

# How new drugs are approved in the US

In the US, drugs are regulated by the Food and Drug Administration (FDA [[www.fda.gov/](http://www.fda.gov/)]). The US drug approval process is considered to be one of the most stringent in the world. The reviewers are very thorough and often reanalyze the data to ensure that it supports the same conclusions reached by a sponsor.

The Federal *Food, Drug and Cosmetic Act* states that a new drug may not be introduced into interstate commerce unless the FDA has approved a [New Drug Application](#) (NDA) for it (21 U.S.C. 355). Every new drug must receive marketing approval from the FDA prior to commercialization. The NDA consists of all the information and data that have been collected on a drug during its development. The goals of the NDA are to permit the FDA reviewer to reach conclusions on the following three key areas:

1. Whether the drug is safe and effective in its proposed use, and whether the benefits outweigh the risks.
2. Whether the drug's proposed labelling (package insert) is appropriate, and what it should contain.
3. Whether the methods used in manufacturing the drug and the controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality and purity.<sup>1</sup>

The documentation that is submitted in the NDA should explain the whole process of drug development including all animal and human studies that have been performed; how the studies were designed and analyzed and the results thereof; the ingredients of the drug; how the drug is manufactured, processed and packaged; and its stability.

It is important to consider the views of the FDA and the goals of an NDA very early in the development of a new drug. For instance, clinical trials must support the claims made with regard to safety and effectiveness. As well, the proposed labelling must be supported by the data from the clinical trials. New claims that are not fully supported by the data package are not likely to be approved. As equally important as the clinical data are the chemistry, manufacturing and controls. Regardless of its safety and efficacy, a new drug may not receive approval if the manufacturing and controls processes cannot ensure consistent quality across numerous batches.

## Priority vs. standard NDA

When an NDA is submitted for review, it is designated as "standard" or "priority." This designation determines whether or not it will be subject to an expedited review. An application is eligible for priority review if the drug provides a significant improvement compared to the current marketed drugs in terms of the treatment, diagnosis or prevention of a disease.

## Main parts of a submission

There can be up to 15 different sections in an NDA:

1. index
2. summary
3. chemistry, manufacturing and controls
4. samples, methods validation package and labelling
5. non-clinical pharmacology and toxicology
6. human pharmacokinetics and bioavailability
7. microbiology (for anti-microbial drugs only)

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<sup>1</sup> US Food and Drug Administration, US Department of Health & Human Services. (2010, February 19). *New Drug Application (NDA)*. Retrieved February 26, 2010, from <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm>

8. clinical data—including controlled clinical trials, uncontrolled clinical studies and other studies
9. safety update report
10. statistics
11. case report tabulations
12. case report forms
13. patent information
14. patent certification
15. other information

### FDA review process

The FDA review team consists of a project manager, a medical officer, a chemist, a microbiologist, a statistician, a pharmacologist, an establishment or facility reviewer, and support personnel.

The goals of the review are to determine if the results of well-controlled studies provide substantial evidence of effectiveness, and if the results show the product is safe under the conditions of use in the proposed labelling.

The NDA review process consists of five phases:

1. filing determination and review planning
2. review
3. advisory committee preparation and conduct (where applicable)
4. action
5. post-action<sup>2</sup>

### Filing determination and review planning (days 0 to 74)

The primary goals of the filing determination and review planning process are to determine whether the submitted application meets the regulatory requirements for filing, to define the scope of review activity needed, and to identify major elements of the application that may pose concerns during the review.

The outcome of this stage is either acceptance of filing, or a refusal to file if issues that are identified cannot be resolved with the sponsor.

Typically by day 45, the decision on accepting a file will have been made. By day 45, the FDA attempts to have conducted an internal planning meeting for the review. However, the decision on the application is not required to be sent until day 60. By day 74, the FDA aims to communicate filing review issues to the sponsor.

### Review

The FDA review process consists of two reviews. In the primary review, reviewers attempt to confirm and validate the sponsor's conclusion that a drug is safe and effective for its proposed use. The review can often involve a reanalysis of data or additional analyses presented by the sponsor. For example, certain patients that a sponsor may have included as "evaluable" may not be considered evaluable by the FDA reviewer, so additional statistical analyses may be performed on different sets or subsets of patients. The primary reviewer summarizes his opinions, conclusions and recommendations in a written review document. A primary review is only considered final after it has been reviewed and signed by a secondary reviewer.

A secondary review is also conducted in which the secondary reviewer summarizes the primary review and writes his own recommendations. The written opinion by the secondary reviewer is optional for biologic drugs unless the secondary reviewer disagrees with the opinions of the primary reviewer.

