TITLE

Clinical Development Strategies and Regulatory Outcomes of FDA Approved Biological License Applications – Therapeutic Domain Considerations

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INTRODUCTION

The prospect of treatment using biological drug products ('biologics') has had a significant impact in almost every therapeutic area. Biologics have greater complexity than small molecule drugs, not only by virtue their large size, but also in their immunogenic properties and unique relationship between their pharmacokinetic (PK) and pharmacodynamic (PD) profiles[1-3]. Whether based on the individual therapeutics, the patient population, or the labeling claims, biologics have had incredibly variable development plans in terms of the supporting clinical pharmacology studies, patient population in pivotal trials, and regulatory influence. Such variability has stymied investigators that often rely on regulatory precedent to design their development plans. While there may be a number of drivers of this variability, the hypothesis of this study is that the therapeutic domain, namely that of oncology versus non-oncology therapeutics, has played a major role, based on the following rationale:

- The risk: benefit considerations are usually different in that most oncologic therapeutics are for fatal diseases, whereas biologics developed for non-therapeutic areas are often chronic, progressive diseases[2,4].
- Characteristically, registrational trials in the oncology domain typically differ from the standard in that they do not use placebo-controls[26]

In this study, characteristics of clinical development programs and regulatory pathways were extrapolated from Summary Basis of Approvals (SBOAs) for 55 biologics approved by the Center of Drug Evaluation and Research (CDER) FDA between 2003 and 2016. Features include the characteristics of the applications, followed by a description of the resource use (i.e. subjects studied and time requirements), and finally the regulatory outcomes, such as first cycle approvals versus complete responses of these programs. While past studies have contrasted the distinct regulatory processes between biologics and drugs[5-6], this analysis is unique, in that it comprehensively addresses efficient and effective use of resources for future development plans and potential implications of the two therapeutic domains.

METHODOLOGY

Data Collection

A database was constructed compiling key variables of clinical programs and regulatory outcomes derived from publically available SBOAs from the Drugs@fda website (***https://www.accessdata.fda.gov/scripts/cder/daf/#apphist***; last accessed: 4/15/17). The programs were classified into two groups based on therapeutic domain, oncology and non-oncology, based on a consideration of three criteria (Appendix I):

- World Health Organization Anatomical Therapeutic Chemical Classification system (ATC) 2nd Level Therapeutic subgroup
- Approved indication
- Review division

Data abstraction and analysis

Descriptive analyses of the key demographics, resources, and outcomes variables (Table 1) was performed with JMP (SAS, version 13.0).

Table 1 Key Analysis Variables

Demographics	• *Anatomical Therapeutic Classification Level 2* • *Accelerated approval* • *Breakthrough therapy* • *Fast Track* • *Priority review*
Resources	• Number of clinical trials • Number of subjects in efficacy program • Non-registrational trials
Outcomes	• Clinical holds • Major amendments • Complete Response • Time to approval- Initial BLA submission to approval date interval • Time to approval- Final PDUFA to approval date interval

RESULTS

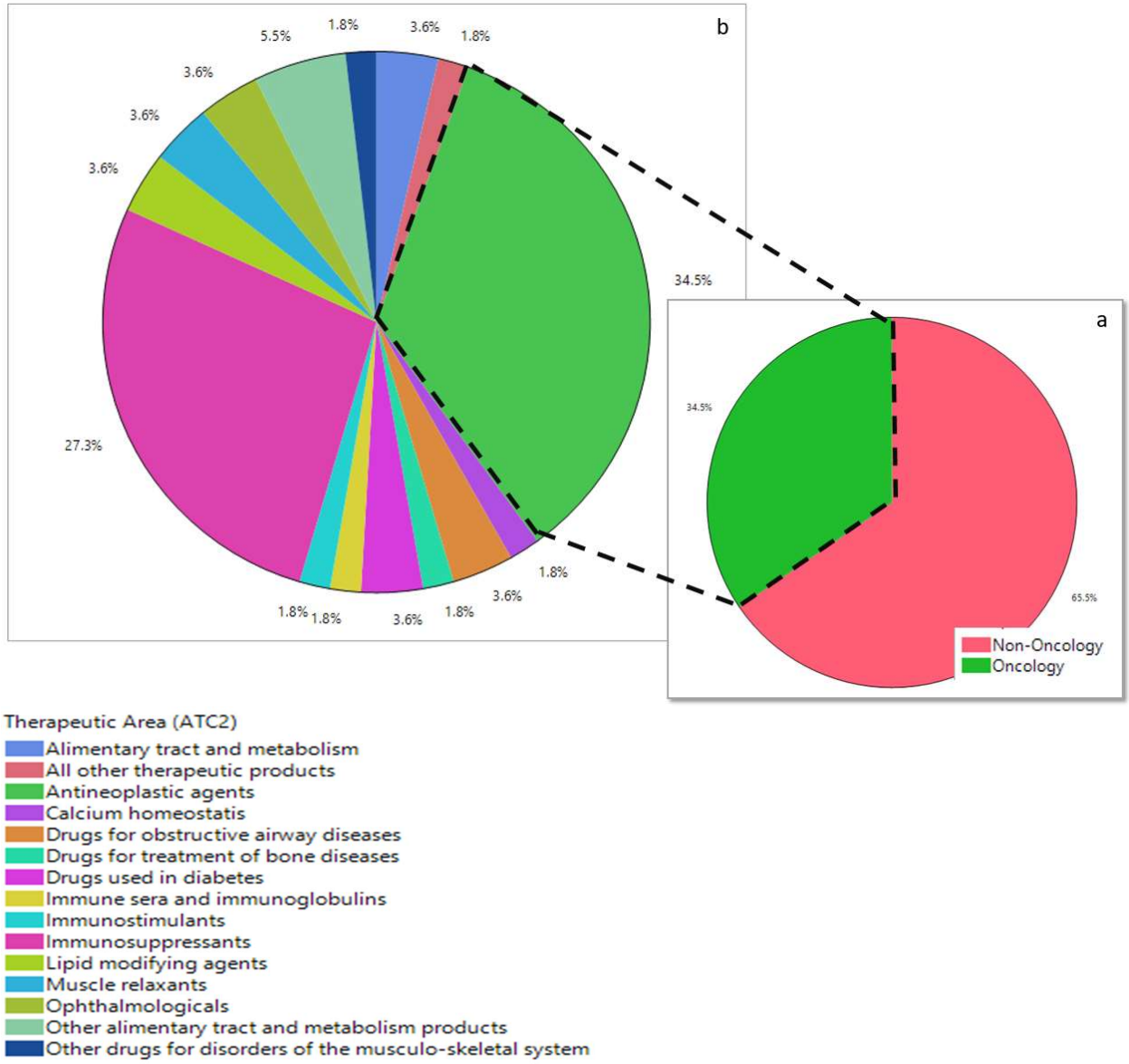
Demographic Characteristics of the Applications

