Why NMEs and Therapeutic Biological Products Fail in the First FDA Review Cycle

PAREXEL Consulting looks at the underlying causes of multi-cycle reviews.

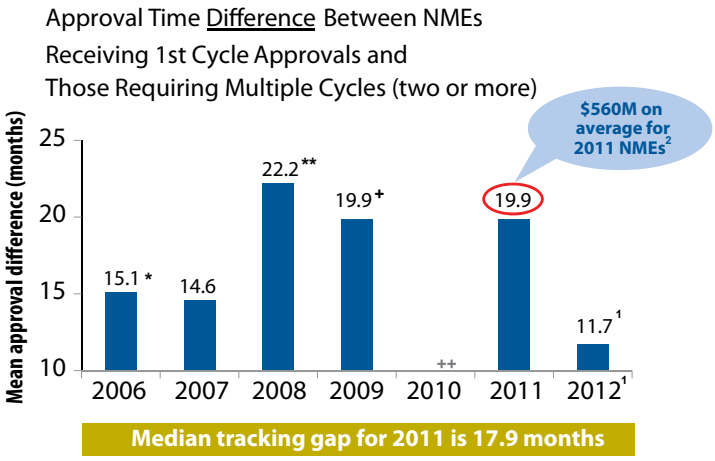
By George Mills, David Chesney, Ravi Harapanhalli, David Morse, Sally Choe, and Mark Mathieu

Patients, companies, and the FDA recognize what is at stake in the first cycle review of new therapies. The need for additional FDA review cycles slows the availability of beneficial new treatments to patients and their caregivers, undermines the return-on-investment for product developers, and sometimes promotes increased scrutiny in the review process. (*See Exhibit 1.*)

FDA reforms in the drug review process (e.g., "21st Century Review Process"), increased staffing and improved infrastructure have benefited review timelines and first-cycle approval rates: First-cycle approvals for new molecular entities (NME)/new biologic entities (NBE) under the Prescription Drug User Fee Act (PDUFA IV) have reached new highs under the user-fee era (1993-today).

Exhibit 1

THE FIRST CYCLE REVIEW IMPERATIVE



* excluding one extreme outlier, 6 year review of Pylera
** excluding multi-cycle 60.3 month review of Vasovist
\+ does not include Sabril (two NDAs with 19.8-month priority review and 182.6-month standard review)
++ Asclera only multi-cycle review (78 months)
[1] excluding 94.8-month review of Surfaxin
[2] using 5-year post-launch sales projection by EvaluatePharma®

SOURCE: PAREXEL Consulting and EvaluatePharma, 2012

POINTED VIEW

About the Authors:

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Exhibit 2

THERAPEUTIC AREAS WITH MULTIPLE-CYCLE NME/BLA APPROVALS 2009-2012

Number of Multi-Cycle Approvals	
Dermatology	4 (2 lice)
Pulmonary	3
Cardiovascular	3
Neurology	3
Rheumatology	3 (2 gout, 1 RA)
Hematology	2
Allergy	2 (2 angiodema)
Inborn Errors	2 (2 ERTs)
Medical Imaging	2
Psychiatry	2
Transplant	1
Ophthalmic	1
Obesity	1
Renal	1
Anti-Infective	1
Osteoporosis	1
Supportive Care (Oncology)**	1

**Through October 1, 2012. **Neutroval (tbo-filgrastim), which FDA "clarified" is not a biosimilar.

SOURCE: PAREXEL Consulting

Now, a new FDA program for NME/NBEs under PDUFA V (October 1, 2012-September 30, 2017) seeks to further improve first-cycle approval rates--in this case, through increased sponsor/FDA communication and by, in effect, extending the drug-review timeline by two months (by moving the 60-day filing review period "off the PDUFA clock").

Despite such improvements and refinements, however, about one-half of all NME/NBEs recently submitted to the Center for Drug Evaluation and Research have stumbled in the initial review cycle. Further, over a third of NMEs and NBEs approved by CDER from January 2009 to late-2012—a success cohort—took multiple review cycles to secure agency approval.

With so much at stake, PAREXEL Consulting systematically evaluated why certain recently approved new drugs and biologics failed in the critical first FDA review cycle. By better understanding the reasons for first-cycle review failure, innovators/developers may gain insights that will enhance future product development and registration programs.

Specifically, we studied the 24 NMEs and, separately, the nine BLAs that were ultimately approved by CDER from January 2009 through late 2012, but that had failed in their first review cycles. In other words, we looked at those newly approved products whose original NDA and BLAs submissions triggered complete response letters or approvable/not-approvable letters.

This study focused solely on recently approved products for a significant and practical reason: Only for approved products could we gain complete access to the internal FDA review documentation necessary to make a true assessment of the reasons why the agency did not approve the medicines in the initial review cycle. Thus, our study is fundamentally different than the 2008 Booz Allen study, which looked at a larger number of drugs that triggered complete response letters, without regard to eventual approval.

