



Accelerating US Regulatory Approval for Drugs and Biologics that Treat Serious Diseases

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What you really need to know about FDA's Fast Track, Accelerated Approval, and Priority Review designations.

Executive Summary

The Food and Drug Administration (FDA) has created three mechanisms to speed the approval of drugs and biologics that effectively treat serious diseases, especially those that are the first of their kind or those that provide increased benefit over existing treatments. Fast Track, Accelerated Approval, Priority Review—their names imply speed of the highest order, and it's tempting to assume that acquiring any of these designations will speed your drug's approval and save you millions of dollars. That's certainly possible, but just like anything that sounds too good to be true, it's worth taking the time to understand the requirements and potential benefits of each, so you can make an informed decision about what's best for your drug development program.

Accelerated Development

An overview of the 3 types of accelerated development mechanisms is below in Table 1. The overlap in benefit and use in development or review is obvious. However, further analysis is provided below as to how to appropriately use the designations to best meet the needs of your development program.

Table 1. Comparison of Accelerated Development Mechanisms

Review Type	Accelerated Approval	Priority Review	Fast Track Designation
Authority	1992 Rule: 21 CFR 314 and 601 (In 1997, FDCA 506(b)).	1996 Agency Procedure: CDER MAPP 6020.3; and CBER SOPP 8405.	1997 Statute: FDCA 506(a).
Procedure	At time of clinical studies, Product Sponsor requests (during meetings). Division-specific decision. (resource availability dependent)	Upon receipt of application, clinical team leader of FDA review team makes recommendation. Division-specific decision.	Any time before marketing approval, Product Sponsor requests designation; FDA grants if criteria are met (within 60 days).
Criteria	Serious or life-threatening illness.	n.a.	Serious or life-threatening condition.
	Potential to address unmet medical need.	Major advance in treatment or treatment where no adequate therapy exists.	Potential to address unmet medical need.
Benefit During Development	Adjusted trial requirements	n.a.	More frequent FDA communication
Benefit During Review	n.a.	Expedited review (e.g., 4-6 months compared with 10-12 months)	Rolling review (submit sections of BLA/CTD as completed)
Post Approval Requirement	Studies to extend results from surrogate to clinical outcome.	n.a.	n.a.

Source: Modification of Table 1 from www.nationalaglawcenter.org/assets/crs/RS22814.pdf

Abbreviations: BLA = Biologics License Application; CTD = Common Technical Document; FDCA = Federal Food, Drug, and Cosmetic Act. n.a. = not applicable.

Fast Track Designation

FDA’s definition of Fast Track is “a process designed to facilitate the development and expedite the review of drugs to treat serious diseases and fill an unmet medical need.” This sounds great for anyone with faster drug approval on the brain, but in reality, Fast Track designation does very little to accelerate the approval process for your drug.

Let’s review the five benefits FDA lists for the Fast Track designation (Points 1

Do Your Homework

It’s worth taking the time to understand the requirements and potential benefits of each acceleration mechanism, so you can make an informed decision about what’s best for your product development program.

through 5 as bulleted on the FDA website <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm>):

1. More frequent meetings with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval.
2. More frequent written correspondence from FDA about such things as the design of the proposed clinical trials.
3. Eligibility for Accelerated Approval, i.e., approval based on a surrogate or substitute endpoint reasonably likely to predict clinical benefit.
4. Rolling Review, which means that a drug company can submit completed sections of its New Drug Application (NDA) for review by FDA, rather than waiting until every section of the application is completed before the entire application can be reviewed.
5. Dispute resolution if the drug company is not satisfied with an FDA decision not to grant Fast Track status.

However, the following should also be noted regarding Points 1 through 5.

1. Regular meetings are already allowed by FDA (pre-IND, EOP2, pre-NDA, etc). In addition, FDA is very willing to provide follow-up meetings and additional technical meetings for products.
2. FDA will provide you adequate correspondence to move quickly with your development program, especially if your product is for a life-threatening disease with no existing therapy.
3. Any drugs or biologics that meet the appropriate requirements (see below for more information) are eligible for Accelerated Approval, regardless of Fast Track designation.
4. Rolling Reviews have always been allowed for NDAs. Agreement must be confirmed by the reviewing Division. However, the Fast Track Designation does provide for rolling reviews of BLAs.
5. Dispute resolution is a standard FDA process already.

Fast Track Designation

In reality, Fast Track designation does very little to accelerate the approval process for your drug.

Accelerated Approval

For many drugs and biologics that treat serious and life-threatening diseases, showing actual improvement for patients, such as living longer or feeling better, can take a very long time. Because of this, FDA created the Accelerated Approval regulation, which allows earlier approval of drugs and biologics based on a surrogate clinical endpoint.

