ACCELERATING REGULATORY PRODUCT DEVELOPMENT AND APPROVAL FOR DRUGS AND BIOLOGICS IN THE US

What you really need to know about FDA's Accelerated Approval, Breakthrough Therapy, Regenerative Medicine Advanced Therapy, Fast Track, and Priority Review programs

Updated May 2019: Discussion of Regenerative Medicine Advanced Therapy designation, other opportunities for accelerating regulatory approval, and general updates to the previous version released in 2016.

By David Shoemaker, Senior Vice President Research and Development, Genna L A Kingon, PhD, RAC, Research Scientist, Kathleen Candando, PhD, Research Scientist, Kevin Barber, MS, PhD, RAC, PMP, Vice President, Regulatory Strategy and Submissions

The Food and Drug Administration (FDA) has created five mechanisms to presumably 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. Accelerated Approval (AA), Breakthrough Therapy Designation (BTD), Regenerative Medicine Advanced Therapy (RMAT) Designation, Fast Track Designation (FTD), and Priority Review (PR) – their names imply speed of the highest order, and it's tempting to assume that acquiring any of these designations will speed your product'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 possible or what's best for your product development program.

An overview of the five types of FDA programs is shown below in Table 1 and is reviewed in the Guidance published in 2014 (Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics; expiration date 05/31/2020)[1] and in a second Guidance published in 2019 (Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions)[2]. The overlap in benefit and use in development or application review is obvious. However, further analysis is provided below as to how to appropriately use these five programs to maximize speed of approval depending on the product type.

Table 1. Comparison of Accelerated Approval Mechanisms

Program Type	Accelerated Approval (AA)	Breakthrough Therapy Designation (BTD)	Regenerative Medicine Advanced Therapy (RMAT) Designation	Fast Track Designation (FTD)	Priority Review (PR)
Authority	1992 *Rule:* 21 CFR 314 and 601. (In 1997, FD&C Act 506(c))	2009 Statute: FD&C Act 506(a)	2016 Statute: FD&C Act 506(g)	1997 Statute: FD&C Act 506(b)	1996 Agency Procedure: CDER MAPP 6020.3; and CBER SOPP 8405
Procedure	During early development meetings with agency, Sponsor requests	Any time before marketing approval, Sponsor requests designation; FDA grants if criteria are met (within 60 days)	Any time before marketing approval, Sponsor requests designation; FDA grants if criteria are met (within 60 days)	Any time before marketing approval, Sponsor requests designation; FDA grants if criteria are met (within 60 days)	Sponsor requests prior to marketing application submission. Clinical team leader of FDA review team, upon receipt of application, makes recommendation
Disease Criteria	Serious or life-threatening disease or condition	Serious or life-threatening disease or condition	Serious or life-threatening disease or condition	Serious or life-threatening disease or condition	n.a.
Qualifying Criteria	Potential to address unmet medical need	Preliminary evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints	Product is a regenerative medicine therapy and preliminary clinical evidence indicates that the product has the potential to address unmet medical needs	Potential to address unmet medical need	Treatment where no adequate therapy exists or major advance in treatment.
Benefit During Development	Adjusted trial requirements	- Guidance on efficient product development - Senior FDA Official Commitment	- Same as BTD benefits - Potential ways to support AA and satisfy post-approval requirements	Frequent FDA communication	n.a.
Benefit During Review	n.a.	Rolling review (Submit sections of NDA or BLA as they are completed)**	Rolling review (Submit sections of BLA as they are completed)	Rolling review (Submit sections of NDA or BLA as they are completed)	Expedited review (e.g., 4-6 months compared to 10-12 months)
Post Approval Requirement	Studies to extend results from surrogate to clinical outcome	n.a.	n.a.	n.a.	n.a.

Abbreviations: AA = Accelerated Approval; BLA = Biologics License Application; BTD = Breakthrough Therapy Designation; CBER = Center for Biologics Evaluation and Research; CDER = Center for Drug Evaluation and Research; CFR = Code of Federal Regulations; FDA = Food and Drug Administration; FD&C Act = Federal Food, Drug, and Cosmetic Act; FTD = Fast Track Designation; MAPP = Manual of Policies and Procedures; n.a. = not applicable; NDA = New Drug Application; PR = Priority Review; RMAT = Regenerative Medicine Advanced Therapy; SOPP = Standard Operating Procedures and Polices.

