Breakthrough Therapy Designation:

Challenges and Opportunities for Innovative Drug Development – A Three-Year Review after PDUFA V

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät

der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von

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Bonn 2016

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Danksagung

An erster Stelle gebührt mein Dank Herrn Dr. Max Wegner, der meine Masterarbeit betreut und begutachtet hat. Für die hilfreichen Anregungen und die konstruktive Kritik bei der Erstellung dieser Arbeit möchte ich mich herzlich bedanken.

Auch Herrn Dr. Michael Berntgen gilt mein besonderer Dank für die Übernahme des Zweitgutachtens der vorliegenden Arbeit.

Ganz herzlich danke ich auch meinen Managern, Frau Kinga Komar-Malinowska und Herr Dr. Gerhard Schlueter, für die zahlreichen interessanten Debatten und Ideen, die maßgeblich dazu beigetragen haben, dass diese Masterarbeit in dieser Form vorliegt.

Ein weiterer herzlicher Dank geht an meine Eltern, die stets an mich glaubten, mir diesen weiterbildenden Studiengang durch ihre Unterstützung ermöglichten, und stets ein offenes Ohr für meine Sorgen hatten.

Doch der größte Dank gilt meinem Verlobten für all die Unterstützung, Geduld und Ermutigung als meinen starken emotionalen Rückhalt und auch für jedes Lächeln, das stets so viel Freude und Zuversicht schenkt.

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Executive Summary

Background: Advances in the science increase significant numbers of drug candidates that show extraordinary effects at early stages of drug development, which challenge the traditional approach to clinical development and FDA`s standards for tolerability and efficacy. The Breakthrough Therapy Designation (BTD) was introduced as part of the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012, to facilitate development and review of drugs and biologics that address unmet medical needs in the treatment of serious or life-threatening conditions.

Objective: Since the inception of BTD program, the number of requests to the FDA has been continuously increased over the years, showing its popularity for pharmaceutical industry. The 22 NMEs with previous BTD have received first-ever approvals by the FDA and have been collected as case studies to represent the impact of BTD program on innovative drug development in the global convergence. Some key measures are pre-defined to evaluate the impact of BTD on drug development, e.g., the grade of combination with other expedited tools, the review time, and the development time and the approval basis. Analyzing the complied post-marketing activities serves to understand the kinds of flexibility that the FDA might commit to BTD approvals. To gain a whole picture of current global convergence of breakthrough therapy, the regulatory status of the 22 case studies in the key ICH region (EU and Japan) are also investigated in this master thesis.

Key findings:

- All of the 22 approved BTD drugs received at least one additional expedited tool by the FDA to maximize the acceleration of development program. As shown in comparison analysis with non-BTD novel drugs, the approved BTD drugs trend to combine more frequently with other expedited tools to accelerate review and pre-market development.
- All of the 22 approved BTD drugs received priority review by the FDA: the average review time of 6.4 months was observed among all indications, which was 3.3 months faster than the average review time of non-BTD drugs under priority review.

- The drugs which were granted as BTD in their early development presented very fast development paths: from IND until approval within 4 years, based on single-arm non-randomized pivotal phase I or phase II trials as accelerated approvals.
- The drugs which the BTD was granted during or after filing could also expect additional benefit from the BTD program, e.g. expedited review, extended resources by the FDA to review additional data, intensive guidance and flexibility by the FDA for CMC readiness.
- A delayed access of 22 BTD drugs to patients underlying serious diseases in the EU as well as the "drug-lag" in Japan were observed, partly due to delayed submission by sponsors and partly due to longer review time and different fundament of decision making by agencies.

Conclusion: The retrospective analysis based on the 22 case studies indeed demonstrate the positive impacts of BTD on innovative drug development, as committed by the FDA. The BTD creates a regulatory environment offering unique benefits from the FDA to expedite access to breakthrough therapy to patients underlying serious diseases with high unmet medical need. It is also important to understand that the BTD is not a guarantee of success but is correlated with certain risks and limitations. It is the sponsor´s own responsibility to overcome all challenges associated with the expedited development pathway. The EMA and PMDA has been developing similar regulatory environment for breakthrough therapies. It will be interesting to analyze the PRIME scheme and Sakigake after two or three years of launch to evaluate this global convergence of BTD program.

Abbreviations

AA	Accelerated Approval
ALK	Anaplastic Lymphoma Kinase
ALL	Acute Lymphoblastic Leukemia
BA	Bio Availability
BC	Breast Cancer
BCRP	Breast Cancer Resistant Protein
BIRC	Blinded Independent Central Review Committee
BLA	Biologics License Applications
BTD	Breakthrough Therapy Designation
BTDR	Breakthrough Therapy Designation Request
CAT	Committee for Advanced Therapies
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDPL	Cross-Disciplinary Project Lead
CF	Cystic Fibrosis
CHMP	Committee for Medicinal Products for Human Use
CLL	Chronic Lymphocytic Leukemia
CMA	Conditional Marketing Authorization
CMC	Chemistry, Manufacturing and Controls
CR	Complete Remission
CR/CRh	the Rate of CR to CR with Partial Hematological Recovery
DDI	Drug Drug Interaction
DoR	Duration of Response
DP	Drug Product
DS	Drug Substance
EC	European Commission
EMA	European Medicines Agency
ER	Estrogen Receptor
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FiM	First in Man

FTD	Fast Track Designation
HCP	Host Cell Protein
HCV	Hepatitis C Virus
HER	Human Epidermal Growth Factor Receptor
HPP	Hypophosphatasia
HR	Hazard Ratios
HTA	Health Technology Assessment
ICH	International Council on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	Investigational New Drug
IPF	Idiopathic Pulmonary Fibrosis
LAL	Lysosomal Acid Lipase
MAPP	Manuals of Policies and Procedures
MCL	Mantle Cell Lymphoma
MHLW	Ministry of Health, Labour, and Welfare (Japan)
MM	Multiple Myeloma
MPC	Medical Policy Council
MRD	Minimal Residual Disease
NDA	New Drug Application
NMEs	New Molecule Entities
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
PFS	Progression Free Survival
Ph	Phase
PMC	Post-Marketing Commitments
PMR	Post-Marketing Requirements
PDUFA	Prescription Drug User Fee Act
PMDA	Pharmaceuticals and Medical Devices Agency (Japan)
PoC	Proof of Concept
PPQ	Process Performance Qualification
PR	Priority Review
PRIME	PRIority MEdicines

Pts	patients
RCC	Renal Cell Carcinoma
REMS	Risk Evaluation and Mitigation Strategy
RFS	Relapse-Free Survival
RPM	Regulatory Project Manager
SMEs	Small and Medium-sized Enterprises
SoC	Standard of Care
WM	Waldenström`s Macroglobulinemia

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1. Introduction of Breakthrough Therapy Designation Program

Breakthrough Therapy Designation (BTD) was established by the Food and Drug Administration Safety and Innovation Act (FDASIA) of 2012[i], as one of four expedited programs to facilitate development and review of drugs and biologics that address unmet medical needs in the treatment of serious or life-threatening conditions. Three of the expedited programs[ii], the accelerated approval (AA), priority review (PR) and fast track designation (FTD), were established in the early and late 90`s and all played a meaningful role in reducing development and review timelines for the drugs that met their criteria[ii] (Table 1).

Table 1 Overview of key features and limitation of four FDA expedited programs:
(Accelerated Approval, Priority Review, Fast Track Designation, Breakthrough Designation)

	Accelerated Approval	Priority Review	Fast Track Designation	Breakthrough Designation
Years	1992	1992	1997	2012
Legal basis	under Subpart H of FDA's New Drug, Antibiotic, and Biological Products regulations	through the passage of the Prescription Drug User Fee Act (PDUFA) 1992	under section 112 (Subpart E) of the Food and Drug Administration Modernization Act.3	through the passage of the Prescription Drug User Fee Act (PDUFA) 2012
Features	+ Reduce **development** time (approval based on surrogate endpoint to predict clinical benefit)	+ Reduce **review** time	+ Reduce **review** time via ``rolling submission``; Accelerate **development** via more frequent interactions	+ Reduce **development** time; Expedite **review** process; Organizational and procedural commitment; Benefit from other program; Flexibility by FDA;
	- No impact on review process; Confirmatory studies needed to prove predicted efficacy and safety	- No impact on development time	- No impact on pivotal trials (enrollment, design, size)	- High rate of denials for application

Nevertheless, none of them are able to shorten the time needed to conduct the major pivotal trials or minimize the number of patients being treated in a placebo or comparative standard of care arm[iii]. In recent years, advances in science increased significant numbers of drug candidates that show extraordinary effects at early stages of drug development, which challenged the

traditional approach to clinical development and FDA`s standards for tolerability and efficacy. Advancing Breakthrough Therapies for Patients Act were introduced into legislation as part of the 2012 PDUFA reauthorization which formed the statutory framework for BTD. The BTD program is distinct from FDA's other expedited programs both in terms of the level of evidence required and the type of engagement that sponsors subsequently receive from the FDA during clinical development.

1.1. Application of Breakthrough Therapy Designation

In general, a sponsor could submit a request for breakthrough therapy designation with the submission of a new Investigational New Drug (IND), or as an amendment to an active IND. Prior to submitting the BTD, a sponsor can request and submit the *"Preliminary Breakthrough Therapy Designation Request Advice"* template as a formal amendment to the IND. A subsequent teleconference between the sponsor and the review division will be set up and a recommendation whether a request for a BTD is appropriate will be made. This Agency's recommendation is an ``advise`` only and is not to be interpreted to predict the Agency's decision on the BTD request. Once a sponsor submits the request to BTD, the FDA will generally respond to the review of IND submissions within 60 days[iv]. The FDA Regulatory Project Manager (RPM) will coordinate and respond to any questions raised by a sponsor outside of formal meetings within 30 days. During these correspondences, all substantial agreements or commitments will be officially documented in the IND administrative file within 15 working days after sending out the response to the sponsor.

In the Center for Drug Evaluation and Research (CDER), which receives the bulk of the requests, the BTD applications are first reviewed by the relevant clinical division, which makes a preliminary assessment. The case is then presented to the CDER's Medical Policy Council (MPC) with participation by the Center for Biologics Evaluation and Research (CBER), which assesses conformance to the developing policies and makes a recommendation to the Office of New Drugs, to make the final decision. This process is intended to keep consistent policy development and cross-organizational learning without being overly intrusive in the day-to-day business[v]. Multiple policy issues related to implementation of the program have arisen, and continue to arise, as requests are evaluated.

1.2. Qualifying Criterion for Breakthrough Therapy Designation

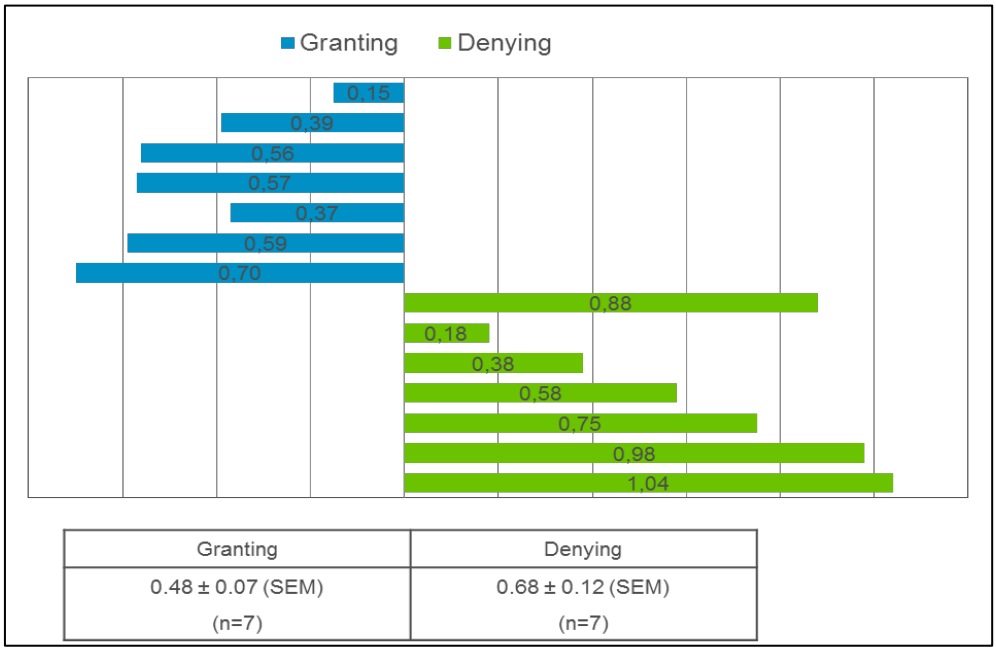
Since launch of BTD by the FDA, sponsor interest in the BTD program has been fairly constant over time. The BTD requests cover a wide range of therapeutic areas: the majority from oncology/hematology, followed by respiratory and infectious disease, but also from cardiovascular disease, ophthalmology, dermatology, gastrointestinal disease and neurological disorders. Antivirals had the highest proportion of grants (41%) as compared to oncology (31%) and other indications (28%). Some of the indications present as ``priority indications`` with several candidates granted BTD under the same indication, including non-small cell lung cancer (NSCLC), chronic lymphocytic leukemia (CLL), cystic fibrosis (CF), hepatitis C virus infection (HCV) and idiopathic pulmonary fibrosis (IPF). Within these indications, novel mechanisms of action have been the focus.