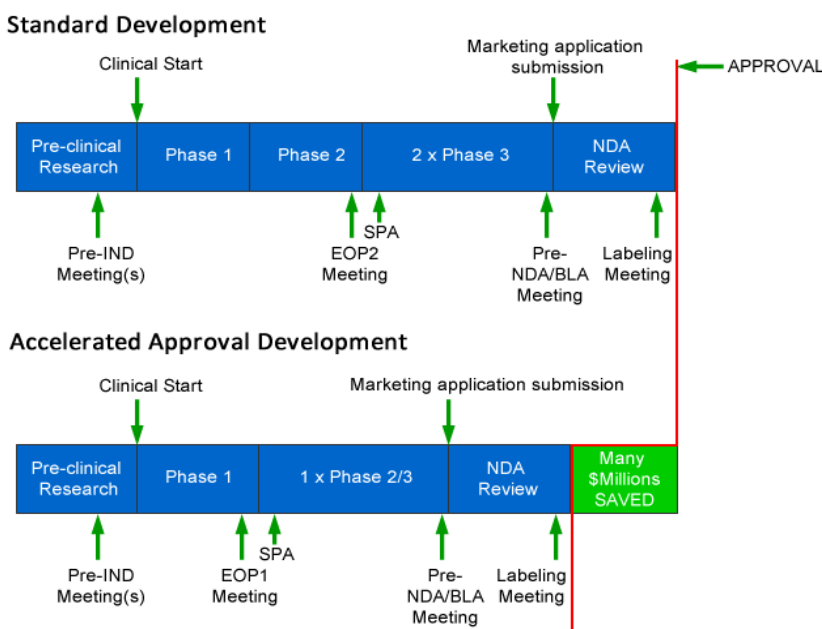
Tumor progression and time to tumor shrinkage are examples of surrogate endpoints for oncology drugs. Using surrogate endpoints instead of clinical outcome data can significantly reduce the time required to receive marketing approval for your compound.

It is important to note that Accelerated Approval does not formally change your marketing application review time. Instead, it shortens the actual research time prior to approval (see Figure 1 below). For example, instead of two adequate and well-controlled studies, if you're granted Accelerated Approval, you might only have to conduct one of these studies prior to FDA approval. It's also important to note that if Accelerated Approval is granted, FDA requires a post-marketing commitment to study actual clinical outcomes.

Important Considerations

Note that Accelerated Approval does not formally change your marketing application review time. Instead, it shortens the actual research time prior to approval. Also, if Accelerated Approval is granted, FDA requires a post-marketing commitment to studying actual clinical outcomes. And, FDA can revoke marketing approval if the post-marketing study(ies) fail to demonstrate efficacy/safety according to those actual clinical outcomes, as was recently done with Genentech's Avastin for its breast cancer indication.

Figure 1. Comparison of Standard and Accelerated Approval Development



Eligibility for Accelerated Approval

1. Applicable to drugs (21 CFR 314 Subpart H) or biologics (21 CFR 601 Subpart E)
2. Only serious or life-threatening diseases and conditions
3. Meaningful therapeutic benefit over existing treatments

Logistics, Restrictions, and Withdrawal of Accelerated Approval

There is no formal submission process to apply for Accelerated Approval. If you're interested in Accelerated Approval, discuss with your reviewing Division at FDA early in your development process.

Accelerated Approval can be granted with restrictions, such as:

- › FDA determination that treatment can be used safely only if prescribed by specially trained physicians
- › Distribution may be conditional on performance of specified medical procedures

FDA can withdraw marketing approval if any of the following apply:

- › Post-marketing studies fail to show a clinical benefit
- › Product Sponsor fails to conduct post-marketing studies

Post-Marketing Commitment Requirements

FDA requires a post-marketing commitment for Accelerated Approval of NDAs (21 CFR 314 Subpart H) or BLAs (21 CFR 601 Subpart E). In the post-marketing phase, Product Sponsors are required to design and conduct adequate and well-controlled confirmatory trials that are intended to validate the results obtained with the surrogate clinical endpoint, i.e., demonstration of true clinical benefit.

These confirmatory trials may be ongoing at the time of approval. In order to ensure compliance, FDA has created a Post-marketing Study Commitments website: <http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>.

Surrogate Endpoints

Using surrogate endpoints instead of clinical benefit endpoints can significantly reduce the time required to receive marketing approval for your compound. Tumor progression and time to tumor shrinkage are examples of surrogate endpoints for oncology drugs.

Priority Review

As part of the Prescription Drug User Fee Act (PDUFA) enacted in 1992, FDA created two classifications of review times for marketing applications: Standard Review and Priority Review.