* Post-approval requirements due to type of designation. It is common for FDA to detail additional post-approval commitments and requirements as part of product approval.

** Although FDA agreement to rolling submission can be obtained via these pathways, FDA review of the portions of the application at the time of submission is not guaranteed and is often dependent on FDA resources, other commitments, etc.

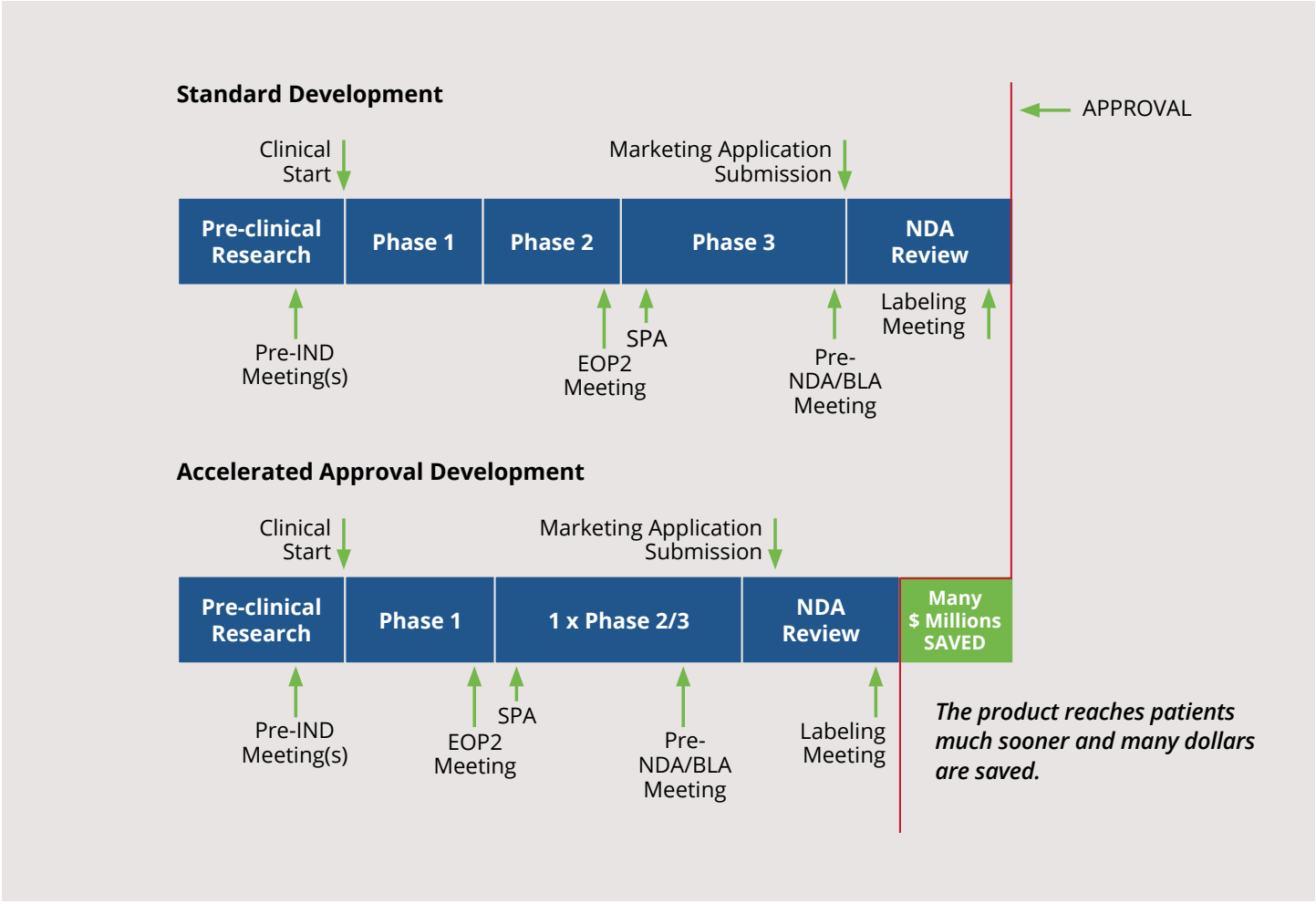
ACCELERATED APPROVAL (AA)

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 AA regulation, which allows earlier approval of drugs and biologics based on a surrogate clinical endpoint.