Absent from our cohort is a single therapeutic for oncology, the area with by far the most NME and BLA approvals in recent years.

Remarkably, there is a complete lack of evidence, over the last several years (and very little over the last decade), that oncology products that fail in the first review cycle are ever resurrected to obtain FDA approval in subsequent review cycles (the last oncology NME approved in multiple cycles was *Dacogen*, which was cleared in 2006). One theory is that many new oncology drugs fail in the initial FDA review cycle due to questions of efficacy, and that because efficacy is a more difficult, time-consuming, and costly hurdle to clear (i.e., additional clinical trials) in subsequent review cycles, fewer of these drugs with efficacy issues recover to gain approval.

Why NMEs Fail in the First Review Cycle

To examine the primary reasons why the 24 NMEs in our sample failed to secure approval in the critical initial review cycle, we first divided the drugs into groups based on how many issue/deficiency areas stood in the way of approval. In this case, a single issue/deficiency could be one problem in a single area (e.g., safety, efficacy, or manufacturing/CMC), or a cluster of issues/deficiencies within in a single area (as is often the case in manufacturing/CMC, for example).

This first analysis, as did every other analysis that we undertook, clearly showed how dominant safety-related deficiencies were in the first-cycle failures of the 24 NMEs examined (see Exhibit 2 below):

For the eight products that had a single issue preventing approval, half failed due to safety, while the remaining four products failed due to efficacy, CMC, labeling, and REMS issues.

For all of the eight products that had two issues preventing approval, safety was the common thread. Effectiveness was also an issue for four of these products, while CMC was the second issue for the other four.

Safety questions were also a common thread among all seven of the eight products with three or more issues preventing approval. Efficacy and CMC/product quality were also common issues among seven of the eight NMEs.

Because the particular reasons underlying NME first-cycle review failures are so diverse and product-specific, even within each category (safety/effectiveness, CMC), offering global commentary applicable to all products is virtually impossible. Our summary analysis does provide ample evidence, however, that drug developers have an opportunity to more carefully address and resolve a range of safety, CMC, dosing, and data integrity issues *prior* to the submission of the original NDA.

As noted, the lack of multiple-cycle approvals for cancer drugs suggests that efficacy issues may be a "death knell" in oncology, as developers might be unable (e.g., company size, lack of funding) or unwilling (given "marginal" efficacy and the prospect of having to leverage additional capital resources and time) to pursue further development. Efficacy issues for non-oncology products appear to be more addressable, given that half of the 24 approved NMEs in our sample had such issues in the first cycle.

Why Are BLAs (Therapeutic Biologics) Failing in the 1st Review Cycle?

Given that CDER receives significantly fewer BLAs than it does NMEs, it was not at all surprising that our sample of multi-cycle BLA approvals between January 2009 and late 2012 was so much smaller. The limited sample of nine multi-cycle BLAs did not fail to tell a definitive story, however: Product quality/CMC issues were key questions/deficiencies for over three-quarters (7 of 9) of the approved products.