Database Composition and Structure

The biologics included in this study were limited to those that were originally approved by CDER during 2003-2016 (**Table 2**)[*]. The 55 programs were categorized by ATC2 level classification resulting in 15 therapeutic areas (**Figure 1**). All programs in the ATC2 '*antineoplastic agents'* (N=14) and five hematology products were designated to the oncologic therapeutic domain (N=19, 34.5%). The thirty-six (65.5%) remaining programs were included in the non-oncology domain, with greatest representations by 1.) the '*immunosuppressants*' class (N=15) comprised of dermatology (N=4, 26.7%) and rheumatology (N=5, 33.3%), and 2.) the inborn errors of metabolism (N=3, 100%) from '*Other alimentary tract and metabolism products'* class.

[*] Only one biologic (Bexxar tositumomab and iodine I131 tositumomab) was approved by CBER within this time period (approval date June 3, 2003), which most likely correlates to the transition of CBER activities to CDER on June 30, 2003[7, 8]. This biologic was therefore excluded from this analysis

Figure 1 Anatomical Therapeutic Classification (ATC) Second Level- Therapeutic Area Oncology and Non-oncology



a.) Programs categorized by oncology (34.5%) and non-oncology (65.5%); b.) Programs categorized by therapeutic area (ATC2) with oncology represented by the '*antineoplastic agents*' class.

Table 2 Distribution of Analyzed BLAs by Therapeutic Area, 2003-2016

Year	Oncology N=19	Non-Oncology N=36
2003	0	1
2004	1	0
2006	1	0
2007	0	1
2009	1	5
2010	0	3
2011	1	3
2012	2	2
2013	2	2
2014	5	8
2015	4	9
2016	2	2

Table represents the distribution of the 55 CDER approved biologics analyzed within this study and not to be misrepresented as total approvals per year

Expedited Development Programs

Of the nineteen oncology programs, ten qualified to receive accelerated approval. Interestingly, only 1 of the 36 non-oncologic products received accelerated approval. Fast track designation was found to be more prevalent within the oncology domain (N = 11, 57.9%) compared to the non-oncology domain (N = 9, 25%). Breakthrough therapy designation was established in 2012, which therefore excludes 20 of the 55 programs from analysis for this particular expedited program[9] †. Of the remaining 35 programs, the oncology domain demonstrated higher ratio of approvals with 9 out of 13 (69.2%) granted breakthrough therapy designation. In comparison, four of the twenty-two (18.2%) non-oncologic programs received the same designation (**Table 3**). For the final expedited program, Priority Review, the non-oncologic therapeutic domain was divided between Priority and Standard Review status, 44% and 56% respectively (**Table 3**). In contrast, most (N= 18, 94.7%) oncology programs received Priority Review status. Only one

† Expedited Programs: Fast Track- Section 506(b) FD&C Act Section 112 FDAMA 1997; Breakthrough Therapy Designation- Section 506(a) FD&C Act Section 902 FDASIA 2012; Priority Review- Prescription Drug User Fee Act of 1992; Accelerated Approval- Section 506(c) FD&C Act 1992

oncology program was refused priority review as it did not provide a significant improvement in safety or effectiveness[10, 11].

Table 3 Expedited Program by Therapeutic Domain

	Accelerated Approval No	**Accelerated Approval Yes**	**Total Responses**	**Test Response Homogeneity Pearson Chisq (Pearson P-value)**
Non-oncologic	35 97.2%	1 2.8%	36	19.3183 (<0.0001)
Oncologic	9 47.4%	10 52.6%	19	
	Priority Review	**Standard Review**	**Total Responses**	**Test Response Homogeneity Pearson Chisq (Pearson P-value)**
Non-oncologic	16 44.4%	20 55.6%	36	13.3268 (0.0003)
Oncologic	18 94.7%	1 5.3%	19	
	Fast Track No	**Fast Track Yes**	**Total Responses**	**Test Response Homogeneity Pearson Chisq (Pearson P-value)**
Non-oncologic	27 75.0%	9 25.0%	36	5.81532 (0.0159)
Oncologic	8 42.1%	11 57.9%	19	
	Breakthrough No	**Breakthrough Yes**	**Total Responses**	**Test Response Homogeneity Pearson Chisq (Pearson P-value)**
Non-oncologic	18 81.8%	4 18.2%	22	9.12098 (0.0025)
Oncologic	4 30.8%	9 69.2%	13	

Resource Characteristics of the Applications

Clinical Pharmacology and Registrational Trials Performed

The number of subjects enrolled in the efficacy program, which includes both treatment and control groups, were more numerous in non-oncology (**Table 4**) (Mean = 1751; s.d.1950) than the oncology programs (Mean= 504; s.d. 367). The subjects in the efficacy programs greatly varied for both domains. The non-oncology domain reached several thousand subjects, whereas the oncology programs barely exceeded 1200 subjects (**Table 4**).