Examples of surrogate endpoints are viral load for HIV progression, low-density lipoprotein cholesterol levels for occurrence of myocardial infarctions, systolic blood pressure for occurrence of strokes, and forced expiratory volume in one second for respiratory diseases such as asthma, cystic fibrosis, or chronic obstructive pulmonary disease. Recently, FDA has compiled a table of surrogate endpoints[3], organized by adult and pediatric disease or use, that were the basis of drug approval or licensure for consideration to product developers. 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 AA does not formally change your marketing application review time. Instead, it shortens the actual development time prior to approval (see Figure 1 below). For example, instead of two adequate and well-controlled studies, if you're granted AA, you might only have to conduct one of these studies prior to FDA approval. Consequently, this program is far and away the most valuable alternative pathway to the standard development of drugs and biologics. It's also important to note that if AA is granted, FDA requires a post-marketing commitment to demonstrate actual improved clinical outcomes in a controlled clinical study.

Figure 1. Comparison of Standard and Accelerated Approval Development



Abbreviations: BLA = Biologics License Application; EOP1 = End-of-Phase 1; EOP2 = End-of-Phase 2; IND = Investigational New Drug Application; NDA = New Drug Application; SPA = special protocol assessment

Eligibility for Accelerated Approval

1. Applicable to drugs (21 Code of Federal Regulations [CFR] 314 Subpart H) or biologics (21 CFR 601 Subpart E)
2. Only serious and 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 AA. If you're interested in AA, begin the discussion with your reviewing division at FDA early in your development process (Pre-Investigational New Drug Application [IND] Meeting) and obtain FDA commitment at the End-of-Phase 1 Meeting.

Accelerated Approval can be granted with restrictions, such as:

- FDA determination that treatment can only be used safely 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
- Use after approval indicates that restrictions are inadequate
- Product sponsor does not adhere to restrictions required by FDA

Post-Marketing Commitment Requirements

FDA requires a post-marketing studies of product sponsors completing AA of New Drug Applications (NDAs; 21 CFR 314 Subpart H) or Biologics License Applications (BLAs; 21 CFR 601 Subpart E). In the post marketing phase, 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 Requirements and Commitments website[4].

BREAKTHROUGH THERAPY DESIGNATION (BTD)

The advent of BTD was seen by many as a replacement for FTD and indeed this has seemed to be the case. There are considerable advantages to obtaining the BTD rather than the FTD, most notably the commitment from senior management at FDA to champion these products through the approval process. There is the requirement for preliminary data to demonstrate safety and efficacy, which although a higher bar than that to obtain FTD, makes practical sense so as not to waste FDA resources reviewing hypothetically advantageous products.

The BTD program has been in existence since enactment of the FDA Safety and Innovation Act of 2012 and is perhaps showing signs of maturation. The number of BTDs granted by both the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) in 2017 (59) and 2018 (66) were relatively constant[5,6]. However, the overall approval rating for BTD applications overall still hovers at approximately 40% indicating that industry still needs counselling from FDA on what constitutes a viable application.

Once granted, the BTD affords the company opportunities for increased support from FDA leveraging the agency's experience with novel study designs to attempt to accelerate the development timeline. A cross-disciplinary project lead is assigned by FDA to the review team who facilitates frequent interactions with the necessary resources at FDA. Unlike portions of marketing applications submitted for FTD products via rolling submissions that often languish at the FDA until the complete marketing application is submitted due to lack of FDA resources, the rolling submissions for products granted BTD may actually be reviewed upon receipt by the agency potentially accelerating review times significantly. This is a direct reflection of the increased awareness of the agency of the importance of products obtaining the BTD.

REGENERATIVE MEDICINE ADVANCED THERAPY (RMAT) DESIGNATION

With the intent to support acceleration of product development in bringing new innovations and advances to patients at a more rapid pace, the 21st Century Cures Act was signed into law in December 2016. One of the components of the 21st Century Cures Act included establishment of the RMAT designation pathway for eligible biologics products. Regenerative medicine therapies are defined in section 506(g)(8) of the Federal Food, Drug and Cosmetic (FD&C) Act as cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products with a few exceptions[7]. The RMAT designation program is similar to BTD and has the same benefits of the BTD program (see above), but is specific for regenerative medicine therapies. The RMAT designation was not created to replace BTD (in fact, regenerative medicine products can qualify for both BTD and RMAT designation), but rather is an alternative and perhaps less burdensome pathway for eligible products as discussed below.

