Parexel Insights Report:

What emerging trends in the FDA's most coveted designations might tell us

parexel BIOTECH

> “One of the quotes I heard from an investor in New York last month was that positive [clinical] data is no longer enough [for biotech’s]. You must have exceptional data these days to go with the initial public offering, secondary offering, or even to keep your stock price from falling.”

BIO’s David Thomas at 2023 BIO-Europe, November 6, 2023

High-order designations granted by the U.S. Food and Drug Administration (FDA) are intended to provide expedited development and review pathways for products that address unmet medical needs or have the potential to advance patient care significantly. High-order FDA designations may offer insights into larger trends in the overall R&D pipeline since the Breakthrough Therapy designation (BTD) and The Regenerative Medicine Advanced Therapy (RMAT) designation involve a formal FDA assessment/validation of emerging therapies’ promise and have implications for FDA resources when granted.

Given this, marked shifts in pursuing and granting such designations, like those we see post-pandemic, raise fascinating questions. For example, what factors are driving sharp downturns in the Center for Drug Evaluation and Research (CDER) breakthrough designations when it has become more critical than ever for companies to signal to investors that their emerging therapies are truly exceptional? And does the sharp post-pandemic upturn in high-order designations by the Center for Biologics Evaluation and Research (CBER) represent a shifting of enthusiasm or excitement in favor of more advanced therapies?

FDA high-order designations: A tale of two centers

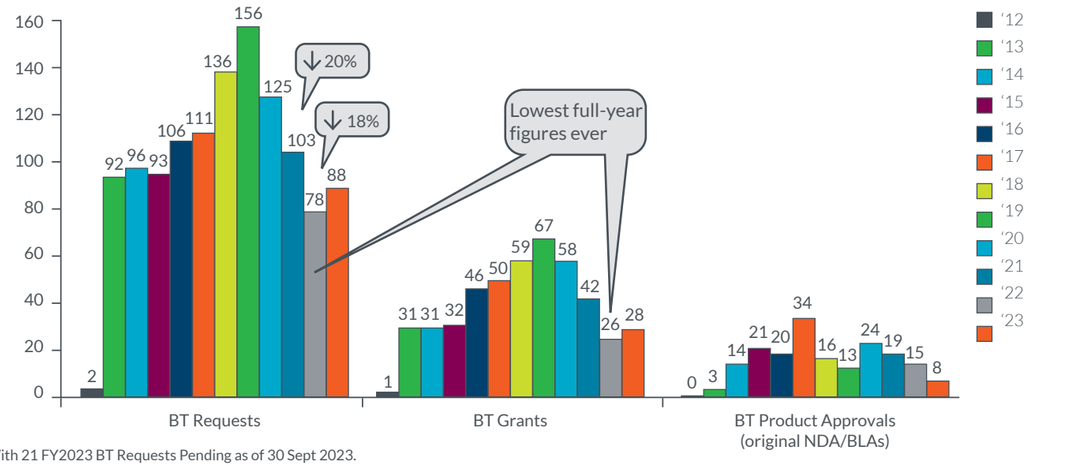
CDER's BTD program shrinks…or right-sizes

in terms of top-line (and available) metrics, CDER's breakthrough therapy program has shrunk rapidly since its peak of activity in 2019. From its founding in late 2012 through 2019, breakthrough-related activity (industry requests and FDA grants) saw virtually immediate acceptance and consecutive records almost every year of its existence.

The pandemic, however, brought an abrupt and sharp three-year decline that saw industry breakthrough requests to CDER plummet by a full 50%. When the industry submitted only 78 BTD requests in 2022 (after 156 in 2019), it was easily the lowest number for any single full year since the program began in 2012. And while there was a small 2023 bounce off the 2022 low, 2023's 88 requests were the second-fewest to CDER in any year.

Meanwhile, CDER's annual BTD grants dropped even further over this span, from a peak of 67 in 2019 to 26 in 2022. BTD grants dropped across virtually all of CDER's new drug review divisions: In fact, 11 of the divisions lacked a single BTD grant in 2022, up from five in 2021 and three in 2020, while another nine divisions had only a single designation each.