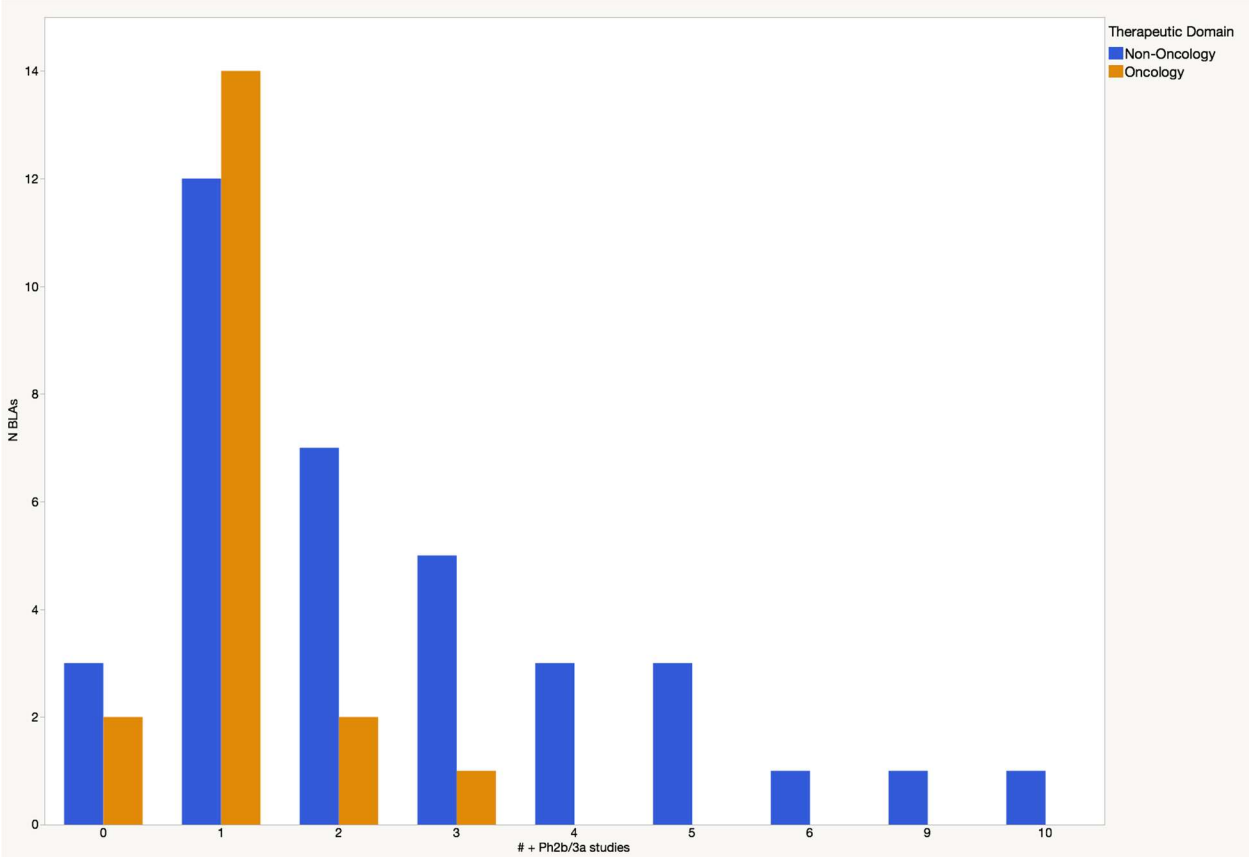
The modal number of trials used to demonstrate Substantial Evidence for both domains amounted to a single pivotal trial; the non-oncology had a greater variance, with several programs providing up to 10 trials (**Table 4; Figure 2**).

Table 4 Overview of Subject and Study Resources

		Non-Oncology	***Oncology***
	N	***(N=36)***	***(N=19)***
Total subjects in efficacy program‡	*Min*	35	41
	Max	7762	1216
	Mean (s.d)	1751 (*1950*)	504 (*367*)
Total number of studies (clinical and clinical pharmacology)	*Min*	2	2
	Max	33	13
	Mean (s.d.)	12 (8)	7 (3)
Total number of registrational trials (Phase 2b and Phase 3a studies)	*Min*	0	0
	Max	10	3
	Mean (s.d.)	2.6 (2.3)	1.1 (0.7)
	Median	2	1
	Mode	1	1

‡ *One program, Raxibacumab (BLA 125349) was excluded from "Total subjects in efficacy program" analysis as no clinical trial participants were enrolled. Approved indication for this program is treatment for inhalation anthrax which allowed studies related to efficacy eligible to be conducted under FDA rule on "Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies are not Ethical or Feasible."*[12]

Figure 2 Total Number of Registrational Trials (Phase 2b and Phase 3a)