Products eligible for RMAT designation may include human gene therapies that lead to a sustained or durable effect on cells or tissues. The question of sustained or durable effect is something less defined and may challenge the developer in determining whether the preliminary clinical data is substantial enough to support the RMAT designation. It is essential, as with all clinical programs, to carefully consider the study design, endpoints, and frequency of data collection that are planned to contribute to the RMAT designation to ensure demonstration of sustained effect. RMAT designation is less challenging to acquire than the BTD given that RMAT designation requires preliminary clinical evidence, but does not necessitate that the evidence demonstrates that the therapy may provide substantial improvement in clinically meaningful endpoints over other available therapies. However, preliminary clinical evidence required for RMAT designation must indicate that the product has potential to address unmet medical

needs, and, in addition, the product must be a regenerative medicine therapy per the FDA definition. Although a single biologic product can be eligible for and granted both BTD and RMAT designation, RMAT designation is predicted to be the best return on investment given the same benefits and no requirement to demonstrate that the product may be able to provide substantial improvement over other available therapies.

Like BTD, RMAT designated products may be eligible for AA; however, AA should be planned for and discussed with FDA well in advance of applying for these designations. An additional eligibility option exists for products with RMAT designation for which AA is also desired. As part of the 21st Century Cures Act, AA eligibility for RMATs may be based on either (1) surrogate or intermediate endpoints as previously agreed-upon with the Agency that are reasonably likely to predict long-term clinical benefit or (2) data obtained from a meaningful number of clinical study sites. This second item is a newer concept and specific to RMAT designated products. The Agency explains that determination of whether the number of investigational sites, even if limited, is "meaningful" is subject to whether the effectiveness observed may be biased by a single site or investigator. Post approval requirements may include the product sponsor providing additional evidence of effectiveness via expansion to additional clinical sites. Also, RMAT designated products that receive AA may have the opportunity to complete post-approval requirements via alternatives to clinical studies, including sources of real world evidence and post-approval monitoring of patients treated with the therapy prior to its approval, for example. See Guidance for Industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions (2019)[2] and section 506(g)(7) of the FD&C Act for additional information.

FAST TRACK DESIGNATION (FTD)

FDA's definition of FTD 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 to anyone who desires a faster drug approval, but in reality, FTD does very little to accelerate the development and speed of the approval process for your drug.

Let's review the five benefits FDA lists for the FTD (points 1 through 4 as bulleted on FDA's Fast Track website[8].

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 and use of biomarkers
3. Eligibility for AA, 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 NDA for review by FDA, rather than waiting until every section of the application is completed before the entire application can be reviewed.

However, the following should also be noted regarding points 1 through 4:

1. Regular meetings are already allowed by FDA (pre-IND, End-of-Phase 2, 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.
3. Any drugs or biologics that meet the appropriate requirements are eligible for AA, regardless of FTD.
4. Rolling Submissions have always been allowed for NDAs (as well as for BLAs since 1992). Agreement must be confirmed by the reviewing division. As stated above submission of parts of the marketing application in a rolling fashion is no guarantee the agency will have resources to initiate the review process.

Hence, it is hard to discern the value in obtaining a FTD.

PRIORITY REVIEW (PR)