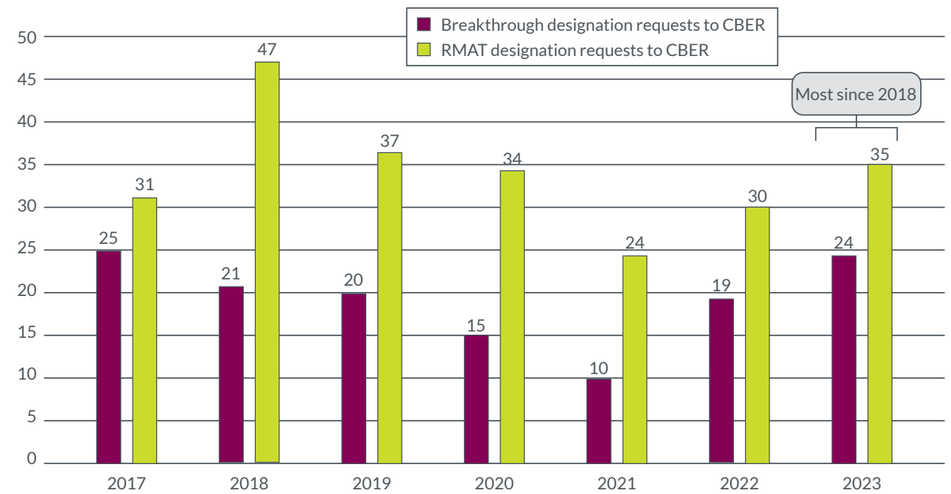
CDER BT submission/grant/approval trends, FY2012-FY2023



*With 21 FY2023 BT Requests Pending as of 30 Sept 2023.

Source: FDA

RMAT vs. Breakthrough Designation to Requests to CBER (FY2017-FY2023)



Source: FDA

Although shrinking BTD requests were the principal driver of the downturn overall, CDER grant rates declined over this span. Across CDER's five cancer review divisions--which tend to drive CDER's BTD-related activity—grant success rates dropped from 67% in 2020/2021 to 54% in 2022.

Meanwhile, CBER's BTD and RMAT Programs rebound from pandemic lows. Perhaps fueled in part by progress in and building excitement over the growing cell and gene therapy pipeline, the promise of mRNA therapeutics and vaccines, and the emergence of other advanced therapies, CBER's dual high-order expedited programs (BTD and RMAT) are on a strikingly different post-pandemic trajectory to CDER's for BTD:

- Industry requests for BTD status jumped from a record low of 10 in 2021 to 24 in 2023, almost matching the record 26 in 2014. Meanwhile, CBER BTD grants jumped from a recent low of 3 in 2020 to 8 in 2022 and could match 2017's record of 9 designations in 2023 (with 2 RMAT requests pending, CBER had granted 7 in 2023 set in 2017).
- Meanwhile, industry RMAT requests for cell and gene therapies continued to bounce off the pandemic low of 24 in 2021 to 35 in 2023. After reaching a record 47 in 2018, RMAT requests declined for three consecutive years before beginning to rebound in 2022.

With the re-ascendency of CBER's dual high-order designation requests from the pandemic lows of 2021, requests for CBER-regulated products (59 BTD/RMAT in 2023) are now almost rivaling the number of BTD requests for CDER-regulated products (88 in 2023), which comprise a significantly larger swath of the total R&D pipeline.

Shifts in these High-order FDA designations are interesting and may offer insights into larger trends in the overall R&D pipeline. In recent years, post-pandemic, we have noticed marked shifts in the industry's pursuit of the most coveted FDA designations and FDA grants (as measured by grant success rates) for the high-order designations of breakthrough therapy and RMAT designations. Perhaps more striking than year-over-year shifts in such metrics is that the trends are moving in exactly (and sharply) opposite directions for CDER-regulated small molecules, monoclonal antibodies, and therapeutic proteins versus the CBER-regulated cell and gene therapies, therapeutic and prophylactic vaccines, and other advanced therapies.

Why are CDER BTD requests stalled at pandemic lows while CBER BTD / RMAT requests are surging again?

As the strikingly different arcs of the CDER and CBER high-order designation programs begin to emerge, so too do early theories about why. To some, it might seem that the transition of the “energy” around FDA high-order designations (a marker for therapies thought to be the most promising) might signal a natural—inevitable--shift in excitement/focus from the CDER-regulated small molecule and monoclonals to the more cutting-edge advanced therapies such as cell and gene therapies.