Development Time to Approval

Three different time epochs were evaluated (**Table 5)**. Time intervals between (1) IND to initial BLA submissions and (2) initial BLA submission to approval provide preliminary estimates on length of clinical development. More successful programs have shorter periods between initial submission and approval if further study is not needed (i.e. Complete Response). The interval of a clinical development plan can be extensive with an average of 12 years from discovery to market according to DiMasi at the Tufts Center for the Study of Drug Development, which translates into 4,380 days[13, 14]. To condense these prolonged timeframes, the differences between dates of IND submission and BLA submission were divided by 365 days to produce the estimated number of years rather than days. The third time measurement is any lapse of the

approval date exceeding the PDUFA date. PDUFA is the Prescription Drug User Fee Act established in 1992 allowing FDA to collect fees on human drug applications [e.g. 505(b)(1) FD&C Act; 505(b)(2)] in exchange for NDA and BLA application review[15]. This process enforces review deadlines on the agency (e.g. 10 month standard review; 6 month priority review). From this data, there was only one outlier in the non-oncology group where the approval date surpassed the PDUFA timeframe by 157 days. Further investigation correlates this extended period of time to the establishment and implementation of an advisory committee. Excluding this single outlier, both therapeutic domains met the PDUFA date or were well within it. Beyond meeting the PDUFA deadline, the oncology domain demonstrated significantly higher intervals, where 42% of these programs were approved with over 50 days preceding the goal date.

Table 5 Epochs between Major Development Milestones by Therapeutic Domain

		Non-Oncology	***Oncology***
Time Interval from IND Submission to BLA Submission (Years)	*N*	27	18
	Min	2	2
	Max	19	22
	Mean (s.d.)	8.4 (4.6)	7.8 (4.3)
Time Interval from BLA Submission to Approval (Days)	*N*	36	19
	Min	182	75
	Max	781	357
	Mean (s.d.)	352.8 (132.1)	190.6 (77.8)
Difference between Approval & PDUFA Dates (Days)	*N*	36	19
	Min	-54	-117
	Max	157	0
	Mean (s.d.)	-0.3 (29.2)	-41.5 (49.3)

Outcome Characteristics of the Applications

Clinical holds, Refuse-To-Files, and Complete Responses are critical regulatory actions in the licensing process. The Complete Response action replaced the Not Approvable and Approvable Action on August 11, 2008 [16]; Applications with the latter two actions are designated as having a Complete Response for the purposes of this study. Applications may also be withdrawn by the applicant or designated as refuse-to-file by the agency. The review cycle may be extended by 3-months by submission of a Major Amendment, which occurs after the initial BLA substantial review. From this analysis, majority of programs never experienced these types of regulatory actions; however, overall, the non-oncology domain had more major amendments and complete responses, with 35% and 15% respectively.

Table 6 Regulatory Outcomes by Therapeutic Domain

		Non-Oncology (N=36)	***Oncology (N=19)***
Major Amendment	*Yes*	35%	5%
Refuse-to-File / Withdrawn	*Yes*	2%	2%
Complete Response	*Yes*	15%	0%

DISCUSSION

Demographics of the Biologics Database

The relationship of the therapeutic domains, oncology versus non-oncology, and key development characteristics of fifty-five approved biologics were investigated. The majority of non-oncology programs were '*immunosuppressants*' (e.g. rheumatology and dermatology). Increase in public awareness to escalating cancer rates in the United States could be presented as a possible explanation for the rise in available oncology therapies[18,31]. Similar urgency in drug development occurred in the early 1990's when prevalence of HIV-related disease (AIDS) erupted, which was coincidentally around the same timeframe that FDA expedited programs were established into the Code of Federal Regulations[9, 17]. Assessment of current available

therapies and their impact to the target disease are essential components for selecting a regulatory pathway and predicting how a pipeline product will compare on the market. Where therapies are non-existent or limited, applications have higher chances of being categorized as an “unmet medical need’ and treatment of a “serious condition” based on the FDA definition of the term: *“…a disease or condition associated with morbidity that has substantial impact on day-to-day functioning*”[30]. If the program can meet specific criteria like those mentioned above, then the product may be eligible for any of the four expedited programs[30]. Oncology had more approvals across expedited programs within the therapeutic domain than non-oncology. For instance, only one of the thirty-six non-oncology programs was granted accelerated approval. This was due to the fact that this particular product happened to be the first specific anticoagulation reversal agent and was approved based on a surrogate endpoint[§]. One explanation to account for the difference in expedited approval rates highlights the fact that products in other therapeutic areas (e.g. CNS, musculoskeletal pain, respiratory, gastrointestinal) do not inherently satisfy the criteria laid out for priority status[19,20]. Additionally, for priority review, only one oncology program was denied because it did not provide sufficient evidence of improvement in safety or effectiveness[**]. These data suggest that biologics in the oncology domain more frequently represent a clinical innovation. This may lead companies to reconsider their development portfolios, advancing candidates with more favorable regulatory prospects.

Resource Strategies

From a clinical development perspective, the term ‘resource” can refer to number of patients and number of trials. Both are targets foreseen to have impact on improving development

[§] Idarucizumab (Praxbind®)

[**] Necitumumab (Portrazza®)

processes (alongside regulatory review) [14]. The number of patients and trials must be sufficient to produce quality data with statistical significance purposefully demonstrating therapeutic benefit, while still within the constraints of cost-effectiveness [21, 22]. Based on efficacy trial enrollment, non-oncology showed a significantly higher mean and wider distribution compared to oncology (**Table 4)**. Analogous results were observed for the total number of studies and registrational trials. Interestingly, the modal number was one trial for both therapeutic domains. Greater sample sizes would seem to be a driver of increased costs overall; however, an analysis by DiMasi suggested that variability of development costs is more impacted by the variability in attrition and clinical success rates[13].