There has been a noticeable absence of drugs in areas such as cardiovascular disease. During 2013 and 2014 only two agents to treat cardiovascular diseases have received BTD (Mydicar to treat heart failure granted on the April 4th 2014 and Serelaxin to treat acute heart failure granted on June 6th 2013) and the year of 2015 shows a total absence.[vi] So far, none of both agents have been approved and Serelaxin even received complete response after granting BTD.

As of September 30th 2015[vii], the FDA has received a total of 341 requests for BTD: only 111 (33%) requests were granted while 185 (54%) were denied and 45 (13%) were withdrawn. It is notable that the rate of granting BTD request remains 30% consistently over the year 2013 to 2015[vii]. The higher rate of failure for breakthrough therapy designation requests showed the less clarity from both sponsors and the FDA on qualifying criterion of a breakthrough therapy as compared to what qualifies for fast track. According to FDA released Expedited Programs guidance[ii], a candidate therapy must be intended to treat a serious or life-threatening illness, and preliminary clinical evidence must indicate that the therapy may demonstrate a substantial improvement over existing therapies on at least one clinically significant endpoint. It is important to note that the FDA defines "*available therapy*" as drugs that have received full FDA approval[ii], excluding drugs that have not been fully approved (e.g. received accelerated approval) or drugs that are still in the investigation phase (e.g. under an IND).

The FDA relies on three primary considerations: 1) the quantity and quality of the clinical evidence being submitted in a designation request; 2) the available therapies that the drug is being compared to; and 3) the magnitude of treatment effect shown. Although these three considerations are clear, it is difficult to define a single threshold that a therapy must meet in order to receive the designation. Under this background, the Center for Health Policy at the Brookings Institution convened a public meeting in agreement with FDA to enhance clarity and understanding of the qualifying criteria for BTD[viii]. The analysis based on case studies found unsurprising trends in terms of clinical trial evidence. Regarding the quantity of clinical trials, the high quality data from one trial tends to be better than lower quality data from many trials. Among granted BTD, 67% were based on data from one single trial. The randomized trials were not always necessary to gain breakthrough status: 39% of those who received grants did not submit data from randomized trials compared to 46% of those who received denials[viii]. In terms of trial enrollment, the appropriate number of patients relying on the specific indications and nature of drugs and the success of granting BTD was not necessarily correlated with number of patients[viii]. In terms of biostatistics, hazard ratios (HRs) used as a standardized method of comparing treatment effects for randomized trials particularly for oncology and hematology BTD requests, were more favorable for grants than for denials. In review materials of 14 BTD requests (Figure 1), HRs seem to average in 0.48 for grants and 0.68 for denials[viii], however, as stated by the FDA, no clear threshold is apparent.

Figure 1 Exploring thresholds of Hazard Ratios for granting or denying BTD requests
(Based on case study analysis performed by the Brookings Institution convened with the FDA on the April 24th 2015)



Granting	Denying
0.48 ± 0.07 (SEM) (n=7)	0.68 ± 0.12 (SEM) (n=7)

In general, the FDA recognizes that there is no "one size fits all" approach when assessing BTD applications and that granting BTD requests is a multi-factorial decision that still needs to be learned and refined. Overall, the FDA has given the advice that "quality trumps quantity," meaning one high-quality trial would have a higher likelihood of being granted BTD status than multiple low-quality trials. A sponsor may seek FDA input prior to submitting the BTD application via BTD request advice and build rapporteur-ship with FDA to create a culture focused on good science throughout collaboration and communication between the FDA and sponsor. To prepare a BTD request, the sponsor should thoroughly assess "*available therapies*" (or standard of care (SoC), where no therapies exist) and design robust Proof of Concept (PoC) studies in the early phases of development[ix].

Many BTD requests were withdrawn prior to FDA granting or denying the request, for administrative reasons or due to potential denial indicated by the division. Some of the small- or medium-sized enterprises (SMEs) approached BTD request as ``try`` to gain any potential expedited tool granted by the FDA. The most common reason for denial was the reliability of clinical evidence submitted. The clinical evidence was too preliminary, such as very small number of patients studied, anecdotal case reports, and inadequate duration of follow-up. The

novel biomarker or surrogate endpoint could not be translated into a meaningful benefit with sufficient evidence. The submitted post-hoc analyses demonstrated the failed studies that identify a subset that may benefit. The second most common reason for denial was the failure to demonstrate "substantial" improvement over available therapy. Moreover, other miscellaneous reasons for denial included lack of clinical evidence, incomplete data, tolerability concerns, and not treating a serious condition.

1.3. Resubmission of previously denied BTD requests

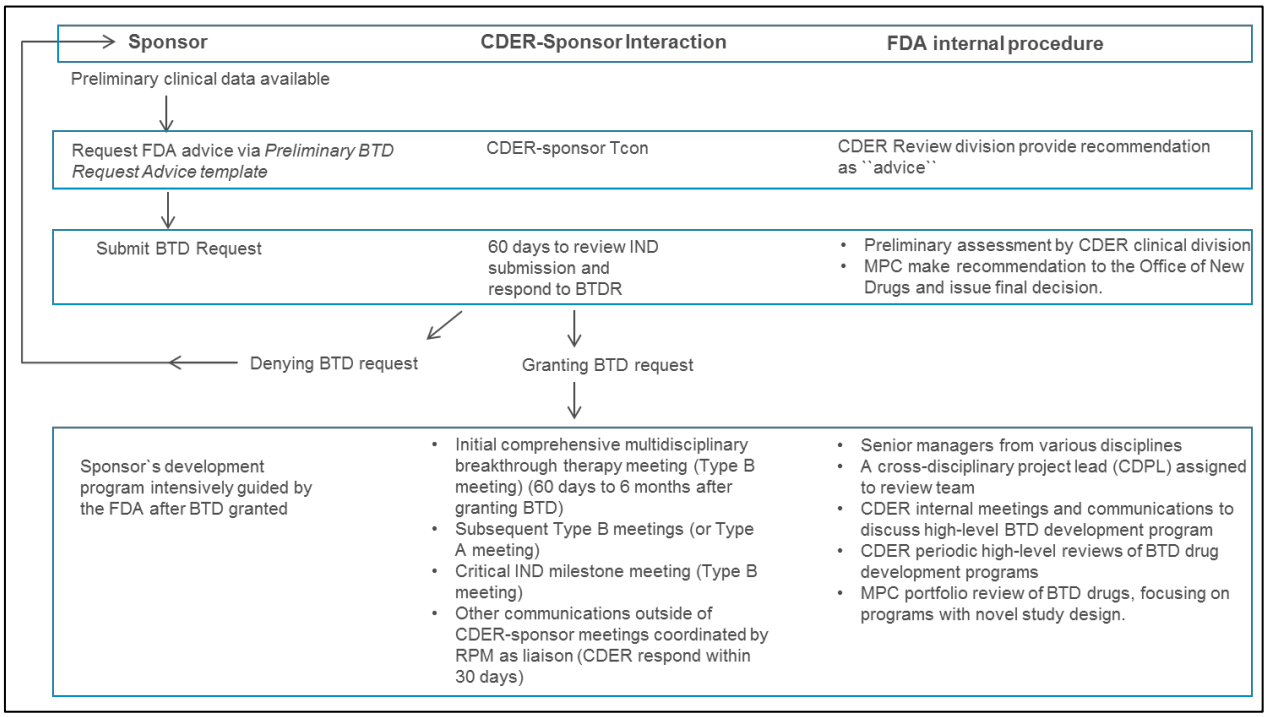
Although a drug might be denied or withdrawn for BTD status on its first round, the sponsors can still reapply and make another request when additional clinical data become available. For example, the Ariad's initial BTD application for AP26113 in indication of anaplastic lymphoma kinase (ALK)-positive NSCLC was denied in August 2013. This initial BTD request was based on an analysis of 24 evaluable patients in the phase I segment of a multi-center Phase I/II trial, demonstrating 14 partial responses and one complete response in a Xalkori-naïve patient. The FDA denied this initial BTD request due to the "*relatively short follow-up*" and small patient population in its trial. But one year later in October 2014, Ariad submitted additional clinical data from phase II segment of the same phase I/II trial. The request on BTD status was based on an analysis of 72 evaluable patients with ALK-positive NSCLC. In the 65 evaluable patients treated with prior crizotinib, the objective response rate (ORR) of 72%, the median duration of response (DoR) of 49 weeks and the median progression-free survival (PFS) of 56 weeks were demonstrated by AP26113 treatment. In the 7 treatment-naïve ALK-positive NSCLC patients, AP26113 demonstrated 2 complete responses and 5 partial responses for an ORR of 100%. Based on those additional submitted clinical data the FDA finally granted BTD status for AP26113.

1.4. Key features of Breakthrough Therapy Designation

Once BTD is granted (Figure 2), the FDA will closely collaborate with sponsors in a dynamic, multi-disciplinary process to expedite the development program to ensure an early access of innovative medicine to patients with underlying serious disease condition with unmet medical needs[ii]. The FDA commits the sponsor with timely advice and interactive communications

throughout drug development. Beginning as early as phase I, the FDA will intensively guide the sponsor for an efficient drug development program. As examples, interim analyses of trial data could be used as well as the alternative clinical trial designs (e.g. adaptive designs, use of historical controls) could be proposed to FDA which might lead to smaller or more efficient trials to expedite development program.

Figure 2 Overview of FDA and Sponsor interactions during BTD drug development



As an organizational commitment, the FDA will intensively involve senior managers from various disciplines and experienced review and regulatory health project management staff for a proactive, collaborative and cross-disciplinary review. A cross-disciplinary project lead (CDPL) will be announced as the scientific liaison between the various cross-functional members of the review team (e.g. pharmacology, toxicology, statistics). The CDPL works closely with the regulatory project manager (RPM), updating the division director on progress of assigned BTD program. Additionally, the CDER Breakthrough Therapy Program Manager will oversee all BTD products under review to ensure policy development of the BTD program and to correspond internal and external inquiries about the BTD program.

In order to demonstrate how BTD should be managed within the FDA, a series of manuals of policies and procedures (MAPP) were published to document good review practices on the specifics of the BTD by the Office of New Drugs. The first MAPP[iv] published in July 2014, entitled *Good Review Practice: Management of Breakthrough Therapy Designated Drugs and Biologics*, detailed procedures as to how the FDA reviewer should manage BTD applications, in terms of review timelines for IND-related submissions, types of additional meetings afforded for BTD, as well as roles and responsibilities of FDA personnel associated with the BTD program. The second MAPP[x] published in March 2015, entitled ``*Good Review Practice: The Review of Marketing Applications for Breakthrough Therapy Designated Drugs and Biologics*`` outlined CDER actions taken from the time of application for Biologics License Application (BLA) or New Drug Application (NDA) submission until an action is taken on the application. This MAPP details the procedure of expedited review for BTD products, when an advisory committee meeting convened can be expected by sponsors, and prevents the inspection delays of clinical, clinical pharmacology, and manufacturing sites.

Once qualified for an expedited review, the FDA review team is obligated to complete their expedited review at least one month before the PDUFA goal date. The qualifying criteria for a BTD drug to be considered for an expedited review are such as (1) preliminary review of the clinical trial results shows that the drug has demonstrated substantial improvement over existing therapies, (2) the application qualifies for a priority review, and (3) the review team has determined that a first cycle approval is likely. However, whether BTD drugs are eligible for this expedited review has to be evaluated on a case-by-case basis at the time point of the NDA/BLA filing, depending on other factors, e.g. resource issue, conduct of the advisory committee meeting, requirement on Risk Evaluation and Mitigation Strategy (REMS) or identified manufacturing issues. Additionally, MAPP has also outlined the advantage of rolling review afforded by BTD. Sponsors are encouraged to submit the manufacturing portions as early as possible to prevent any issues that might arise from delaying a marketing approval[ix].