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

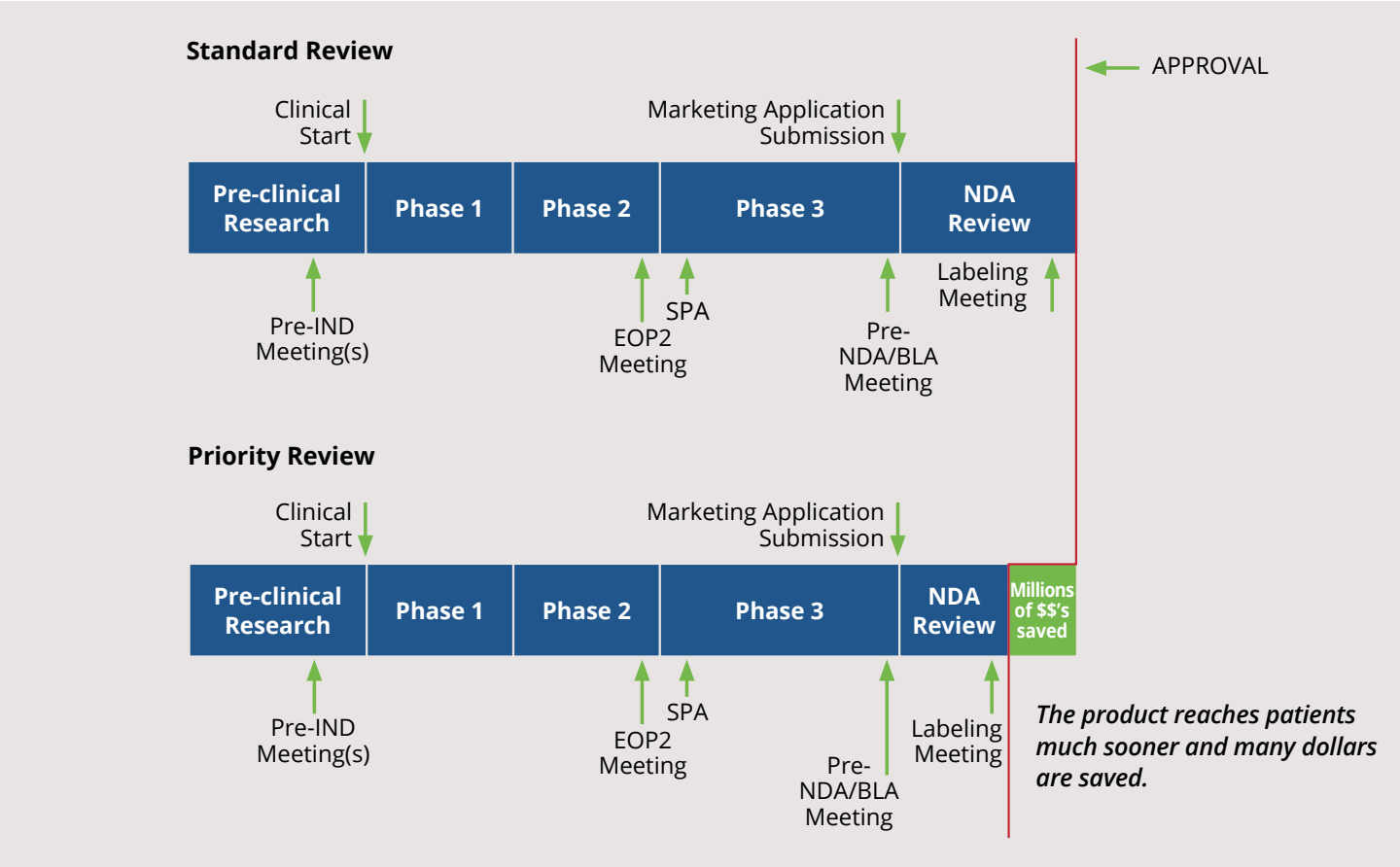
Standard Review applies to drugs or biologics that offer only minor improvements over current marketed products. ***FDA has committed to review and act on 90% of NDAs/BLAs with a Standard Review designation within 12 months of receiving a complete submission.***

Priority Review classification is a possibility for drugs or biologics that "that offer major advances in treatment, or provide a treatment where no adequate therapy exists." Note that the seriousness of the disease is not an eligibility factor for PR – drugs and biologics that treat serious or non-serious diseases are eligible. Product sponsors should be aware that the definitions required by CBER and CDER to grant a priority review are slightly different. CDER is less stringent in its requirement for granting PR classification requiring only that the product provide significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease. CBER, on the other hand, 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. ***FDA has committed to review and act on 90% of NDAs/BLAs with a PR designation within eight months of receiving a complete submission.***

Criteria for Demonstrating Significant Advances in Treatment for PR 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

Figure 2. Comparison of Standard and Priority Review



Abbreviations: BLA = Biologics License Application; EOP2 = End-of-Phase 2; IND = Investigational New Drug Application; NDA = New Drug Application; SPA = special protocol assessment

Obtaining Priority Review Status

The product sponsor must request PR classification, and the designation is given only after the application is filed. In our experience, the possibility of receiving PR should be discussed no later than the pre-BLA/NDA meeting. The FDA's filing meeting should occur by Day 30 if your application is likely to qualify for priority review as compared to 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 the applicant in writing by Day 60 of review. It's important to note that FDA's review classification decision is **resource dependent,** which means that even though your drug or biologic qualifies for PR, it may not be granted if your division at FDA does not have the resources to review your application within eight months.