Although two well-controlled clinical trials is considered the regulatory standard, single pivotal trials are allowed in certain circumstances, as described in the FDA's Effectiveness Guidance and the 1997 Section 215(a) of the Food and Drug Modernization Amendment to the FD&CA[23]. A previous study demonstrated that a substantial number of approved programs were based on a single pivotal study and in some cases, oncology programs had uncontrolled studies as the basis of approval [23-24]. Although small sample sizes and single pivotal trials may be cost-effective and efficient to speedier reviews, there are quite a few precautions that sponsors should recognize. Reduced sample sizes and single trials can only produce a certain amount of safety data which may lead to consequences once the drug is marketed to a wider population. Hence, why current strategies are increasing the utilization of companion diagnostics and biomarkers[25, 27].

As a final assessment in this area, exploratory analysis was performed that categorized the objectives of trials that provided no contribution or substantial support to the actual registration. Frequent study objectives included single and multiple ascending or fixed dose, long-term extension, and cardiac QT. The most prevalent included additional Phase 2 and Phase 3 studies related to PK/PD profiles, efficacy and safety, and dose-related. From this assessment, it seems that clinical pharmacology studies are background strategies. From the database, all

but two programs included clinical pharmacology studies in their development plan. Interestingly, these two programs (1 biologic; 2 indications[††]) later experienced a PDUFA clock extension and Complete Response for a Risk Evaluation & Mitigation Strategy. One indication in the program unfortunately had to undergo refuse-to-file/withdraw. Clinical pharmacology studies may provide valuable insight to tie into the drug's safety profile[3]. Biologics quite prone to adverse events by virtue of their immunogenicity and species specificity, if they contain non-human domains. Strategic planning to gain the clinical pharmacology information needed to support clinical trials may reduce risks of delay in approval.

Outcome Strategies

Between the domains, there was little difference seen in the 'clinical development interval' (IND to BLA submission) as both medians were estimated at 7-8 years. The period following initial submission, sometimes referred to the 'NDA- or 'BLA period', however, did demonstrate an expected trend. Programs with expedited approvals had briefer intervals between initial submission and approval. Likewise, programs that experienced a 'negative' regulatory action (Major Amendment; Complete Response) had longer intervals[28-29]. To address the latter, further analysis examined the eight Complete Responses in the non-oncologic domain. Generally reasons for Complete Response were found to be safety and CMC-related (Chemistry Manufacturing Controls) related.

Lastly, time differences between approval and PDUFA dates conformed to PDUFA deadlines across both therapeutic domains. The only observations worthy-of-mention are instances when approval dates significantly preceded the PDUFA date. For several oncology programs, approval letters were granted as much as 90+ days before the set PDUFA date, which is a significant amount of time given to the sponsor. The faster a new product can get to the US

[††] AbobotulinumtoxinA (Dysport®)

market the sooner a sponsor can reap back the rewards and profits expended during development and review.

CONCLUSIONS

In this study, a comparison was made between development programs for oncology and non-oncology programs leading to approval of BLAs by the US FDA. Comparisons were made between the development programs, resource use, and regulatory outcomes. In general oncology programs were smaller, with less supportive studies and fewer clinical trials. Consequently, they also used fewer patients and were briefer. Perhaps because of the greater unmet needs in this domain, BLAs in the oncology domain benefited from Expedited Programs in their development and review. These may have led to even more effective and efficient use of resources. Most BLA programs do not experience negative regulatory outcomes such as Major Amendments, Clinical Holds, or Complete responses[28-29]. This is remarkable given the greater complexity of these molecules and complicated nature of their production (i.e. CMC)[1]. This positive aspect of BLA development may represent the very resource intensive efforts with innovative therapeutics from manufacturers attempting to fulfill the great therapeutic needs of patients.