Another unique aspect of this MAPP is the opportunity to have additional FDA meetings beyond the typical developmental milestone interactions (e.g. pre-IND, end of Phase I, end of Phase II, and pre-NDA). A key meeting uniquely afforded by BTD is the Initial Comprehensive Multi-

Disciplinary Breakthrough Therapy Meeting, which allows the FDA and sponsors to discuss the high-level clinical development plan to expedite the drug development process. In this meeting a communication plan will be established to account for additional meetings needed outside of the typical developmental milestone meetings for BTD development program. The standard milestone meetings can also begin much earlier than those in traditional clinical development.

2. Objective of Master Thesis

This master thesis is based on the retrospective analysis of case studies to explore deep insight into the impact of BTD on innovative drug development. The selected case studies are the 22 novel New Molecule Entities (NMEs) which were previously granted as BTD and were approved as original NDA or BLA by the CDER. The lessons learned from approved BTD drugs in US as well as in key ICH regions (EU and Japan) will also be shared and discussed in this thesis. The published materials consisting of journal articles, press releases, government documents, and news articles from top pharmaceutical publishers were identified through online databases (i.e., PubMed), the health authority websites (FDA, EMA, PMDA), and Internet search engines (e.g., Google) in order to capture a complete picture of this program.

An overview on approved BTD drugs up to December 31st 2015 will be presented in terms of their drug nature and their clinical development stages when BTD status was granted. To investigate the impact of BTD on drug development, some key measures are defined, e.g. the use of other expedited tools, the approval time, the clinical pre-market development time and the approval basis. Some selected case studies will be presented to outline how BTD impacted the drug development program: case studies which the BTD were granted at the early development stage (phase I or at the early stage of Proof of Concept Phase II study) as well as case studies in which the BTD were granted after NDA/BLA filing, in order to gain a whole picture of multiple-dimensional impact of BTD.

To compensate the high regulatory approval standards with expedited development program of BTD, the FDA agreed with sponsors to complete some of their development activities as post-marketing commitments or requirements, to make possible early access of innovative therapeutics to patients underlying serious disease with unmet medical needs. In this second part of the analysis, the complied post-marketing activities will be presented and discussed by using case studies, in order to understand the kinds of flexibility that the FDA might commit to BTD approvals.

In the third part of the analysis, the impact of BTD on global regulatory convergence will be investigated, focusing on the key ICH regions of EU and Japan. The regulatory status of these 22

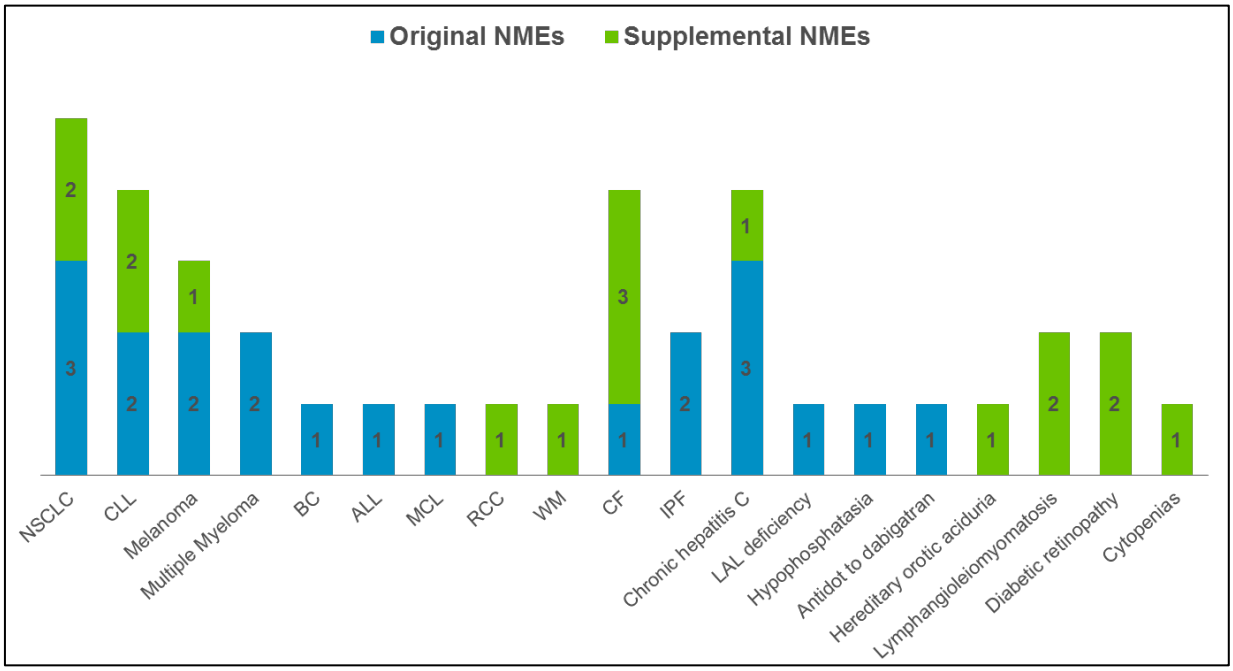
selected case studies in EU and Japan will be demonstrated and analyzed to gain a whole picture of current global convergence of breakthrough therapy.

At the end, the challenges and opportunities of BTD on innovative drug development will be discussed based on the retrospective analyses of case studies after three years` launch of BTD. The impact of BTD program on global regulatory environment and the trends in key ICH regions will also be discussed.

3. Overview of approved BTD drugs in year of 2012-2015

From inception of BTD in July 09th 2012 up to December 31st 2015, 38 approvals were granted by CDER with previous designation as breakthrough therapy, including 24 original NDAs/BLAs and 14 supplemental NDA/BLAs, covering 19 different indications (Figure 3). In the calendar year 2012 none of approval with previous BTD was granted by the FDA. In the calendar year 2013, the first three NMEs with previous BTD were approved by the FDA, representing 11% of the total 27 NMEs approved for that calendar year. In 2014, nine NMEs with BTD were approved, accounting for 22% of the total 41 NMEs approved for that calendar year. Similarly, ten NMEs with BTD were approved in 2015, accounting for 22% of the total 45 NMEs approved for that calendar year. In terms of nature of drugs, 12 biologics and 17 small molecules were approved under BTD. Some of drugs were approved for multiple indications previously designated as breakthrough therapy (e.g. Imbruvica for MCL and CLL, Keytruda for melanoma and NSCLC, Opdivo for melanoma, NSCLC and RCC). The master thesis will focus on retrospective analysis of the 22 first-ever approved NMEs with previous BTD by the FDA from 2013 to 2015.

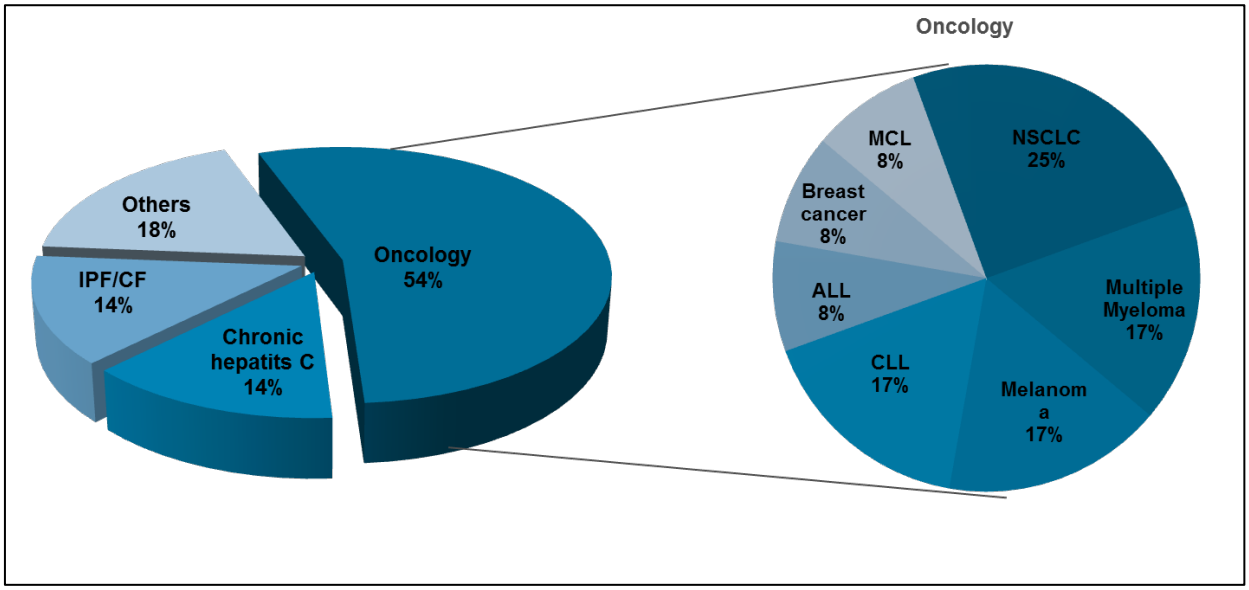
Figure 3 Overview of approved BTD indications in the year of 2013 to 2015



3.1. Insights in approved indication landscape

The 22 approved BTD drugs are distributed over the three top therapeutic areas oncology (54%), infectious disease (14%), and pulmonary disease (14%) (Figure 4). Moreover, the top oncology indications in which BTD drugs have been approved include non-small cell lung cancer (NSCLC) (25%), multiple myeloma (MM) (17%), melanoma (17%), chronic lymphocytic leukemia (CLL) (17%), mantle cell lymphoma (MCL) (8%), acute lymphoblastic leukemia (ALL) (8%), and breast cancer (BC) (8%). If supplemental approvals are considered, the oncology indication could be extended further to renal cell carcinoma (RCC) and Waldenström`s macroglobulinemia (WM) (Figure 3).

Figure 4 Insight in the indication landscapes of the 22 approved BTD drugs in the year of 2013 to 2015



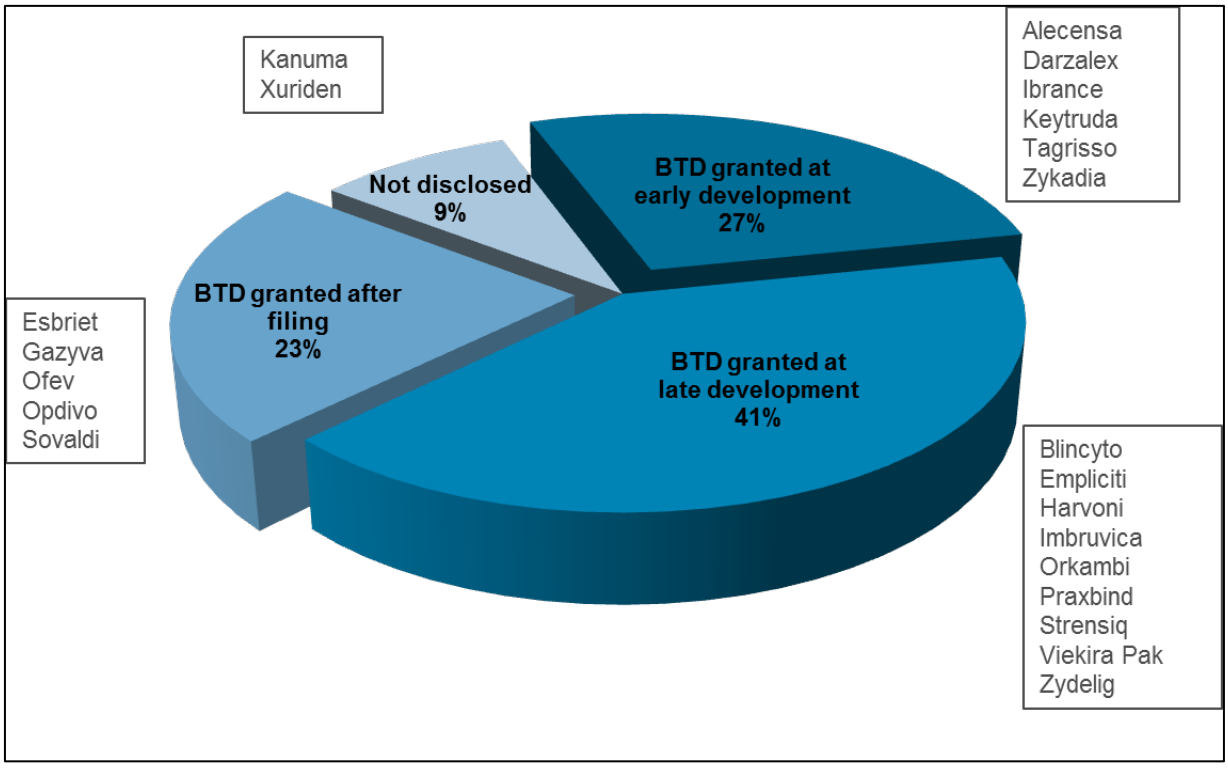
Of the 22 approved BTD drugs 77% are first-in-class for the approved indication. For patients with IPF, the approvals of Esbriet (pirfenidone) and Ofev (nintedanib) represent the first-ever FDA approved therapies to treat the underlying cause of IPF, rather than just the previously available symptomatic treatments. Nevertheless, five of approved BTD NMEs are not first-in-class and all are distributed in oncology, including ALK inhibitors (Alecensa, Zykadia) for NSLC, EGFR inhibitor (Targisso) for NSCLC, immunotherapy (Opdivo) for melanoma, as well as targeting CD20 (Gazyva) for CLL. This phenomenon points out that the BTD is primarily focusing

on the breakthrough for therapeutic option, not necessarily the breakthrough for novel mechanisms.