A sponsor may receive questions and requests for additional clarifying information during this review process. The completion of the primary review is expected by the end of the eighth month after submission.

During the review, the manufacturing sites are inspected to ensure they can produce the product in a high-quality manner and according to the specifications submitted. In addition, clinical trial sites may also be inspected to verify the accuracy of the data within the clinical portion of the file.

Throughout the review, the FDA reviewers communicate with sponsors to clarify information whenever necessary. Towards the end of the review, the FDA starts to discuss the product's final labelling. This includes indications and contraindications, dosing information, directions for use, and safety information. All aspects of the labelling must be supported by data in the NDA.

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<sup>2</sup> US Food and Drug Administration, US Department of Health & Human Services. (2009, May 23). *Good Review Practices (GRPs)*. Retrieved February 26, 2010, from <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm118777.htm>

## Advisory committee meeting

The review division and office director may decide to convene an advisory committee meeting to seek the advice of external experts. Advisory committee meetings are typically required in the following situations:

1. The review concerns new molecular entities, especially if a product is the first member of a new drug class.
2. The clinical study design uses novel clinical or surrogate endpoints.
3. The application raises significant issues about the safety or effectiveness of the drug.
4. The application raises significant public health questions on the role of the drug or biologic in the diagnosis, cure, mitigation, treatment or prevention of disease.<sup>3</sup>

When all the technical reviews are complete (i.e., pharmacology, toxicology, medical, biopharmaceutical and microbiological), a written evaluation is prepared to summarize the conclusions and recommendations. The director of the division or the office director then evaluates the reviews and recommendations and decides upon a course of action. This course of action is presented in a *Complete Response Letter* or *Approval Letter*.

## Action phase

The FDA summarizes all review activity and a preliminary decision is made on the regulatory action. Consideration is given to risk management, major labelling issues and post-marketing commitments.

During this phase, the determinations from the review help form the basis for discussion on the labelling of products that are expected to be approved. The labelling discussions are typically expected to occur about three weeks prior to division sign-off. During this time, if necessary, negotiation of post-marketing commitments and negotiation of the risk management program take place. The action letter (i.e., *Approval* or *Complete Response*) is then drafted and internally reviewed prior to sign-off. The final action is sent to the sponsor, ideally by the PDUFA (*Prescription Drug User Fee Act*) date. The PDUFA date is the FDA's target time to complete its review and provide a decision on the application to the sponsor (see Exhibit 1).

## Post-action phase

The goal is to learn from the review process and identify what was successful and what can be improved upon. This phase may involve meetings with the sponsor to clarify deficiencies and what is expected in a response, if the final decision was not an approval letter.

## Potential outcomes

As noted above, the outcome of the review of an NDA can be either an *Approval Letter* or a *Complete Response Letter*.

With an *Approval Letter*, the sponsor receives authorization from the FDA to commercialize a drug with the approved labelling.

The *Complete Response Letter* indicates that the review is complete and the application cannot be approved in its current form. It provides information to the sponsor on changes that must be made before an application can be approved, and lists all the deficiencies identified by the FDA. The deficiencies may be major (e.g., additional clinical trials are required) or minor (e.g., labelling changes are required). Where possible, the letter may also outline actions the sponsor may take to prepare the application for approval.

Following the receipt of a *Complete Response Letter*, the sponsor may elect to prepare a response, withdraw the submission from further review, or request an opportunity for a hearing. If a response is submitted, it is categorized as either class 1 or class 2, depending on the data submitted.

**Class 1 resubmission:** A class 1 resubmission starts a new two-month review cycle. The following items are classified as class 1:

- final printed labelling
- draft labelling
- safety updates in the same format (including tabulations) as the original safety submissions, with new data and changes highlighted
- stability updates to support provisional or final dating periods
- commitments to perform phase IV studies including proposals for such studies
- assay validation data

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<sup>3</sup> US Food and Drug Administration, US Department of Health & Human Services. (2009, May 23). *Good Review Practices (GRPs)*. Retrieved February 26, 2010, from <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm118777.htm>

- final-release testing on the last one to two lots used to support approval
- a minor reanalysis of data previously submitted to the application
- other minor clarifying information<sup>4</sup>

**Class 2 resubmission:** A class 2 resubmission includes any other information not listed above. Any submission that warrants a re-inspection of facilities is classified as class 2.