REFERENCES

1. Geigert J. Demystifying CMC regulatory strategy for biologics- Part 1: Biologics CMC regulation is complex. Regulatory Focus. 2011; 16(9):40-46. Part 2: Biologics are not chemical drugs. Regulatory Focus. 2011; 16(11):48-51.
2. Hoos, A. Development of immuno-oncology drugs- from CTLA4 to PD1 to the next generations. Nature Reviews. Drug Discovery. Perspectives. Vol. 15. 235-247. April 2016. Accessed April 11, 2017.
3. Kingham, G., Klassa, G., Carver, K. Key Regulatory Guidelines for the Development of Biologics in the United States and Europe. Biologic Drug Products: Development and Strategies. First Edition. 2014. John Wiley & Sons, Inc. 75-109.
4. Kane, R. FDA Oncology Drug Approval: Endpoints, Effectiveness, and Approval. Division of Drug Oncology Products. Office of Oncology Drug Products. CDER. FDA. Accessed April 26, 2017. https://www.fda.gov/downloads/aboutfda/centersoffices/cder/ucm103366.pdf
5. Kinch MS. An overview of FDA-approved biologics medicines. Drug Discov Today. 2015;20(4):393.
6. Pariser AR, Slack DJ, Bauer LJ, Warner CA, Tracy LA. Characteristics of rare disease marketing applications associated with FDA product approvals 2006–2010. Drug Discov Today. 2012;17(15):898.
7. Bexxar approval letter. Masiello, S. A., & Risso, S. T. (2003, June 27). [Letter to M. Krieger, Corixa Corporation]. Department of Health & Human Services. Food and Drug Administration. BL 125011/0. Accessed April 23, 2017. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/125011s000_Approv.pdf
8. Transfer of Therapeutic Products to the Center for Drug Evaluation and Research (CDER). U.S. Food and Drug Administration. Updated April 15, 2015. Accessed April 23, 2017. https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cber/ucm133463.htm
9. Raggio, M. Overview of FDA Expedited Programs with a Focus on Breakthrough Therapy. FDA Small Business and Industry Assistance. Regulatory Education for Industry (RedI) Conference. 2015. Accessed April 8, 2017. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM466480.pdf
10. Keegan, P. (2015, January 7). Review Designation Memo for BLA 125547 (necitumumab; Eli Lilly and Company) [Letter to BLA 125547]. Division of Oncology Products 2. Office of Hematology and Oncology Products. Office of New Drugs. Center of Drug Evaluation and Research.
11. Portrazza. SBOA
12. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). Guidance for industry providing clinical evidence of effectiveness for human drugs and biological products. Clinical. Accessed April 14, 2017. https://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf+Providing+clinical+evidence+of+effectiveness+for+human+and+bio&client=FDAgov&site=FDAgov&lr=&proxystylesheet=FDAgov&output=xml_no_dtd&ie=UTF-8&access=p&oe=UTF-8. Updated May 1998.
13. DiMasi, J., Hansen, R., Grabowski, H., Lasagna, Louis. Research and Development Costs for New Drugs by Therapeutic Category. PharmacoEconomics. 7(2): 152-169. 1995.
14. DiMasi, J. The Value of Improving the Productivity of the Drug Development Process: Faster Times and Better Decisions. PharmacoEconomics. 2002; 20 Suppl. 3: 1-10.

15. U.S. Department of Health and Human Services. Food and Drug Administration. Prescription drug user fee act (PDUFA). https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm. Updated December 16, 2016. April 15, 2017.
16. Department of Health and Human Services. Federal register: Applications for approval to market a new drug; complete response letter; amendments to unapproved applications. Food and Drug Administration 21 CFR parts 312, 314, 600, and 601. Action: Final rule. July 10, 2008. Vol. 73 (No. 133): 39588.
17. Katz, R. Biomarkers and Surrogate Markers: An FDA Perspective. NeuroRx. April 2004. 1(2): 189-195. doi: 10.1602/neurorx.1.2.189. Accessed April 29, 2017. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC534924/
18. National Cancer Institute at the National Institutes of Health. Cancer Statistics. Updated March 22, 2017. Accessed April 15, 2017. https://www.cancer.gov/about-cancer/understanding/statistics
19. Rawson, N. Health Canada's use of priority review status for drugs for unmet needs. Regulatory Toxicology and Pharmacology. 73. 391-395. August 8, 2015. Accessed April 20, 2017
20. Boucaud-Maitre, D. Ropers, J. In response to Alqahtani et al. (2015 Jul; 24(7):709–15): suggesting an international regulatory harmonization for priority review drugs need further investigations. Letter to the Editor. Pharmacoepidemiology and Drug Safety 2016; 25: 743-744. doi: 10.1002/pds.3973
21. Glick, H.A. Sample Size and Power for Cost-Effective Analysis. Pharmacoeconomics (2011) 29: 189. doi:10.2165/11585070
22. Manju MA, Candel MJJM, Berger MPF. Sample size calculation in cost-effectiveness cluster randomized trials: Optimal and maximin approaches. Stat Med. 2014; 33(15):2538.
23. Downing, N., AB, Aminawung, J., Shah, N., Krumholz, H., Ross, J. Clinical Trial Evidence Supporting FDA Approval of Novel Therapeutics, 2005-2012. JAMA. January 22, 2014.; 311(4): 368-377, doi: 10.1001/jama.2013.282034. Accessed April 23, 2017.
24. Hatswell, A., Baio, G., Berlin, J., Irs, A., Freemantle, N. Regulatory approval of pharmaceuticals without a randomized controlled study: analysis of EMA and FDA approvals 1999-2014. BMJ Open. June 2, 2016. 6:e011666. doi: 10.1136/bmjopen-2016-011666. Accessed April 25, 2017.
25. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Devices and Radiological Health. Center for Drug Evaluation and Research. Center for Biologics Evaluation and Research. Principles for codevelopment of an in vitro companion diagnostic device with a therapeutic product- draft guidance for industry and food and drug administration staff. https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM510824.pdf. Updated July 15, 2016April 21, 2017.
26. Guidance for Industry FDA Approval of New Cancer Treatment Uses for Marketed Drug and Biological Products. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) December 1998. Clin 7
27. U.S. Department of Health and Human Services. Food and Drug Administration. Paving the way for personalized medicine: FDA's role in a new era of medical product development. https://www.fda.gov/downloads/scienceresearch/specialtopics/personalizedmedicine/ucm372421.pdf. Updated October 2013. April 21, 2017.
28. U.S. Food and Drug Administration. Complete Response Letter Final Rule. Laws, Acts, and Rules. Updated March 8, 2016. Accessed May 3, 2017. {FDA Complete