3.2. Insight in granting BTD status

The guidance has been enacted to expedite the whole development program. Ideally the request should be submitted as early as preliminary clinical data are available, recommended as no later than end of phase II. However, the designation may be granted during any different stage of development. Due to the very recent inception of BTD program from July 09th 2012, of the 22 approved BTD drugs the majority of their designations have been granted in the late development stage: 23% granted with or after NDA/BLA filing, 41% granted at the late development (phase III or end of phase II trials), while only 27% granted at the early development (phase I or early phase II trials) (Figure 5). All six drugs which are designated as BTD at the early development are all distributed in the therapeutic area of oncology, including Alecensa, Tagrisso and Zykadia for NSCLC, Keytruda for melanoma, Darzalex for MM, and Ibrance for BC.

Figure 5 Insight in the development stage at the time of granting BTD for the 22 approved BTD drugs



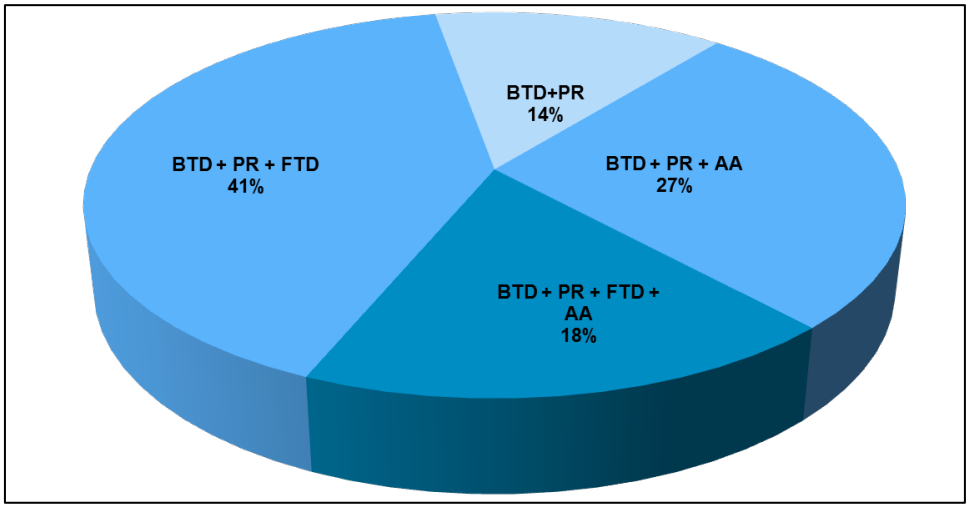
For the BTD requests submitted later in the clinical development timeline, the data showing clinical efficacy of treatment was not that challenging, but tolerability was more of a concern for the FDA in this case. Compared to that, for the BTD requests submitted in the early clinical development, the robust clinical data to demonstrate potential of significant treatment effect over available therapy could be very challenging.

4. Analysis of impacts of BTD on drug development

4.1. Analysis on impact of BTD with respect to use of other expedited tools

Once BTD is granted, FDA gives the sponsor the commitment to facilitate the development program, e.g. via intensive guidance, involving senior managers, as well as using other expedited tools in combination with BTD. Of the 22 approved BTD drugs, all received another expedited programs in addition to BTD: all 22 BTD drugs (100%) received priority review (PR); 10 BTD drugs (45%) received accelerated approval (AA); 13 BTD drugs (59%) received fast track designation (FTD) (Figure 6). Four of the 22 approved BTD drugs received even all four expedited tools by the FDA, e.g. Darzalex, Imbruvica, Opdivo, and Tagrisso, all for oncology indications. Of the 12 approved oncology BTD drugs, 9 approvals (75%) were based on surrogate endpoints as AA, while only 3 approvals (Empliciti for MM; Gazyva and Zydelig for CLL) as standard approvals.

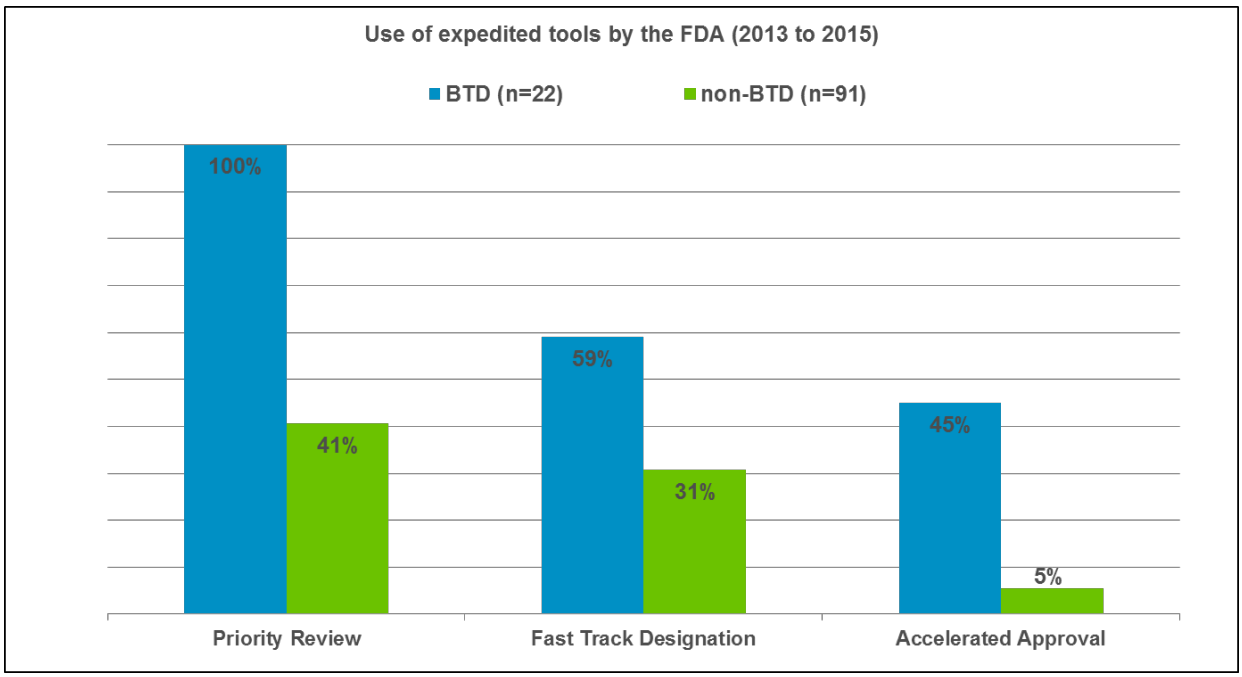
Figure 6 Insight in the combination with additional expedited tools for 22 approved BTD drugs



In the years from 2013 to 2015, the 113 NMEs were approved as novel drugs by the FDA including 22 BTD drugs and 91 non-BTD drugs (Figure 7). Comparing to the non-BTD NMEs, the expedited tools were significantly more frequently used for the BTD NMEs. While all 22 BTD drugs (100%) received priority review by the FDA, only 37 of non-BTD drugs (41%) benefited from this expedited review tool to reduce review time. Similar trends were also observed for the other expedited tools, AA and FTD. Comparing 59% of BTD drugs designated as FTD, only 31% of non-BTD drugs received this designation to facilitate development program. Of 22 BTD drugs,

10 (45%) were approved based on surrogate endpoints as AA to reduce pre-market development time. Of 91 non-BTD drugs, only 5 (5%) were approved based on surrogate endpoints as AA, while majority as standard approvals.

Figure 7 Comparing the frequency of combination with other expedited tools between the BTD (n=22) and the non-BTD drugs (n=91) in the year of 2013 to 2015

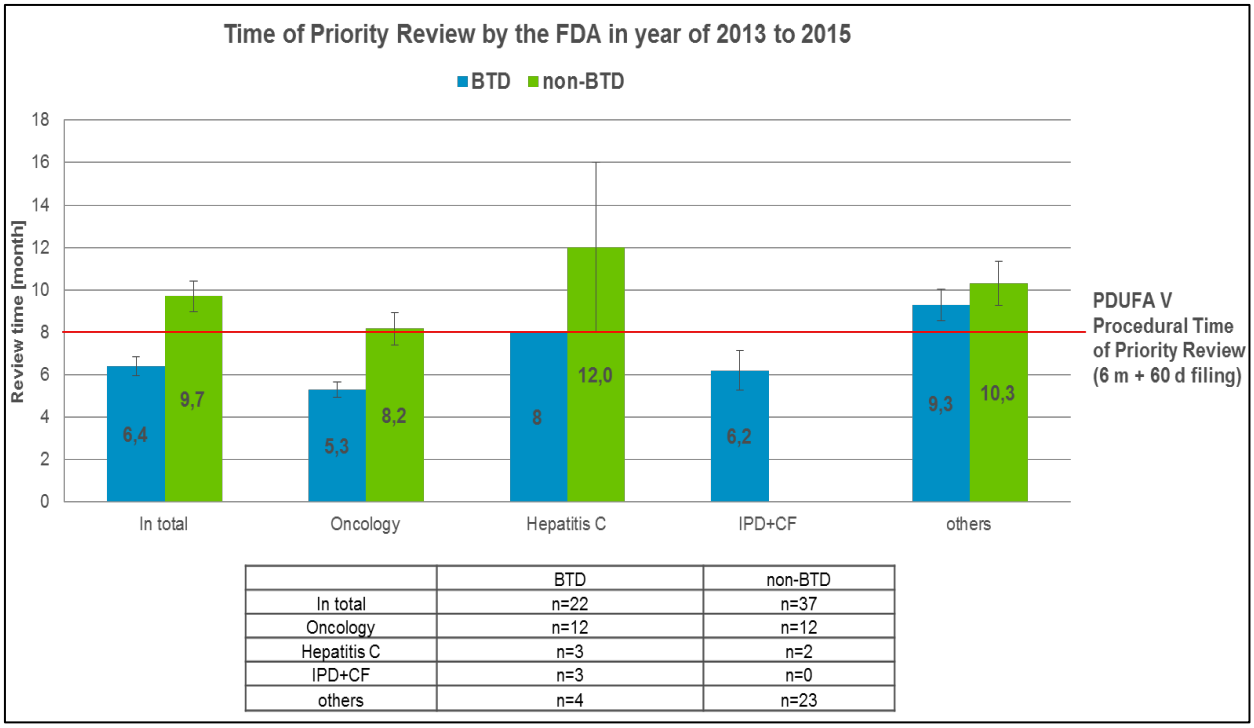


4.2. Analysis on impact of BTD with respect to review time

Once the BTD is granted, the investigational drug can move rapidly through the FDA review process by using different tools, e.g. priority review, expedited review, rolling application. In the analysis, the review time was defined as time between submission and approval, in case of rolling submission calculated from submission completion until approval. As discussed in section 4.1, all of the 22 approved BTD drugs were assessed under priority review. The overall average review time of all 22 BTD drugs was 6.4 months, in average 1.6 months faster than the PDUFA goal date for priority review (60 days filing time and 6 months' review time) (Figure 8: blue bars). Among all review divisions in CDER, the division for oncology and hematology has shown the shortest review time with 5.3 months. The fastest review was performed for Blincyto for oncology indication CLL: FDA approval was granted after just 76 days of review time. The

Strensiq for hypophosphatasia (HPP) and Kanuma for lysosomal acid lipase (LAL) deficiency were reviewed as priority review, nevertheless, due to the major amendment during review the PDUFA date was extended and final review time was 10 months and 11 months, respectively.

Figure 8 Analysis on review time of 22 BTD drugs as compared with 37 non-BTD drugs which were approved as priority review by the FDA in the year of 2013 to 2015
(Review time expressed as mean±SEM)



	BTD	non-BTD
In total	n=22	n=37
Oncology	n=12	n=12
Hepatitis C	n=3	n=2
IPD+CF	n=3	n=0
others	n=4	n=23

To investigate whether the reduced review time of BTD drugs as an additional benefit of BTD program beyond the priority review was, a comparison analysis was performed between BTD drugs and non-BTD drugs. In the years from 2013 to 2015, the 22 BTD NMEs and the 37 non-BTD NMEs were all approved as priority review. As demonstrated in Figure 8, the BTD priority review indeed reduced the review time additionally by up to 3.3 months in average, as compared to non-BTD priority review. Particularly in oncology and chronic hepatitis C infectious disease, the review time of BTD priority review was reduced by up to 2.9 months and 4 months as compared to non-BTD priority review, respectively.

