités de tutelle. Aux Etats-Unis, les équipes de développement regroupent non seulement des membres des disciplines clés de la découverte moléculaire, tels la recherche clinique, le bureau de régulation, le marketing, la chimie, la toxicologie et les affaires légales, mais aussi des membres de la FDA (Food and Drug Administration). Les nouveaux règlements sont favorables à des réunions aux stades de nouveau médicament réservé aux essais, de fin de phase II et de pré-AMM (Autorisation de Mise sur le Marché) d'une nouvelle molécule. Des contacts informels par télécopie ou téléphone chaque fois que le besoin s'en fait sentir sont également souhaitables. En travaillant en liaison active avec la FDA, l'industrie pharmaceutique augmente ses chances de succès dans le programme de développement moléculaire.*

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