Not surprisingly, the issues varied, ranging from failed sterility processes

Exhibit 3

NMES THAT FAILED IN THE FIRST REVIEW CYCLE, 2009-2012

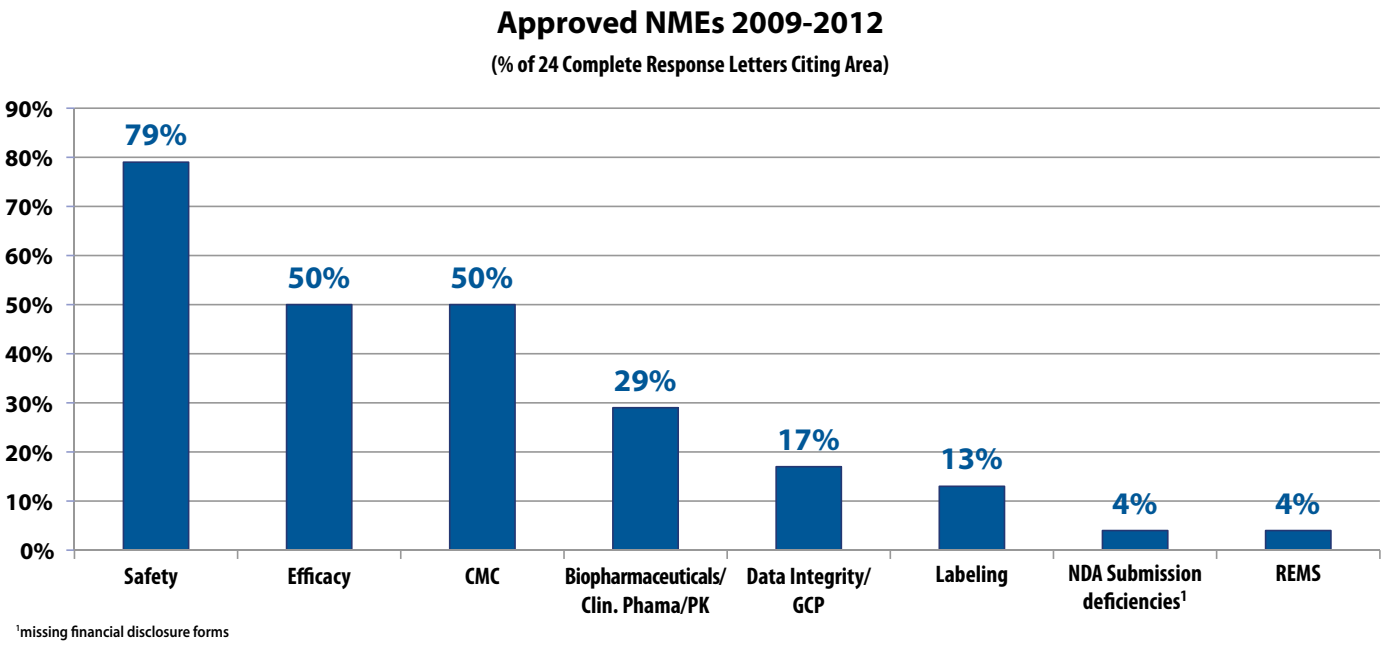
	1	2	3	4
1 Issue				
Labeling	DaTscan			
Safety	Horizant	Daliresp[3]	Uloric	Saphris
Efficacy	Brilinta			
REMS	SAMSCA			
CMC	Zioptan			
2 Issues				
Safety/CMC	Ulefsia	Natroba	Potiga[9]	Surfaxin[11]
Safety/Effectiveness	Fanapt[7]	Sabril[8]	Arcapta Neohaler[4]	Belviq
3+ Issues				
Effectiveness/CMC/ProdQual/Labeling	Amyvid[10]			
Saftey/CMC/Data Integrity	Xarelto			
Efficacy/PK/Dosing/Saftey/CMC	Firazyr[1]			
Saftey/Efficacy/CMC/Data Integrity	Asclera[5]			
Saftey/Efficacy/Biopharmaceutics	Multaq[6]			
Saftey/Efficacy/CMC/NDA	Vibativ			
Saftey/Effic. CMC/Clin.Pharm/Data Integ.	Ferriprox[2]			
Saftey/Effic./Clin.Pharm/ Immunogencity/ProdQual/Microbiol.	Elelyso			
Number of NMEs	**1**	**2**	**3**	**4**

1) Efficacy was repeatedly identified as primary issue. 2) CRL had 29 deficiencies/requests (11 under clinical, 3 under clinical pharmacology, and 15 under product quality). 3) CRL listed 3 issues preventing approval, 1 of which not identified (redacted). Two others were safety related. Implication was other was safety-related as well, but not clear. There appeared to be consensus that safety was a key issue, but disagreement about whether efficacy was an issue. 4) All dose-related issues. 5) Multiple issues, but efficacy called "the critical issue." ClinPharm/biopharmaceutics issue mentioned as well, but was more of a data integrity issue. 6) Multiple issues, but safety issue called "overwhelming impediment to drug approval." 7) Two "major deficiencies" identified, although four other issues needed addressing (considered "not reasons for not approvable action"). 8) Safety concerns called "most critical" to non-approval. While safety/efficacy concerns were main issues, approvable letter also requested biopharmaceutics information. 9) Primary CR reason was high-specification limit for mutagenic impurity (called "chemistry/carcinogenicity issue"). Also, "less important deficiency" was potential to cause urinary symptoms. 10) Clinical reviewer noted that "major deficiencies" were clinical in nature (need for a reader training program suitable for marketplace). 11) Cross discipline team leader review notes that "clinical recommendation for the original submission was Approval; however, there were major CMC deficiencies that led to "initial and subsequent review cycles."

SOURCE: PAREXEL Consulting

Exhibit 4

REASONS WHY NMES FAIL IN FIRST REVIEW CYCLE



SOURCE: PAREXEL Consulting

and facility inspections to the failure of the product proposed for marketing to be representative of the product used in the pivotal trials used to support marketing. Among the nine products assessed, only Prolia and Dysport did not have product quality/CMC issues standing in the way of approval.

Clearly, these findings are consistent with the conventional wisdom that the challenges involved in manufacturing large-molecule products are more complex than those associated with producing synthetic drugs.

Although product quality/CMC issues were more common for the biological products, safety issues certainly did not disappear. More than half of the multi-cycle therapeutic biologic approvals (67%) had key safety-related issues cited in their complete response letters.

Interestingly, efficacy issues were not frequent issues for the multiple-cycle biologic approvals. Only one of the nine products—*Kalbitor*—had an efficacy-related question/issue preventing approval. RPM

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