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## Timelines for review

### Exhibit 1: FDA performance standards–PDUFA goals for fiscal years 2008-2012

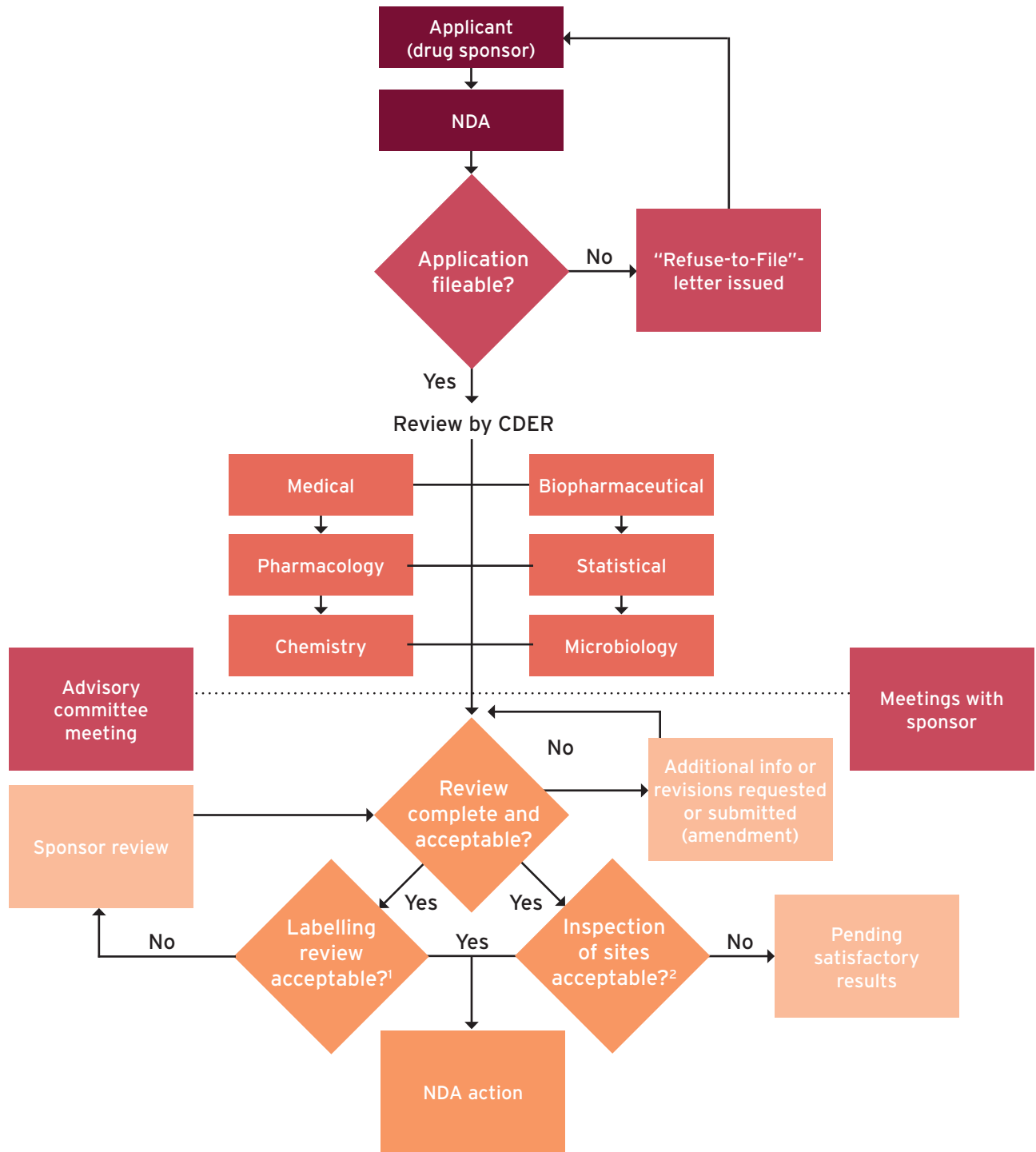
Submission type	Standard	Priority
Original applications	90% in 10 months	90% in 6 months
Class 1 resubmissions	90% in 2 months	90% in 2 months
Class 2 resubmissions	90% in 6 months	90% in 6 months

Source: US Food and Drug Administration,  
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119243.htm>

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<sup>4</sup> US Food and Drug Administration, US Department of Health & Human Services. (1998, April). *Guidance for Industry: Classifying Resubmissions in Response to Action Letters*. Retrieved March 2, 2010, from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079303.pdf>

Exhibit 2: New drug application review process



(1) Labelling in this context means official instructions for use

(2) Manufacturing sites and sites where significant clinical trials are performed

Source: US Food and Drug Administration