Reponses}. https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084138.htm
29. Guidance for Industry Major, Minor, and Telephone Amendments to Abbreviated New Drug Applications. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). December 2001. Revision 2. OGD. Accessed April 29, 2017. https://www.fda.gov/downloads/Drugs/.../Guidances/ucm072888.pdf
30. Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). May 2014. Accessed April 8, 2017. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf
31. Deaths and Mortality. Centers for Disease Control and Prevention. National Center for Health Statistics. Updated March 17, 2017. https://www.cdc.gov/nchs/fastats/deaths.htm

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APPENDIX I

No.	*BLA No.*	*Trade Name*	*Established name*	*Year of Approval*	*Class: ATC2*	*Abbreviated Indication*	*CDER Approval (Current Division)*
NON-ONCOLOGY							
1	125276	ACTEMRA	tocilizumab	2010	Immunosuppressants	Adult Patients With Moderately-To Severely- Active Rheumatoid Arthritis	DPARP
2	125472	ACTEMRA	tocilizumab	2013	Immunosuppressants	Rheumatoid Arthritis (Ra)	DPARP
3	125370	BENLYSTA	Belimumab	2011	Immunosuppressants	Active, Autoantibody-Positive Systemic Lupus Erythematosus	DPARP
4	761033	CINQAIR	Cinqair	2016	Drugs for obstructive airway diseases	Severe Asthma In Patients With Elevated Blood Eosinophils	DPARP
5	125504	COSENTYX	secukinumab	2015	Immunosuppressants	Treatment Of Psoriasis	DDDP
6	125274	DYSPORT	abobotulinumtoxinA	2009	Muscle relaxants	Treatment Of Adults With Cervical Dystonia	DNP
7	125274	DYSPORT	abobotulinumtoxinA	2009	Muscle relaxants	Temporary Improvement In The Appearance Of Moderate To Severe Glabellar Lines Associated With Procerus And Corrugator Muscle Activity In Adult Patients, <65 Years Of Age	DDDP
8	125476	ENTYVIO	vedolizumab	2014	Immunosuppressants	Adult Ulcerative Colitis	DGIEP
9	125507	ENTYVIO	vedolizumab	2014	Immunosuppressants	Adult Crohn'S Disease	DGIEP

APPENDIX I

No.	*BLA No.*	*Trade Name*	*Established name*	*Year of Approval*	*Class: ATC2*	*Abbreviated Indication*	*CDER Approval (Current Division)*
10	125387	EYLEA	aflibercept	2011	Ophthalmologicals	Treatment Of Patients With Neovascular (Wet) Age-Related Macular Degeneration (Amd)	DTOP
11	125319	ILARIS	Canakinumab	2009	Immunosuppressants	Cryopyrin-Associated Periodic Syndromes (Caps)	DPARP
12	125422	JETREA	ocriplasmin	2012	Ophthalmologicals	Treatment Of Symptomatic Vitreomacular Adhesion	DTOP
13	125561	KANUMA	Sebelipase alfa	2015	Alimentary tract and metabolism	Adult- Lysosomal Acid Lipase (Lal) Deficiency	DGIEP
14	125561	KANUMA	Sebelipase alfa	2015	Alimentary tract and metabolism	Pediatric- Lysosomal Acid Lipase (Lal) Deficiency	DGIEP
15	125390	MYALEPT	metreleptin	2014	Other alimentary tract and metabolism products	Treatment Of The Complications Of Leptin Deficiency In Patients With Congenital Or Acquired Generalized Lipodystrophy	DMEP
16	125511	Natpara	Recombinant Human Parathyroid Hormone or (rhPTH[1-84])	2015	Calcium homeostatis	Hypoparathyroidism Associated Hypocalcemia	DMEP
17	125526	NUCALA	mepolizumab	2015	Drugs for obstructive airway diseases	Add-On Maintenance Treatment Of Patients With Severe Asthma Aged 12 Years And Older, And With An Eosinophilic Phenotype	DPARP

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18	125288	NULOJIX	belatacept	2011	Immunosuppressants	Prophylaxis Of Organ Rejection In Adult Patients Receiving A Kidney Transplant, In Combination With Basiliximab Induction, Mycophenolate Mofetil, And Corticosteroids	DTOP
19	125499	Plegridy	peginterferon beta-1a	2014	Immunostimulants	Relapsing Multiple Sclerosis	DNP
20	125559	PRALUENT	alirocumab	2015	Lipid modifying agents	Heterozygous Familial Hypercholesterolemia Or Clinical Atherosclerotic Cvd, Who Require Additional Lowering Of Ldl-C	DMEP
21	761025	PRAXBIND	idarucizumab	2015	All other therapeutic products	Reversal Of The Anticoagulant Effects Of Dabigatran Is Needed	DHP
22	125320	PROLIA	denosumab	2010	Drugs for treatment of bone diseases	Treatment Of Postmenopausal Women With Osteoporosis At High Risk For Fracture	DBRUP
23	125075	RAPTIVA	efalizumab	2003	Immunosuppressants	Chronic Moderate To Severe Plaque Psoriasis	DDDP
24	125349	Raxibacumab	raxibacumab	2012	Immune sera and immunoglobulins	Inhalational Anthrax	DAVP