Standard Review applies to drugs or biologics that offer only minor improvements over current marketed products. *FDA has committed to review and act on 90% of NDAs/BLAs with a Standard Review designation within 10 months of receiving a complete submission.*

Priority Review classification is a possibility for drugs or biologics “that offer major advances in treatment, or provide a treatment where no adequate therapy exists.” Note that Priority Review may be granted for drugs and biologics that treat serious or non-serious diseases. However, Product Sponsors should be aware that CBER does consider disease seriousness in making this determination. CBER requires that the product provide significant improvement in the safety or effectiveness of the treatment, diagnosis, or prevention of a serious or life-threatening disease. By contrast, CDER requires only that the product provide significant improvement compared with marketed products in the treatment, diagnosis, or prevention of a disease. *FDA has committed to review and act on 90% of NDAs/BLAs with a Priority Review designation within 6 months of receiving a complete submission.*

Criteria for Demonstrating Significant Advances in Treatment for Priority Review Designation

- › Increased effectiveness in treatment, diagnosis, or prevention
- › Elimination or substantial reduction of treatment-limiting Adverse Drug Reactions
- › Enhanced patient compliance
- › Evidence of safety and effectiveness in a new subpopulation

Priority Review Timelines

FDA has committed to reviewing and acting on:

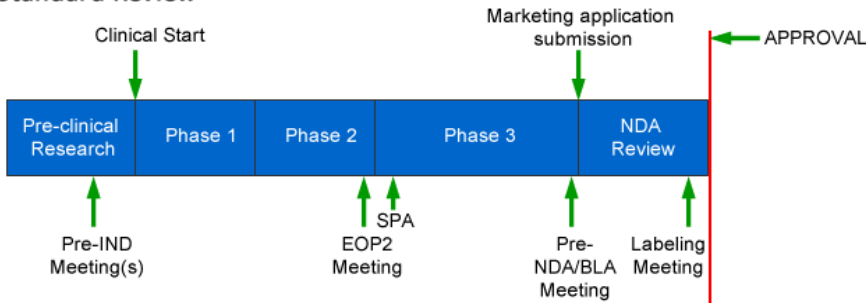
- 1) 90% of NDAs/BLAs with a Standard Review designation within 10 months of receiving a complete submission.
- 2) 90% of NDAs/BLAs with a Priority Review designation within 6 months of receiving a complete submission.

Figure 2. Comparison of Standard and Priority Review

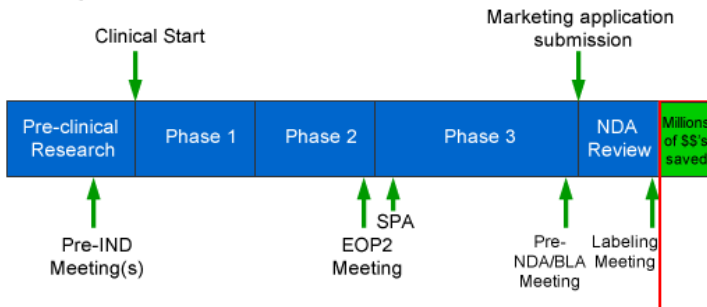
Obtaining Priority Review Status

The Product Sponsor must request Priority Review classification, and the designation is given only after the application is filed. In our experience, the possibility of receiving Priority Review should be discussed at the pre-NDA/BLA

Standard Review



Priority Review



meeting. The FDA's filing meeting should occur by Day 30 if your application is likely to qualify for the standard Day 45 meeting for a normal review. The review Division determines review classification within 14 days of submission, and the Division will inform applicant in writing by Day 60 of review. It's important to note that FDA's review classification decision is resource dependent, meaning that even if your drug or biologic qualifies, Priority Review may not be granted if your division at FDA lacks the resources to review your application within 6 months.

Review Classification Decision

Note that FDA's review classification decision is resource dependent, meaning that even if your drug or biologic qualifies, Priority Review may not be granted if your division at FDA lacks the resources to review your application within 6 months.

Conclusion

Understanding the differences between Fast Track, Accelerated Approval, and Priority Review designations is imperative if you're to make an informed decision about the best way to speed the approval of your drug or biologic. If you have additional questions about any of these designations/classifications or about which one might be right for your product program, please see the references below or contact us at info@rhoworld.com.

References

<http://www.nationalaglawcenter.org/assets/crs/RS22814.pdf>

<http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm>

Author Bio



Dr. David Shoemaker has more than 25 years of experience in research and pharmaceutical development. He has served as a Program Leader or Advisor for multi-disciplinary program teams and has been involved with products at all stages of the development process. Dr. Shoemaker has managed the regulatory strategy for programs involving multiple therapeutic areas, including hematology, oncology, cardiology, pulmonology, infectious diseases, genetic enzyme deficiencies, antitoxins, and anti-bioterrorism agents. He has extensive experience in the preparation and filing of all types of regulatory submissions, including primary responsibility for four BLAs and three NDAs. He has managed or contributed to more than a dozen NDAs, BLAs, and MAAs. Dr. Shoemaker has moderated dozens of regulatory authority meetings for all stages of development. His primary areas of expertise include clinical study design and regulatory strategy for development of novel drug and biological products.