4.3. Analysis on impact of BTD with respect to clinical development program

Since the intention of BTD is to expedite an entire development program, in my opinion only the cases studies of which the BTD was granted at early stage of development, are eligible to analyze the real impact of BTD on an entire development program. In this analysis, the six approved drugs of which the BTD was granted at the early development stage were analyzed, focusing on their development time, development program after granting BTD, approval basis and interactions supported by FDA, to understand the impact of BTD program in the real cases.

Case study from indication of NSCLC: Zykadia, Alecensa and Tagrisso

Zykadia (INN: ceritinib): The BTD was granted on March 6th 2013 based on initial data from a Phase I trial investigating the maximum tolerated dose (MTD), safety, pharmacokinetics and antitumor activity of ceritinib in 88 patients: a response rate of 80% in the patients who had experienced disease progression after crizotinib treatment. The same phase I trial also formed the basis for approval of Zykadia for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. This Phase I trial was designed as dose escalation and expansion, multi-center, single-arm and open-label. The approval basis was the ORR from the enrolled 163 patients' population, as determined by a Blinded Independent Central Review Committee (BIRC), was 44% (95% CI: 36, 52) and the median DOR was 7.1 months (95% CI: 5.6, NE) (Table 2). A rolling NDA was accepted by FDA. This accelerated clinical development program was compiled with challenging CMC development. Two weeks prior to FDA's internal goal date of April 17th 2014, the FDA's Office of Compliance issued their cGMP concerns on one of manufacturers involved in the production of the drug substance ceritinib[xi]. A series of teleconferences started on April 2nd and a discussion including the senior management and the CDER director was held on April 9th. The inclusion of the CDER director in discussion indicates that the review team went straight to the top in an attempt to resolve this issue to avoid delay of approval. Finally, Zykadia was approved on April 29th, showing that the issue was resolved in less than a month. Considering the development time that IND was effective on the November 8th 2010 until the receiving of accelerated approval on April 29th 2014, 3 years and 6 months pre-market development time was needed to make Zykadia developed and approved to

treat patients with ALK positive metastatic NSCLC who have progressed on or are intolerant to crizotinib in US (Figure 9).

Alecensa (INN: Alectinib): The BTD was granted based on an early analysis of the phase I/II studies (AD-002JG/NP28761) in the US, showing ORR of 48% in 21 evaluable ALK positive NSCLC patients who progressed on crizotinib. Together with this US study, also supportive data from the Phase I/II study (AF-001JP) in Japan of 70 ALK positive NSCLC patients who were crizotinib-naive showing an ORR of 94% (95% CI: 82, 99). One month after granting BTD, an inter-disciplinary Type B BTD meeting was held to discuss potential for AA based on demonstration of durable ORR and design of a confirmatory trial. From granting BTD until submission, eight official FDA meetings were held to discuss CMC, study designs, as well as filing strategy. Finally, a rolling NDA was agreed with the FDA. The final approval under AA was granted on the December 9th 2015 based on ORR and DOR from two single-arm phase I/II, open-label, multi-center trials with 225 patients (Table 2). As post-marketing activities, a confirmatory study BO28984 (ALEX), a randomized phase III trial to compare Alecensa versus crizotinib in patients with advanced NSCLC without a history of prior systemic therapy for advanced disease and whose tumors harbor an ALK re-arrangement were required by FDA. If development time is considered as time period between IND effective date and approval date, less than 4 years are needed for Alecensa to achieve approval state in the US (Figure 9).

Tagrisso (INN: Osimertinib): The BTD was granted on the April 16th 2014 based on an ongoing phase I trial (AURA1) with dose expansion. After granting BTD, two Type B BTD Meetings were held to discuss the clinical and non-clinical components of a potential AA as well as CMC components for a potential AA, respectively. The final approval was granted on the November 10th 2015, 5 months later after the completion of a rolling NDA submission. The accelerated approval relied on the pooled analysis of 411 patients enrolled in one clinical trial (AURA2) and a dose-expansion cohort of a larger trial (AURA extension). Both trials were designed as open-label, single-arm, non-randomized, non-comparative, multiple cohort phase II trials with prospectively centrally confirmed T790M mutation metastatic NSCLC who progressed on EGFR TKI. The approval was based on ORR (primary) and not reached DOR (secondary) (Table 2). The pooled analysis showed ORR of 59% (95% CI: 54, 64) with 0.5% complete response and 59%

partial response. At the time of approval, median DOR was not reached in the combined Phase II studies, only shown in the Phase I study as 12.4 months. From the effective IND on the July 11th 2013, the pre-market development time of 2 years and 2 months was needed for Tagrisso to achieve AA in US (Figure 9).

Case study from indication of Melanoma: Keytruda

Keytruda (INN: pembrolizumab): On the January 17th 2013, Keytruda was designated as breakthrough therapy for the treatment of unresectable or metastatic melanoma that was refractory to ipilimumab treatment as well as for the treatment of unresectable or metastatic melanoma in patients without previous ipilimumab treatment. BTD was based on early interim results of a large, multi-stage, multiple-cohort dose-finding, activity-estimating, safety and tolerability Phase I trial (PN001) in 85 patients with inoperable and metastatic melanoma, which showed an objective response in 51% of patients and 9% of those had a complete response at or after the 12-week assessment. A rolling BLA was received for the submission. The AA was received on the September 04th 2014 for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, which based on the data from the a single, randomized (1:1), open-label, dose-ranging, multicenter cohort (Cohort B2) comprised of 173 patients within the same Phase I trial PN001 (Table 2). The results of a large, multi-stage, multiple cohort dose-finding, activity-estimating, safety and tolerability trial, Study PN001. The approval was based on the primary endpoint of ORR 24% with 1 complete response and 20 partial responses. At the time of approval, Keytruda was the first approved immune checkpoint therapy targeting PD-1 for melanoma. From an effective IND on the January 10th 2010 to granted AA, 3 years and 8 months were needed to achieve approval of Keytruda in US (Figure 9).

At the time of granting BTD, the Keytruda was in the phase I stage and its CMC development was for the small clinical supply. Keytruda is illustrative of the flexible approach that the FDA takes in collaborating with sponsors to facilitate early access of BTD drugs to patients. From April to October 2013, four CMC meetings in the frequency of every two months were conducted to discuss and align on a risk-based approach of CMC development to compensate CMC development timelines with clinical development timelines. The DS Process Performance Qualification (PPQ) was de-coupled from DP PPQ, in order to enable parallel execution and

completion of DS and DP development activity, resulting in a shortened CMC development by 4 to 6 months. To meet the commercial and clinical demand, an additional DS manufacturing site was rapidly brought online before BLA filing. Nevertheless, due to multiple CMC issues and not synchronized site inspections, the FDA finally decided to remove one of the manufacturing sites during BLA review, which were re-submitted and approved rapidly afterwards. Other initially time-critical CMC issues, e.g. transition of a new dosage form (from lyophilized powder for solution for infusion to a liquid vial), use of commercial well-established Host Cell Protein (HCP) assay instead of a process or product specific HCP method, were all agreed and solved together with the FDA, partly as post-marketing commitments. A frequent and data-driven interaction between Merck and the FDA enabled a timely CMC development leading to a quick launch to the market[xii].

Case study from indication of Multiple Myeloma: Darzalex

Darzalex (INN: daratumumab): the BTD was granted on the May 01st 2013 based on data of Phase I/II dose escalation study (GEN501). This was a first-in-man (FiM) dose-escalation trial designed as not randomized, open-label, single-arm with Darzalex as monotherapy in patients with relapsed and refractory MM. Two years after BTD, AA was granted for Darzalex for the treatment of MM in patients who have received at least three prior lines of therapy including proteasome inhibitor and an immune-modulator or who are double refractory. The approval was based on data from the same Phase I/II study (GEN501) and one additional Phase II trial (MMY2002). This Phase II trial was designed as open-label randomized dosing trial with dose expansion in patients with relapsed MM with prior treatments including proteasome inhibitors and immune modulatory agents. For both trials, the primary endpoint was ORR and median DOR: in the GEN501 trial with 42 patients showing ORR of 36% (95% CI: 22-52%) and median DOR of 6.9 months; in the MMY002 trial with 106 patients showing ORR of 29% (95% CI: 21-39%) and median DOR of 7.4 months (Table 2).

Case study from indication of Breast Cancer: Ibrance

Ibrance (INN: palbociclib): In April 2013, the BTD was granted based on preliminary Phase I/II trial (PALOMA-1) data in post-menopausal patients with estrogen receptor (ER) positive, human

epidermal growth factor receptor (HER)-2 negative locally advanced or metastatic breast cancer, showing a statistically significant improvement in median PFS for palbociclib in combination with letrozole versus letrozole alone as the first-line treatment (26.1 months and 7.5 months, respectively). This study had a dose escalation phase I component (12 patients) followed by the Phase II component. The Phase II consists of two part cohorts, part 1 in patients with unselected BC and part 2 in patients with biomarker selected BC. However, this Phase II component trial was not designed as registration trial. Several issues were identified and the concerns were presented by the FDA during multiple pre-NDA meetings including: concerns over data-driven amendments to the statistical analysis plan, incorrect stratification, concern on protocol deviations, unequal censoring and discrepancy between BICR analysis and the investigator assessment, underperforming control arm in part 1 of investigator analysis. The FDA requested conducting an independent blinded review on all patients in phase II component of the trial and also requested an analysis of the imbalance in censoring on the two arms and reasons for censoring observations in both investigator assessments and BICR analysis. Moreover, during clinical site inspection, protocol deviations, GCP compliance deficiencies and underreporting of adverse events in one of four sites were revealed. As a consequence, the data generated at this site was not recommended to be used, but no evidence was found that suggested the issues were systemic across the study. Given the large magnitude of improvement in PFS which was further supported by ORR and OS conferred, the FDA granted AA finally in February 2015. Ibrance is a case that was illustrative of the flexible approach of the FDA to resolve the regulatory issues.

In addition to those regulatory issues, during commercial scale-up the manufacturer identified a drop in dissolution performance at the end of each batch, which did not occur at smaller scale. To continue uninterrupted supply to clinical study, a batch cut-off at 85% was instituted and the final 15% of each batch was thrown away, which was agreed by the FDA as an appropriate interim measure until a permanent corrective action being identified. The applicant ultimately made a set of successful modifications in the manufacturing process and at the end these corrective actions were confirmed successfully by the stratified data across multiple batches

and strengths. Finally, this 85% cut-off was eliminated for commercial process and for all future clinical batches[xii].

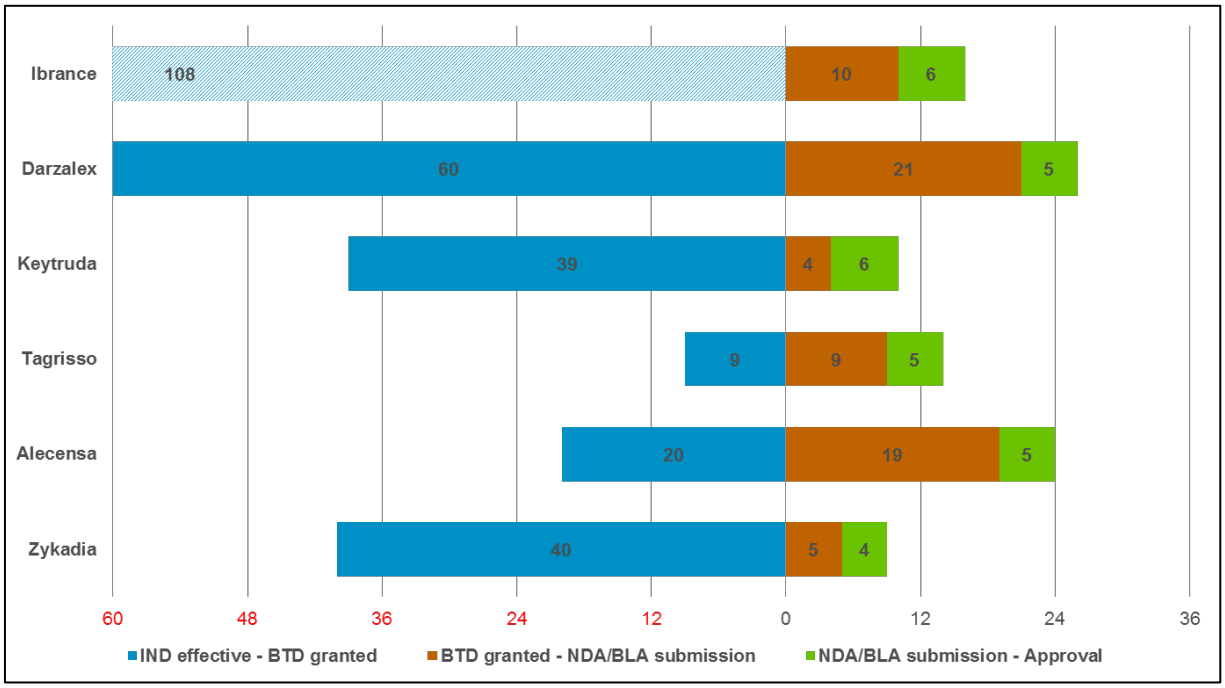
Table 2 Overview of approval basis from 6 approved BTD drugs of which the BTD was granted at the early development