> “While small molecules and monoclonals have generated significant advances in terms of clinical outcomes, some believe that the best opportunity for ‘cure’ may be exclusively reserved for the most promising cell and gene therapies.”
>
> Chris Learn, SVP, Cell and Gene Therapy Center of Excellence, Parexel

And while 2023 certainly was punctuated by advances and landmark approvals in cell and gene therapies, it was also characterized by surging interest in more "traditional" treatment modalities. With the meteoric rise of GLP-1s in diabetics/obesity, spiking interest in antibody-drug conjugates, radio-immunotherapeutics, T-cell engagers, and metabolic modulators, and a resurgent focus on everything from cardiometabolic disease to many difficult-to-treat conditions in the neurosciences, the opportunities for the more traditional approaches regulated by CDER seem legion.

Another theory is that any perceived malaise in CDER's BTD program is part of a pandemic hangover. Support for this theory might seem to exist in the European Medicines Agency's (EMA) most recent experience with the high-order PRIME scheme, which is designed to offer enhanced EMA support for investigational medicines targeting unmet medical needs and is often considered broadly similar to the FDA's BTD program (although the two programs have fundamental differences). As the table below indicates, industry requests for the coveted PRIME status have softened about 19% since the pandemic years (2020 and 2021). In fact, the 47 PRIME requests in 2022 and 52 in 2023 were the two lowest annual totals since the start of the program and were down 40% since the first two years of the program.

Annual Industry Requests for EU PRIME Status, 2016-2023

Industry Requests for PRIME

2016:	84
2017:	81
2018:	57
2019:	60
2020:	68
2021:	54
2022:	47
2023:	52

Source: EMA

"PRIME is relatively new and was created to have something in the EU that could match the FDA's breakthrough therapy designation in some ways," says Dr Sinan B. Sarac, MD, MSc, PhD, Parexel's VP, Regulatory Strategy and former CMO with the Danish Medicines Agency and long-standing member of EMA's Committee for Medicinal Products for Human Use (CHMP). "In the program's first few years, PRIME had considerable interest. However, sponsors quickly realized that PRIME's qualifying bar was high and securing this designation was not easy. This could explain the drop in the industry's PRIME requests over time."

According to EMA data, PRIME grant success rate was 21% in the program's first two years and has risen to 25% for the scheme's first five years, well below the FDA's BTD grant success rate.

The "pandemic hangover" argument also becomes more difficult to make the further we put the COVID-19 pandemic itself in the rear view mirror, and the closer we look at the health of the overall R&D pipeline. While it is true that industry-sponsored, CDER-regulated clinical program starts (commercial IND filings) in both FY2022 (down 10.5%) and FY2023 (down 7.0%) were off the record highs set during the pandemic (2021), it's also true that trial starts remain up 13.1% over pre-pandemic (FY2019) levels. Further, most analyses find the total R&D pipeline remaining resilient in the face of pandemic effects, biopharma funding downturns, and a variety of other challenges in recent years (total preclinical-Phase 3 pipeline +2.8% May 2022 to May 2023—Biomedtracker). In other words, it seems unlikely that a downturn in BTD submissions is a function of a significantly less active R&D pipeline.

Perhaps more importantly, the "pandemic hangover" theory seems to falter given that CBER-regulated therapies are now a full two years into their pandemic recovery, at least as measured by BTD and RMAT industry requests and CBER grant levels. It's also true that, for both CDER and CBER, the lower-order fast-track designation remained at or near record high levels of requests/grants during and now post-pandemic (although the time/resource implications for FDA of supporting development programs granted fast-track status are in no way comparable to those associated with either BTD or RMAT).

Some theorize that more than a decade into the BTD program, the most fundamental changes associated with the program have, in some ways, spread to all development programs—BTD or no BTD. And while emerging data continue to show clear time-to-market advantages associated with BTD status, it's also true that there are small hints that those advantages are shrinking—not because BT-designated programs are taking longer, but because non-designated programs are beginning to catch up. The Friends of Cancer Research's rolling study of median development times for oncology therapies shows that a long-standing 2.7-year time-to-market advantage for BTD drugs has recently—and suddenly—dropped to just 2.0 years. The reason: six non-BTD cancer products were approved from mid-February to Fall 2023, most under Subpart H and four of which had rapid development times.