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25	125522	REPATHA	evolocumab	2015	Lipid modifying agents	Heterozygous Or Homozygous Familial Hypercholesterolemia (Hefh/Hofh) Or Clinical Atherosclerotic Cvd, Who Require Additional Lowering Of Ldl-C	DMEP
26	125289	SIMPONI	golimumab	2009	Immunosuppressants	Moderately To Severely Active Rheumatoid Arthritis (Ra) In Adults, In Combination With Mtx; Active Psoriatic Arthritis (Psa) In Adults, Alone Or In Combination With Mtx; Active Ankylosing Spondylitis In Adults (As)	DPARP
27	125433	SIMPONI ARIA	golimumab	2013	Immunosuppressants	Adult Patients With Moderately To Severely Active Rheumatoid Arthritis (Ra) In Combination With Mtx	DPARP
28	125166	SOLIRIS	eculizumab	2007	Immunosuppressants	Treatment Of Patients With Paroxysmal Nocturnal Hemoglobinuria (Pnh) To Reduce Hemolysis	DHP
29	125261	STELARA	ustekinumab	2009	Immunosuppressants	Treatment Of Psoriasis	DDDP

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30	125513	STRENZIQ	asfotase alfa	2015	Other alimentary tract and metabolism products	Treatment Of Patients With Perinatal/Infantile-And Juvenile- Onset Hypophosphatasia (Hpp)	DGIEP
31	125496	SYLVANT	siltuximab	2014	Immunosuppressants	Treatment Of Patients With Multicentric Castleman'S Disease (Mcd)	DHP
32	125521	TALTZ	ixekizumab	2016	Immunosuppressants	Treatment Of Adults With Moderate-To-Severe Plaque Psoriasis	DDDP
33	125431	TANZEUM	albiglutide	2014	Drugs used in diabetes	Adults With Type 2 Diabetes Mellitus	DMEP
34	125469	TRULICITY	dulaglutide	2014	Drugs used in diabetes	Adults With Type 2 Diabetes Mellitus	DMEP
35	125460	VIMIZIM	elosulfase alfa	2014	Other alimentary tract and metabolism products	Mucopolysaccharidosis Type Iva (Mps Iva; Morquio A Syndrome)	DGIEP
36	125338	XIAFLEX	collagenase clostridium histolyticum	2010	Other drugs for disorders of the musculo-skeletal system	Dupuytren's Contracture	DPARP
ONCOLOGY							
37	125236	ARZERRA	ofatumumab	2009	Antineoplastic agents	Treatment Of Patients With Chronic Lymphocytic Leukemia (Cll)	DOP

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38	125557	BLINCYTO	blinatumomab	2014	Antineoplastic agents	Adult- Philadelphia Chromosome-Negative Relapsed Or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia (All)	DHP
39	125557	BLINCYTO	blinatumomab	2014	Antineoplastic agents	Pediatric- Philadelphia Chromosome-Negative Relapsed Or Refractory B-Cell Precursor Acute Lymphoblastic Leukemia (All)	DHP
40	125477	CYRAMZA	ramucirumab	2014	Antineoplastic agents	2L Treatment For Advanced Gastric Cancer Or Gastro-Esophageal Junction Adenocarcinoma, As A Single-Agent	DOP
41	761036	DARZALEX	daratumumab	2015	Antineoplastic agents	Multiple Myeloma, If Received 3 Prior Lines Of Therapy Including A Proteasome Inhibitor And Immunomodulatory Agent	DHP
42	761035	EMPLICITI	elotuzumab	2015	Antineoplastic agents	Treatment Of Patients With Multiple Myeloma In Combination With Lenalidomide And Dexamethasone	DHP

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43	125084	ERBITUX	cetuximab	2004	Antineoplastic agents	In Combination With Irinotecan, In The Treatment Of Egfr-Expressing Metastatic Colorectal Carcinoma	DOP
44	125486	GAZYVA	obinutuzumab	2013	Antineoplastic agents	Patients With Chronic Lymphocytic Leukemia, In Combination With Chlorambucil	DHP
45	125427	KADCYLA	ado-trastuzumab emtansine	2013	Antineoplastic agents	Treatment Of Patients With Her2-Positive, Metastatic Breast Cancer	DOP
46	125514	KEYTRUDA	pembrolizumab	2014	Antineoplastic agents	Treatment For Unresectable Or Metastatic Melanoma And Disease Progression	DOP
47	761038	LARTRUVO	olaratumab	2016	Antineoplastic agents	Treatment In Combination With Doxorubicin Of Adult Patients With Soft Tissue Sarcoma (Sts)	DOP
48	125554	OPDIVO	nivolumab	2014	Antineoplastic agents	The Treatment Of Patients With Unresectable Or Metastatic Melanoma	DOP

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49	125409	PERJETA	pertuzumab	2012	Antineoplastic agents	Treatment Of Her2-Positive Metastatic Breast Cancer In Combination With Trastuzumab And Docetaxel	DOP
50	125547	PORTRAZZA	Necitumumab	2015	Antineoplastic agents	Treatment Of Patients With Squamous Non-Small Cell Lung Cancer	DOP
51	761034	TECENTRIQ	atezolizumab	2016	Antineoplastic agents	Treatment Of Patients With Locally Advanced Or Metastatic Urothelial Carcinoma	DOP
52	125516	UNITUXIN	dinutuximab	2015	Antineoplastic agents	Treatment Of Neuroblastoma	DOP
53	125147	VECTIBIX	panitumumab	2006	Antineoplastic agents	Treatment Of Egfr-Expressing, Metastatic Colorectal Carcinoma With Disease Progression On Or Following Fluoropyrimidine-, Oxaliplatin-, And Irinotecan-Containing Chemotherapy Regimens.	DOP
54	125377	YERVOY	ipilimumab	2011	Antineoplastic agents	Treatment Of Unresectable Or Metastatic Melanoma	DOP

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55	125418	ZALTRAP	ziv-aflibercept	2012	Antineoplastic agents	Patients With Metastatic Colorectal Cancer (Mcrc) In Combination With Folfiri	DOP