Trade name	Indication	Approval date	Approval basis	
Zykadia	Treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib	AA 04/ 29/ 2014	Ph I trial (X2101) single-arm; non-randomized; N=163 pts	ORR 44% (95% CI: 36, 52); Median DOR 7.1m (95% CI: 5.6, NE)
Alecensa	Treatment of patients with ALK-positive metastatic NSCLC who have progressed on, or are intolerant to crizotinib	AA 12/ 09/ 2015	Two Ph I/II trials: single-arm; non-randomized; N=225 pts NP28761 (N=87 pts); NP28673 (N=138 pts)	ORR 44% (95% CI: 36, 53) and 38% (95% CI: 28, 49); DOR 7.5 months and 11.2 months
Tagrisso	Treatment of patients with T790M mutation-positive NSCLC, who have progressed on or after EGFR TKI therapy	AA 11/ 10/ 2015	Two Ph II trials: single-arm; non-randomized; N=411 pts	ORR 59% (95% CI: 54, 64); Median DOR not reached (Ph I cohort with 63 patients: DOR 12.4m)
Keytruda	Treatment of patients with advanced or unrespectable melanoma who are no longer responding to other treatments	AA 09/04/2014	Ph Ib trial (PN001) randomized (1:1); N=173 pts (Cohort B2)	ORR 24% (95% CI:15, 34) with 1.2% CRR and 22.5% PRR; Median DOR not reached (2mg/kg Q3W with 1.4+; 8.5+) (10mg/kg Q3W with 1.8+; 6.2+)
Ibrance	For use in combination with letrozole as first-line treatment of postmenopausal women with estrogen receptor (ER)-positive and HER2- negative metastatic breast cancer	AA 02/03/2015	Ph I/II trial (PALOMA-1): randomized (1:1); palbociclib plus letrozole versus letrozole alone; N=12 pts (ph1 part) N=165 pts (ph2 part)	PFS was 20.2 months (95% CI 13.8, 27.5) in the palbociclib plus letrozole arm and 10.2 months (95% CI 5.7, 12.6) in the letrozole alone arm [HR 0.488 (95% CI 0.319, 0.748)]
Darzalex	treatment of Multiple Myeloma in patients who have received at least three prior lines of therapy including proteasome inhibitor and an immune-modulator or who are double –refractory	AA 11/16/2015	Ph I/II trial (GEN501) single-arm; non-randomized; N=42	ORR of 36% (95% CI: 22-52%); median DOR 6.9 months
			Ph II trial (MMY2002) Randomized (1:1) N=106	ORR 29% (95% CI: 21-39%); median DOR 7.4m

As shown in these six case studies which were designated as breakthrough therapy at their early development, the FDA made resources available to work closely together with the applicant to

accelerate a successful development of breakthrough therapies. After granting BTD, an average time of 12 months was observed to complete clinical and CMC development and get ready for filing. In four case studies of BTD drugs, four-year development time was observed to complete clinical development program and complete CMC development for commercial supply of safe drugs in the market (Figure 9). Using biomarkers to stratify patient population, the single-arm trial without comparator was accepted to grant accelerated approvals. With this approach, the patients` numbers in placebo or less efficient treatment group could be reduced or avoided for pre-market development. To compensate the CMC development with fast-moving clinical development program, the FDA went straight in an attempt to quickly resolve issues that could have delayed the approval.

Figure 9 Analysis on development time of 6 approved BTD drugs of which the BTD was granted at early development
(Development time presented in [months])



4.4. Analysis on impacts of BTD in case that the BTD granted after filing

It is noticeable that even for the agents for which BTD was granted during review of NDA or BLA, some benefits could still be expected by the sponsors. One considerable benefit could be the 1-month advantage ahead of PDUFA date given for drugs qualified for expedited review. Of the 5 approved drugs of which the BTD was granted after filing, an average review time of 5.9 months was observed, as 2 months faster than the PDUFA clock time.

In the cases of Ofev and Esbriet to treat IPF: Shortly after Boehringer Ingelheim announced the granting BTD for Ofev to treat IPF, InterMune also announced the granted BTD of their competitor Esbriet for the same indication of IPF. After granting the BTDs to both products, the FDA allowed equivalent resources to review both products[xiii]. In this case BTD was really important for companies to compete to get the first approved therapy in the US to market. Indeed, if only one drug had been granted the BTD, the other one would not have had the equivalent chance to be approved first.

In case of Gazyva: The CMC development was mostly completed at the time of filing. Nevertheless, to get a one-month earlier launch, the FDA showed very supportive interaction with the applicant to encourage the conversion of clinical material to commercial launch material. The granting of BTD allowed the FDA to make resources available and to intensively guide the sponsors to accelerate CMC readiness for an early launch of breakthrough therapy.

In case of Solvadi: During the late review cycle, the FDA asked Gilead to request a BTD to allow the additional resources to review new data from two additional ongoing clinical trials (VALENCE and PHOTON-1), which resulted in a broader indication in final approved label[xiv]. The granting of BTD allowed the FDA more resources to review additional early data.

Taken together, for the approved drugs which the BTD was granted after filing, the additional benefit could still be expected on a case-by-case basis. A designation as BTD allowed the FDA to make their resources available to work closely with applicant in a more dynamic and flexible way.

5. Analysis on post-marketing activities for approved BTD drugs

The breakthrough therapy designation is based on the effect of the drug that will be greater compared with available therapies. The development program for the breakthrough therapy could be shorter than for other drugs intended to treat the same disease being studied. Nevertheless, the statutory standard for approval is still the same based on adequate data to demonstrate the safety and efficacy. Due to the expedited development program, the approval of certain drugs is often associated with post-marketing activities, to complete all development programs. The main subject in this section is to retrospectively analyze the required or committed post-marketing activities for the 22 approved BTD drugs and to explore the kinds of flexibilities that the FDA may offer or negotiate with sponsors.

The post-marketing requirements and commitments refer to studies and clinical trials that sponsors conduct after approval. While the post-marketing requirements (PMRs) include studies and clinical trials that sponsors are required to conduct under one or more statutes or regulations, the post-marketing commitments (PMCs) are studies or clinical trials that a sponsor has agreed to conduct, but that are not required by a statute or regulation.

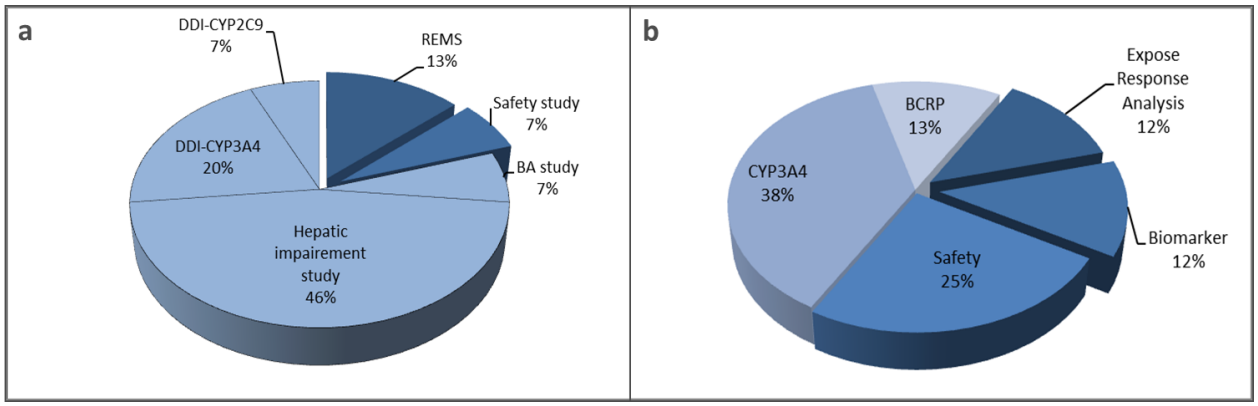
5.1. Post-marketing activities in terms of clinical perspective

All drugs approved under AA have to fulfill the condition (21 CFR 314.510 and 21 CFR 601.41) to conduct post-marketing studies or clinical trials to demonstrate clinical benefit. Typically, at least one phase III confirmatory study was required to demonstrate the significant efficacy over available therapy, designed as randomized and comparator-arm controlled study. For oncology drugs, the common validated clinical benefit should be evaluated as PFS and OS for the confirmatory studies as required by the FDA[xv].

The most common PMRs for oncology (Figure 10a) were to conduct PK studies in patients with moderate to severe hepatic impairment. The second common PMR was to investigate drug-drug-interaction (DDI) with strong CYP3A4 inducer (Rifampin) or with strong CYP inhibitor on the pharmacokinetics of approved drugs. For Zykadia, PK studies were required to investigate its DDI with midazolam (CYP3A4 substrate) as well as warfarin (CYP2C9 substrate). In addition, a bioavailability (BA) study with gastric acid reducing agents was also required for Zykadia. The

safety study of food effects on different doses on ceritinib was also required as a PMR. As post-marketing requirements, REMS with communication plan and routine surveillance were required for Blincyto and Zydelig to ensure that the benefits outweighed the risks. This requirement was due to the major safety concerns identified by the FDA: for Blincyto the cytokine release syndrome and the neurological toxicities as well as for Zydelig the hepatoxicity including fatalities, bowel perforation, colitis and pneumonitis.

Figure 10 Analyze on clinical related post-marketing requirements (a) and post-marketing commitments (b) in therapeutic area of oncology



In contrast, the clinical relevant PMCs are much diverse, there is no common trend observed among oncology drugs (Figure 10b). In general, PK studies and safety related studies are most commonly committed by the FDA and sponsors. The PK study included DDI with CTP3A inducer (Tagrisso and Ibrance). PK studies with repeated doses of Tagrisso on a probe substrate of CYP3A4 and on a probe substrate of Breast Cancer Resistant Protein (BCRP) were also recommended by the FDA for Tagrisso approval. Two safety studies related PMR were agreed for Zydelig to characterize the long-term safety of follow-up of Zydelig in combination therapy. In addition, the exposure-response analysis for safety and efficacy to determine whether a post-marketing trial needed to optimize dosing was committed by sponsor at the time for approval of Empliciti. For Ibrance, a clinical study for genetic alteration to the safety and efficacy (biomarker) was recommended by the FDA.

5.2. Post-marketing activities in terms of non-clinical perspective

The post-marketing activities for non-clinical study are generally less common than clinics and CMC: only 27% (6) of 22 approved drugs receive non-clinical post-marketing activity. For non-

oncology drugs, conduction of long-term carcinogenicity study was the most commonly required post-marketing activity (Table 3). But there was no common trend observed and the non-clinical post-marketing activities were on a case-to-case basis.

Table 3 Analysis on non-clinical post-marketing activities for approved BTD drugs

• determine the effect of a broad range of concentrations of ibrutinib on platelet function by in vitro studies	PMR for Imbruvica
• conduct animal study for primary immune response.	PMC for Keytruda
• submit the final study reports for the two-year carcinogenicity studies. • determine the phenotypic susceptibility of sofosbuvir against different announced genotypes	PMR for Solvadi
• Conduct study to assess the impact of NS5B substitutions A112T, E237G, and S473T on the phenotypic susceptibility of sofosbuvir in the GT1a HCV replicon system • Submit final report of the two-year carcinogenicity study in rats and LDV 26-week carcinogenicity study in rasH2 mice	PMR for Harvoni
• Develop an assay to directly compare the complement activation capacity to that of human IgG1	PMC for Strensig
• A two-year carcinogenicity testing in rats	PMR for Orkambi

5.3. Post-marketing activities in terms of CMC perspective

With expedited clinical development timelines, drug manufacturing development timelines have been put under significant strain to guarantee readiness at the time of marketing approval. To balance the risks of less CMC data at the time of filing versus patient benefit, the FDA allowed certain flexibility depending on the type and extent of manufacturing information, but the level of flexibility would be determined on a case-by-case basis. It would be possible to propose an integrated post marketing plan including some post marketing commitments and requirements. Indeed, 11 of 22 approved BTD drugs have included CMC related PMR/PMC in their approval package to allow the early timelines to put them on the market. In this section, the PMRs and PMCs agreed by the FDA and sponsors for approved BTD drugs will be retrospectively presented and analyzed to explore the kind of flexibility that the FDA might offer to facilitate early assess to patients.