> "BTD has driven so many changes that have enhanced multiple aspects of drug development for BTD drugs… [but] the changes have been so profound that they've trickled down even to non-BTD drugs."
>
> Martha Donaghue, MD, deputy director of CDER's Division of Oncology 2, acting associate director of OCE's pediatric and rate cancer development program, and head of OCE's Project Beyond Breakthrough.

Meanwhile, the FDA has taken steps to emphasize the limits of its expedited programs, breakthrough therapy in particular, in shielding the industry from emerging agency expectations. “Sponsors should note that the development of a [cancer] drug under an FDA expedited program (e.g., breakthrough therapy designation) is not a significant justification to avoid identifying an optimal dosage(s) before submitting a marketing application,” the agency noted in its January 2023 “Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases” industry guidance.

Yet another theory is that CDER, in reviewing almost 1,200 and granting almost 500 breakthrough designation requests (through September 30, 2023), has refined its expectations and criteria for BTD, and has begun to communicate the refined expectations to industry (e.g., in preliminary BTD informal advice meetings). Since “available therapies” form the qualifying hurdle for BTD and RMAT, the approval of many cancer drugs since 2012 (the advent of the BTD program) would set an increasingly high bar for the High-order designations for approved indications. This would also be consistent with comments from OCE Director Richard Pazdur, MD, suggesting that the growing number of cancer approvals over the last decade will make it more challenging for companies to establish that their emerging oncology therapies address “unmet medical needs” going forward.

On the other hand, it’s also true that CDER informal advice to companies on their eligibility for BTD have not traditionally encouraged immediate BTD requests at the time of the informal BTD advice meeting. According to an internal CDER analysis of 245 preliminary BTD advice meetings from May 2015-April 2018, in only 20% of the cases did CDER review divisions encourage companies to request BTD status immediately. In 44% of the cases, the CDER divisions believed that it was “premature” to submit for BTD status at that time (e.g., the data summarized at the time were encouraging, but that a company should wait for more clinical data, more patient follow-up, or other information before making a formal BTD request).

FDA High-order designation: Nice or need to have?

52%

CBER's Novel Approvals held either BTD or RMAT designation in 2023

January 2024 Pink Sheet

Emerging trends seem to provide fresh evidence that, while the FDA's high-order designations can be "nice to haves" (and even "great to haves") in some cases, they are in no way "need to haves" in a regulatory sense. A January 2024 CDER analysis found that, while the center approved a near-record (55) drug/biologic approvals in 2023, far fewer of these therapies will launch with the coveted breakthrough therapy moniker. ["Advancing Health Through Innovation: CDER's New Drug Therapy Approvals 2023," FDA CDER report, January 2024]

The analysis showed that, of CDER's 55 new chemical entity (NME)/novel biologic entity (NBE) approvals in 2023, only 16% (9) had earned BTD status. This compares to 35% in 2022, 28% in 2021, and 42% in 2020. ["Advancing Health Through Innovation: CDER's New Drug Therapy Approvals 2023," FDA CDER report, January 2024]

Meanwhile, a January 2024 Pink Sheet analysis found that a far greater percentage of new therapies approved by CBER in 2023 had high-order regulatory designations. According to the findings, no less than 52% of CBER's record-setting number of novel approvals in 2023 (17) held either BTD or regenerative medicine advanced therapy (RMAT) designation.

"BTD has been shown to be useful and is a good marker for those investigational therapies that may truly leverage the most clinical benefit," notes Learn. "I do think it's important, however, to counterbalance those thoughts by saying that good should not the enemy of great here, and that whether an asset is designated under an FDA expedited program or not, good science can still be had along with good clinical outcomes. Every clinical advance need not be a homerun. That's a very dangerous expectation to set."