As an alternative to qualifying and gaining PR for a current marketing application, three FDA programs offer PR vouchers (PRVs): Tropical Disease (FDA Amendments Act, 2007), Rare Pediatric Disease (FDA Safety and Innovation Act, 2012), and Material Threat Medical Countermeasure PRV (21st Century Cures Act) programs. As a way to incentivize the development of products in these challenging areas, FDA created these programs in which the sponsor who receives an approval for a drug or biologic in one of these three areas may qualify for a voucher. Once a sponsor obtains a PRV, the voucher can be redeemed by the recipient on any other application that does not already qualify for priority review or the voucher could be sold to another company. The agency is not enamored with these programs inasmuch as the companies purchasing these vouchers may apply them to products with voluminous marketing applications restricting the reviewers' time on what may not even be a product with significant therapeutic applications. Nonetheless, Congress continues to enact these provisions.

OTHER FDA OPPORTUNITIES FOR ACCELERATING PRODUCT DEVELOPMENT AND REGULATORY APPROVAL

Two additional avenues in which FDA is working to encourage the development of products for special populations, the Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD)[9] and the Qualified Infectious Disease Product (QIDP) designation[10], offer an acceleration in product development and regulatory approval for products meeting the criteria. LPAD (21st Century

Cures Act), provides more opportunity to streamline development of qualifying products for unmet medical needs (e.g., smaller, shorter, or potentially fewer clinical studies required); however, specific labeling requirements are imposed. An initial application that has QIDP designation (FDA Safety and Innovation Act in 2012) automatically qualifies for priority review. The main incentive of QIDP designation is a 5-year exclusivity extension following product approval which is additive with the 5-year exclusivity conferred on a new molecular entity or the 7-year exclusivity conferred on an orphan product.

CONCLUSION

Understanding the value proposition differences among Accelerated Approval, Breakthrough Therapy Designation, Regenerative Medicines Advanced Therapy Designation, Fast Track Designation, and Priority Review is imperative if you are to make an informed decision about the best way to speed development and 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.**

DR. DAVID SHOEMAKER, *Senior Vice President Research and Development, 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 two 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.*

GENNA L A KINGON, PHD, RAC, *Research Scientist, has led and contributed to the regulatory strategy and submission management from pre-IND to post-approval. With over a decade of experience in scientific writing and editing clinical and non-clinical documentation, which includes several publications in peer-reviewed scientific journals, she also serves as lead regulatory author on multiple programs for submissions to FDA and to various international regulatory authorities. Her regulatory submission management, authorship, and research expertise encompasses a broad range of therapeutic areas, including acute and chronic pain, dermatology, inner ear disorders, gastrointestinal disorders, ADHD, oncology, immunology, musculoskeletal disorders, and drug addiction.*

KATHLEEN CANDANDO, PHD, *Research Scientist, authors regulatory submission documents and contributes to regulatory strategy and product development services. Dr. Candando has more than 10 years of experience in writing, reviewing, and editing scientific documents and frequently leads authorship of regulatory submissions including US IND and NDA modules, clinical study reports, clinical study protocols, and orphan drug designation applications. Dr. Candando's therapeutic experience is broad and includes multiple areas of allergy and immunology, infectious diseases, oncology, and neurology.*

KEVIN BARBER, PHD, RAC, PMP, VP, *Regulatory Strategy & Submissions has more than 20 years of experience in regulatory affairs and product development, working for both sponsor companies and CROs, across all stages of development from pre-clinical through product launch and post-approval life cycle management. He has led the preparation and execution of integrated regulatory strategy and clinical development plans for drug, biologic, and medical device products in therapeutic areas including dermatology, nephrology, urology, women's health, CNS/neurology, cardiovascular diseases, virology, oncology, immunology, infectious diseases, blood products, and gene therapy. Dr. Barber has significant experience preparing and filing regulatory submissions, including more than 40 US INDs and more than 35 marketing applications in the US, Canada, Europe, Latin America, Australia, and New Zealand. He also has experience with medical device and in vitro diagnostic development programs and regulatory submissions including pre-IDE meetings, IDEs, 510(k)s, and PMAs.*

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