CMC related post-marketing activity for Small Molecules

Among 13 BTD approved Small Molecules, only 23% (3/13) committed to CMC post-marketing activities after NDA approval: Imbruvica, Xuriden and Zykadia. The post-marketing CMC commitments were all related to the finished DP, from the dissolution profile and particle size

within DP specification to the long-term real-time stability data of finished DP (Table 4). The readiness of small molecules CMC dossier is generally complete at the time of filing, and standard of FDA requirements is not lower than other approval types.

Table 4 Analysis on CMC related post-marketing activities for approved BTD Small Molecules

Control of DP	
Collect the dissolution profile of ibrutinib under various conditions (release and stability)	PMC for Imbruvica
Develop a discriminating dissolution method appropriate for the proposed product and set dissolution method acceptance criteria based on data from at least 5 commercial batches.	PMC For Xuriden
Determine the particle size distribution of the final DP and, using the updated dissolution method, evaluate the impact of the particle sized distribution on dissolution. The studies should also include an evaluation of batches submitted in the application. Based on findings from these studies, update the final drug product particle size specification and the in-process controls.	PMC For Xuriden
Revise testing monograph (method and specification for DP-capsule content)	PMC For Zykadia
Stability of DP	
9 m stability data for 3 registration stability batches and up to 24 m for one batch from supportive stability	PMC For Zykadia

CMC related post-marketing activity for Biologics

In contrast to the field of small molecules, the majority (8/9) of BTD approved biologics required post-marketing activities to complete entire CMC development, with the only exception of Praxbind as antidote therapy. As post-marketing activities only Darzalex and Opdivo received just the PMRs, while majority BLAs were agreed with PMC. As PMRs, three immunoassays were required for Darzalex, e.g. anti-drug antibody response, binding antibodies to daratumab, neutralizing antibodies to daratumab. The rest of PMCs are primarily focusing on completing process optimization and well distributed in the fields of manufacturing process, container closure system, impurity profile, control of DS and DP, as well as microbial control process (Table 5).

In general, the accelerated CMC development for BTD drugs will necessitate risk-based approaches to product & process development, commercial readiness, launch and regulatory filings. The CMC requirement at the final approval is not lower than standard CMC package. But differing from traditional CMC development, the sponsor should consider deferring some activities to post-filing. The accelerated CMC development approach should focus on a reliable

supply of quality product at launch, but not process optimization. At the time of filing and launch of a breakthrough drug product, some CMC/GMP activities may be incomplete, e.g. process validation, process characterization, real-time stability data of commercial products, validated transfer to commercial manufacturing site/scale, provisional control system and optimized final commercial formulation. But the fundamental assumption for an approval is that risk assessments demonstrate that having less data at the time of filing and launch of a breakthrough product will not compromise patient safety or product supply.

Table 5 Analysis on CMC related post-marketing activities for approved BTD Biologics

Manufacturing Process	Complete the ongoing studies regarding use of multiple cells from master cell bank
	Evaluate the manufacturing process and develop a control strategy accordingly
	Characterize potential formed variants and implement control strategy (Kanuma)
	Microbiology Control **Hold time** • A formal verification for hold times from manufacturing scale samples • Provide additional maximum hold times using a surrogate solution that supports microbial growth **Bio-burden test** • Develop and implement optimized bio-burden test method for continued microbial control **Endotoxin control** • Develop and implement optimized endotoxin control method • Risk assessment to microbial control and mitigation risks of endogen contamination during DS, DP, IVSS manufacturing • Study to assess endotoxin recovery • Re-evaluate endotoxin limits after data from thirty batches is available • Pyrogenic response in rabbits to DP and IVSS • Study to understand the mechanism of endotoxin masking and or interference in DP Provide data to demonstrate adequacy of microbial growth promotion properties Perform a repeat microbial retention study for sterilizing filter using a suitable surrogate solution.
Container closure system	Conduct DS storage container leachate studies Conduct DP storage container leachate studies
Control of DS	**Specifications** • Re-evaluate DS lot release and stability specifications after certain lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. • Re-evaluate Intermediate lot release and stability specifications after certain lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. **Testing methods:** • Develop and optimize agreed test methods in release specification • Develop and validate process-specific host cell protein assay for DS release **Stability:** • Perform worst-case shipping studies for DS.
Control of DP	**Specification** • Re-evaluate DP lot release and stability specifications after certain lots have been manufactured using the commercial manufacturing process and tested using the commercial specification methods. **Test method** • Develop and implement improved CE-SDS to control purity profile in DP specification • Develop and implement improved SDS-PAGE to control purity profile in DP specification • Develop and implement assay for receptor binding assay or enzyme activity assay in DP specification • Evaluate the capability of used dye ingress test method of stability of DP samples to detect small defects **Stability** • Perform worst-case shipping studies for DP

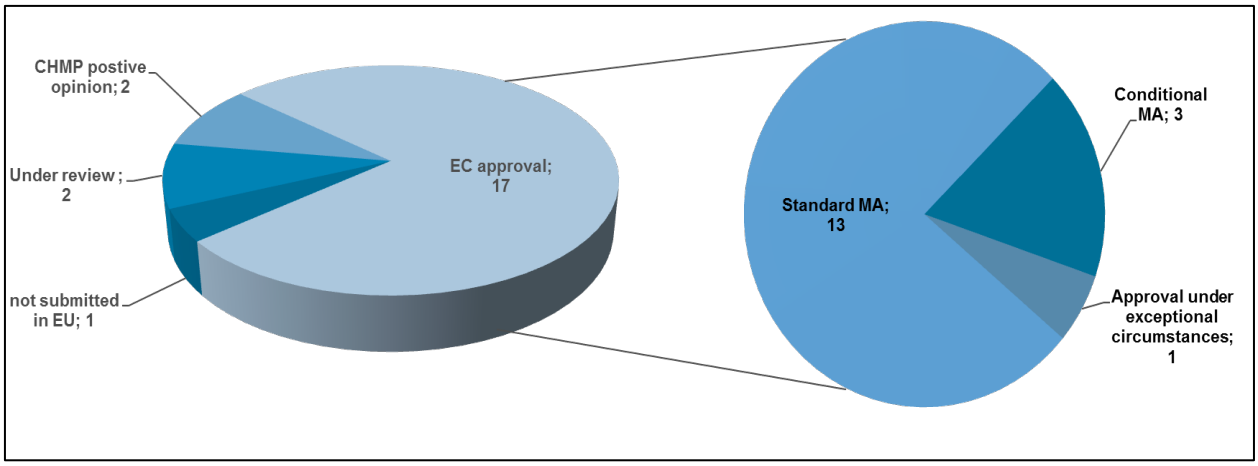
6. Analysis on status of BTD drugs in EU and Japan

6.1. Overview on regulatory status of BTD approved drugs in EU and Japan

In Europe, the accelerated assessment and the conditional approval programs are available as expedited regulatory tools to accelerate the path to market for the products. The accelerated assessment is a similar regulatory tool in EU as the priority reviews in the US, primarily focusing on cutting the review time until the opinion of the Committee for Medicinal Products for Human Use (CHMP) given within 150 days instead of 210 days[xvi]. The conditional marketing authorization (CMA) in EU is a similar regulatory tool as the accelerated approval in the US, focusing on approval based on the benefit of immediate availability outweighs the risk of less comprehensive data than normally required[xvii]. Differing to AA by the FDA, the CMA is subject to specific obligations and valid for only one year. As compared to the use by the FDA, these expedited tools are rarely used by the EMA: since their inception from 2006, only 28 options for CMA were issued and 22 drugs were evaluated under AA as announced by the EMA[xviii].

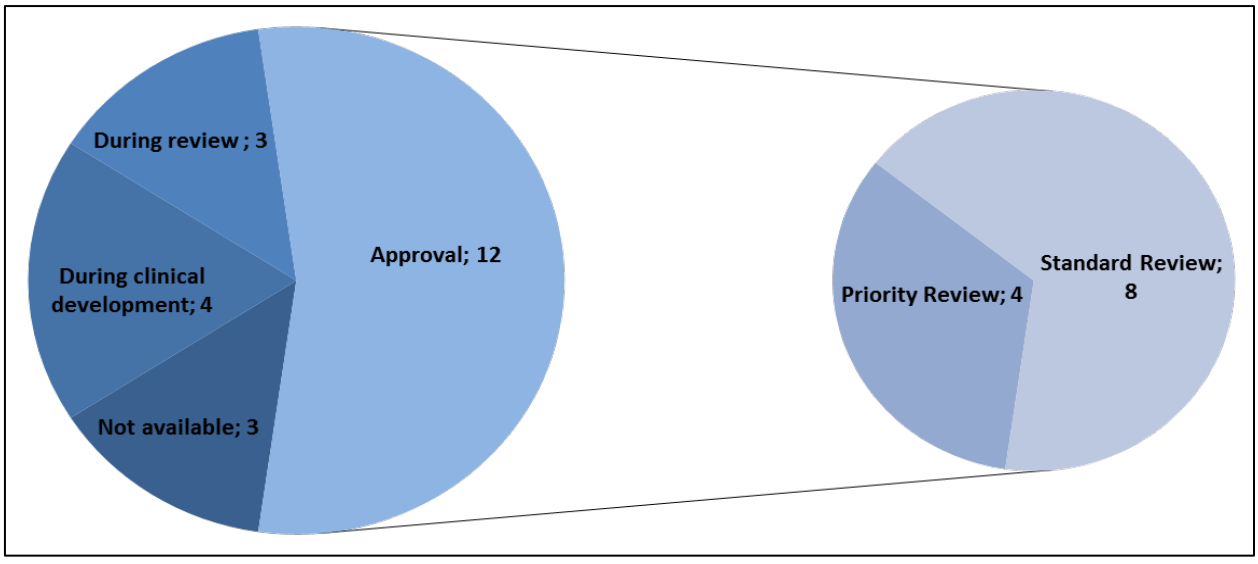
Until the cutoff date of this master thesis, 21 of the 22 approved BTD drugs have been submitted to EMA: 17 approvals have been granted, two approvals (Alecensa and Ibrance) are still pending, two oncology drugs (Darzalex and Empliciti) received positive CHMP opinions and are pending for EC approval decision (Figure 11). Of the 17 approved medicinal products in EU, only 18% (3/17) were granted under CMA, while in US 45% (10/22) of approved BTD were granted under AA. Similar trend was also observed for accelerated assessment; while in US 100% (22/22) of approved BTD received priority review, only 41% (7/17) received accelerated assessment.

Figure 11 Analysis on regulatory status of the 22 approved BTD drugs in EU



The NDA submission and review/approval processes in PMDA and their requirements are similar to other authorities in ICH regions (e.g. FDA or EMA). However, there is a mandatory submission of key results of the Japanese population if Japan participates in global studies (or regional studies e.g. Asian studies). This could be one of the greatest challenges of ``drug lag´´ in Japan that caused delay falling behind US and EU approval. Of the 22 approved BTD drugs, only 12 approvals were also granted by the PMDA, while 4 drugs were still under clinical development and approvals of 3 drugs were still pending in Japan (Figure 12). Of 12 approvals by PMDA, only 30% (4/12) received priority review: Harvoni, Solvadi and Viekira Pak to treat hepatitis C virus infection as well as Tagrisso for oncology indication (NSCLC).