In fact, there are metrics suggesting that a High-order FDA designation is not absolutely necessary for the FDA to consider a new therapy to be important advance for patients. Of the 60 NMEs that were approved by CDER in 2021 and 2022 and without breakthrough therapy designation, 30 earned priority review status (that figure was 7 of 11 for CDER-approved cancer therapies in 2021 and 2022). This means that, when all the clinical data were in, FDA viewed them as offering important new benefits to patients, despite lacking the coveted breakthrough designation.

Meanwhile, for important and growing segments of the CBER-regulated pipeline (i.e., cell and gene therapy products), there remain more options in securing high-order FDA expedited designations. And these options present at earlier points in the development process.

“While the regulatory bar is lower for RMAT than for BTD, the tangible benefits are essentially the same;” notes Steve Winitsky, MD, Parexel’s VP-Technical, Regulatory Strategy and a former clinical team lead and branch chief in what is now CBER’s Office of Therapeutic Products. “So for CGT sponsors, it makes sense to try for RMAT, which can generally be done at an earlier point in development than BTD. A key difference in the regulatory bar for RMAT and BKTD is that the primary evidence to support BTD must come from an endpoint that FDA would accept for accelerated approval or standard approval, whereas for RMAT, you can leverage the totality of evidence (including biomarkers) to support RMAT. For example, you can use secondary and exploratory bioactivity endpoints to provide evidence of biological plausibility to fill in gaps for what’s usually a fairly small dataset, with limited duration of follow-up.

"But sponsors should understand that the High-order designations don't lower the evidentiary bar for licensure," he cautions. "I still come across that misconception when I talk to companies."

> "But sponsors should understand that the High-order designations don't lower the evidentiary bar for licensure..."

Steve Winitsky, MD, Parexel's VP-Technical, Regulatory Strategy and a former clinical team lead and branch chief at FDA

Citing a variety of real and potential benefits, Winitsky remains bullish on both RMAT and BTD designations. "I'd advise clients similarly to what the former OTP/CBER Director, Wilson Bryan, conveyed internally to OTP reviewers: that CGT sponsors should be encouraged to apply for any expedited program designations that they feel they would meet the criteria for. In addition to sponsors getting the recognition that they deserve, there are tangible current benefits (e.g., all future meetings granted at Type B priority) and potential future benefits (e.g., reimbursement considerations that may automatically apply, say, to an RMAT-designated product) related to High-order expedited program designations that may not yet be apparent."

For cell and gene therapies and other advanced therapies, sponsors can view the latest trends in approvals and expedited pathway designations as opportunity, particularly for those development programs that hit the sweet spot for a number of critical factors, such as novel mechanisms of action and transformative treatment effects in patient populations with high unmet need. “Despite 2023 being a really challenging year, FDA had a banner year, and that’s very encouraging,” says Parexel Chief Medical Officer and Head of Oncology Center of Excellence Amy McKee, M.D. “CBER had a record year for approvals. CBER announced that it’s open for business essentially… They’re open for business and they’re building their staff, they’re creating new regulatory pathways for all of us. And we need to keep up with them and push them.”

There may be different opportunities for developers of small molecules and monoclonals regulated by CDER, which saw near-record innovative approvals in 2023 but also saw new therapies obtaining breakthrough designations at rates far off record levels once again. In fact, one might argue that a breakthrough designation is far more valuable—and notable in the markets—today given that there are so many fewer of them being granted. And, from a regulatory perspective, breakthrough designated therapies today will have significantly fewer likewise designated products to compete with for attention and resources within CDER’s new drug review divisions.

You’re on a mission to change lives. We want to help you get there.

Keeping pace with the rapidly evolving biotech environment requires the expertise to anticipate and adapt to development challenges before they happen. At Parexel Biotech, we work side-by-side with biotech companies to break down the development journey into a series of connected decisions, steps, and milestones - to get to that breakthrough innovation – from regulatory and commercial strategy to cutting-edge trial design and execution. We use our deep experience to bring you and your patients closer to better outcomes so you can get your innovation from the lab to the patients who need it most, faster. **#NeverStopBioteching**

With Heart™

››› Contact Parexel Biotech to see how we can help with your next breakthrough therapy

We're always available for a conversation.

With Heart™

Parexel International Corporation
2520 Meridian Pkwy, Durham, NC 27713, USA
+1 919 544-3170

Offices across Europe, Asia, and the Americas
www.parexel.com

parexel®