Figure 12 Analysis on regulatory status of 22 approved BTD drugs in Japan

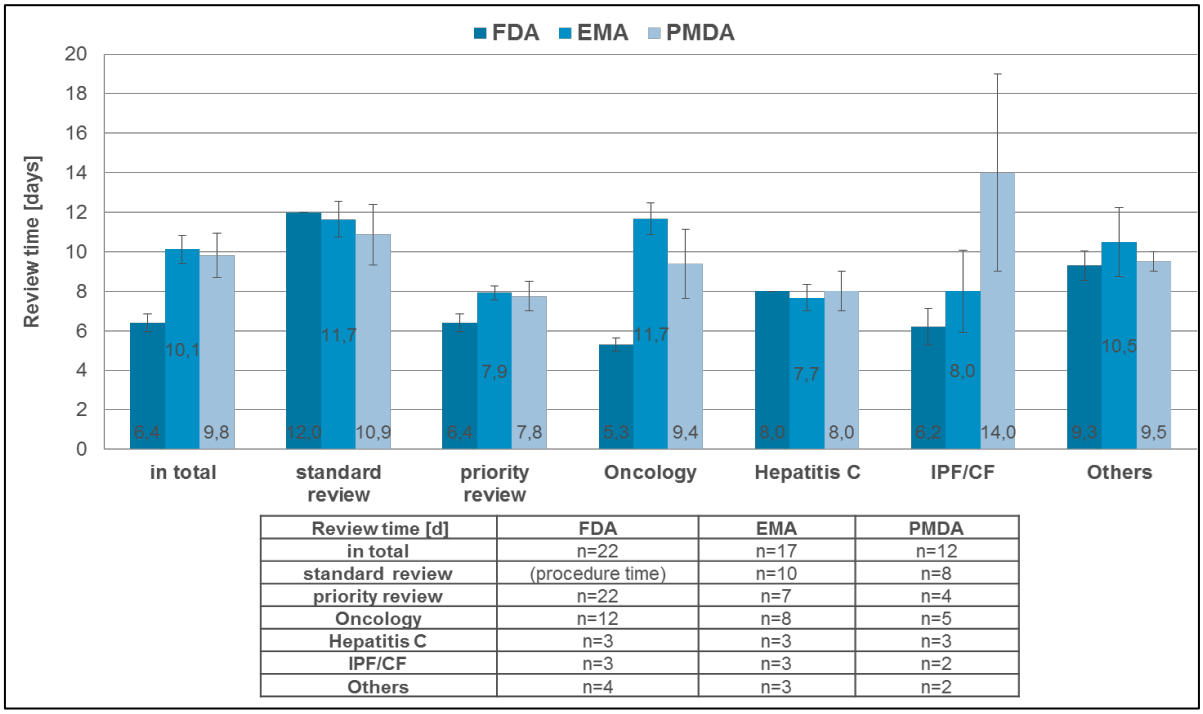


6.2. Analysis on review time of BTD drugs in EU and Japan vs. US

The average review time of the 17 approvals was 10 months by the EMA, approximately 3.6 months longer than the average review time by the FDA (Figure 13). Of the 17 approvals, 7 drugs have received accelerated assessment by the EMA, with an average of 7.9 months' review time. Similarly with the FDA, the discrepancy on review time among different indications was also observed by the EMA. Nevertheless, the fastest review time by the EMA was observed for indication of hepatitis C and IPF/CF with 8 months for both of them. This phenomenon is controversial as compared to the FDA shown fastest review for oncology drugs. The fastest approval by the EMA was Esbriet for the indication of IPF within 5 months. And the slowest approval taken 14 months by the EMA was for Strensiq which was granted as approval under exceptional circumstances.

From 2005 toward 2014, the review time of new drugs approvals in Japan has gradually reduced by more than 50%[xix]. While the standard review time of PMDA is 12 months, review time for priority review is 9 months. Based on the 12 approved drugs in Japan, an average review time of 9.8 months were observed, while an average review time of 7.8 months' priority review (Figure 13). A difference of review time among therapeutic area was also observed, with the shortest review time of 8 months for drugs treating hepatitis C and longest review time for the IPF/CF indication. The Opdivo and Viekira Pak received PMDA approval after the shortest review time of 6 months.

Figure 13 Analysis on review time of 22 BTD drugs by FDA (US), EMA (EU) and PMDA (Japan)
(Review time expressed as mean±SEM)

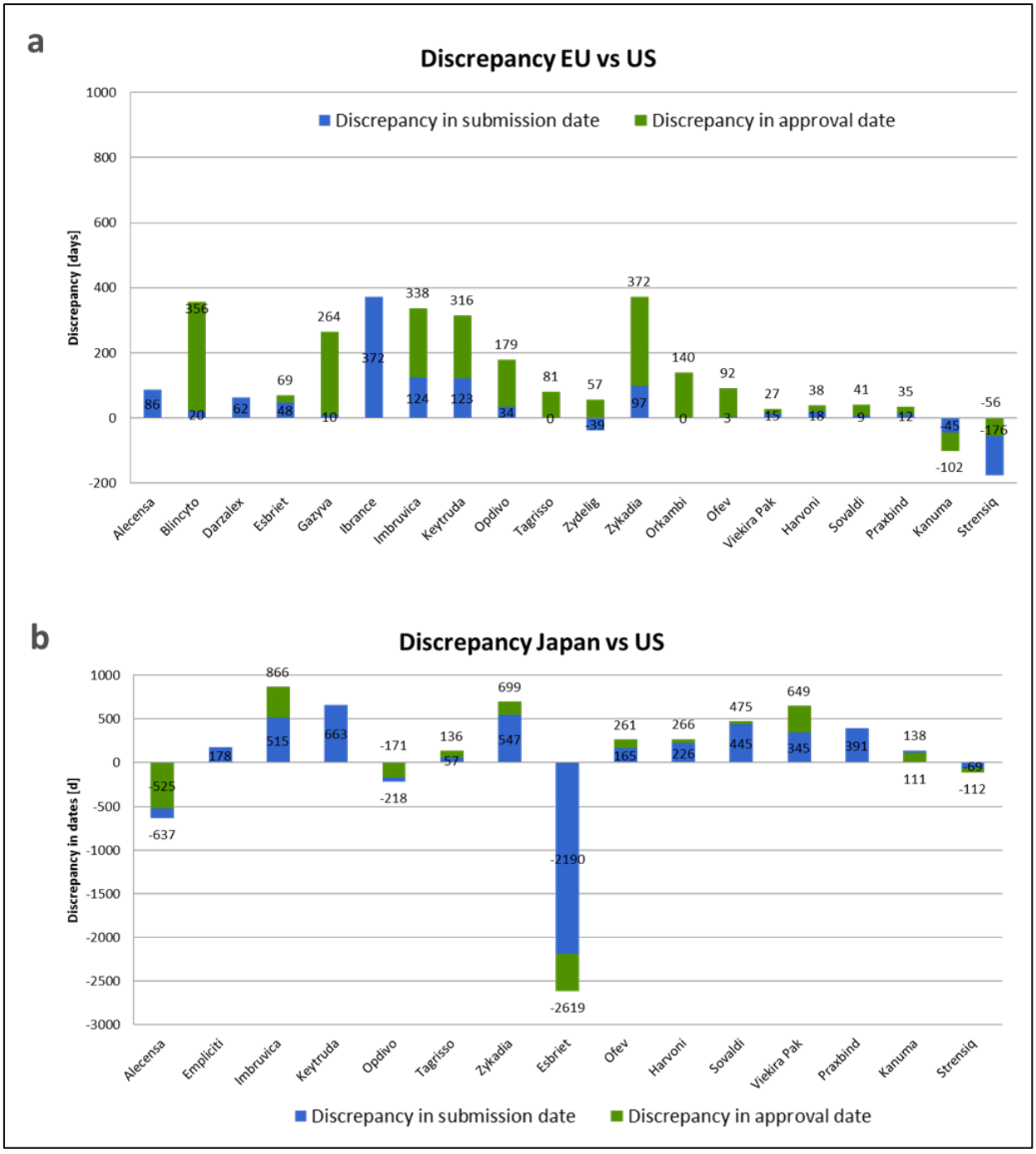


Review time [d]	FDA	EMA	PMDA
in total	n=22	n=17	n=12
standard review	(procedure time)	n=10	n=8
priority review	n=22	n=7	n=4
Oncology	n=12	n=8	n=5
Hepatitis C	n=3	n=3	n=3
IPF/CF	n=3	n=3	n=2
Others	n=4	n=3	n=2

In addition to review time, the discrepancy of submission date was also analyzed to investigate the reason causing the discrepancy on access of the BTD drugs to patients in EU (Figure 14a) and Japan (Figure 14b). For indication of chronic hepatitis C infection, the submission and approval dates for Viekira Park, Sovaldi, and Harvoni were all very close in EU and US. In contrast, their submission and approval dates were significantly delayed in Japan. For indication of pulmonary disease, the submission of Orkambi for CF and Ofev for IPF in EU was almost on the same day as in the US, but their delay in approval dates was observed in EU which was resulted from the discrepancy in review time in this case. For oncology indication, Imbruvica, Keytruda and Ibrance were submitted in EU significantly later than in the US, while Targrisso, Gazyva and Blincyto were submitted very closely in EU as compared in the US. There is no common trend on submission discrepancy was observed in oncology area for EU. The similar phenomenon was also observed for Japan.

Figure 14 Analysis on discrepancy in submission date and approval date of the BTD drugs between FDA and EMA (a)(n=20) and PMDA (b)(n=15)

(baseline: the submission date in US; blue bars: discrepancy in submission date vs. US; green bars: discrepancy in approval date vs US) (In EU, the approvals of Alecensa, Darzalex and Ibrance are pending on the cut-off date of master thesis; in Japan, the approvals of Empliciti and Praxbind are pending on the cut-off date of master thesis.)



6.3. Analysis on using conditional approvals for BTD drugs in EU vs. US

Case studies: accelerated approval in US vs. conditional marketing authorization in EU

Of the 22 BTD drugs, 10 approvals were granted as accelerated approvals based on surrogate endpoints by the FDA. Particularly in oncology, 9 of 12 approvals were granted as accelerated approvals. However, in EU only 3 of 17 approvals (Blincyto, Tagrisso, and Zykadia) were granted as conditional marketing authorization. As shown in Table 6, the approved indications for these three BTD drugs (Blincyto, Tagrisso, and Zykadia) are identical both in EU and US. Using biomarker to identify patient population, the single-arm non-randomized studies served as basis for conditional approvals in both US and EU. However, the two agency`s approval basis are not identical.

In case of Blincyto, approvals were based on different interpretation of importance of primary and secondary endpoints by the EMA and FDA. In the US, the accelerated approval was based on data from pivotal phase II trial (MT103-211). The trial was designed with the rate of complete remission to complete remission with partial hematological recovery (CR/CRh) within the first 2 cycles of treatment with Blincyto as primary endpoint, while the CR and DOR as secondary endpoint. The study of MT103-211 met its primary objective to demonstrate that the CR/CRh rate within 2 cycles of treatment with Blincyto exceeded the pre-specified efficacy threshold: 42% with CR 32.4% and CRh 9.2%. However, due to the single-arm design feature of Study MT103-211 and limited amount of information, a firm recommendation for approval cannot be made from the statistical perspective, as stated by the FDA. The regulatory decision-making process by the FDA relied on the secondary endpoints: 32% (95% CI, 26%-40%) of patients (n=185) in the intended population achieved CR with 2 cycles of treatment with single agent Blincyto, and the DOR measured as relapse-free survival (RFS) for the subjects who achieved CR was durable (median 6.7 months; range, <0.1-16.5 months). The conclusion of effectiveness by the FDA was strengthened by the finding that 31% (95% CI, 25%-39%) of the patients in the study had not only a remission but also a reduction in minimal residual disease (MRD) to less than 10^{-4} to predict clinical benefits of Blincyto. In EU, Blincyto was approved based on the same main pivotal study in targeted patient population with Philadelphia chromosome-negative relapsed or refractory B-precursor ALL. The decision making process relied on the primary endpoint of

CR/CRh rate within 2 cycles of treatment with Blincyto. The study showed that 42.9% (81 out of 189) (CR = 33%; CRh = 9.5%) of patients given Blincyto responded to treatment. In most patients (63 of 81 responding patients), there was no evidence of cancer cells left. The average relapse-free survival (RFS) time for CR/CRh was 5.9 months (95% CI, 4.8-8.3 months), which could enable suitable patients to undergo a blood stem cell transplant.

In case of Zykadia, data from an additional single-arm study was needed to grant the approval by the EMA as compared to FDA. The AA by the FDA relied on results from one Phase I trial (CLDK378X2101) that enrolled 163 patients with metastatic ALK-positive NSCLC whose cancer had progressed. The approval basis was the endpoints of ORR and DOR in this population: as determined by a BIRC, ORR of 44% (95% CI: 36, 52) and the median DOR of 7.1 months (95% CI: 5.6, NE). The CMA granted by EMA for Zykadia was based on data from two main studies involving 303 patients in whom the disease progressed despite previous treatment with crizotinib (Xalkori). Primary endpoint was ORR with additional evaluations including DOR, PFS and OS. In one study 56% of patients (92 of 163) showed a complete or partial response to Zykadia with an average length of response of 8.3 months. In the second study, the overall response rate at the time of analysis was 37% (52 of 140 patients) and the average length of response was 9.2 months. In case of Zykadia, conditional approval in EU required more comprehensive data.

Table 6 Comparison of review time and approval basis in US (accelerated approval) vs. EU (conditional approval) based on case studies of Blincyto, Tagrisso and Zykadia

	Indication	Review time		Approval basis	
		US	EU	US AA	EU CMA
Blincyto	treatment of patients with Philadelphia chromosome negative relapsed or refractory precursor B-cell acute lymphoblastic leukemia	3m	13m	Ph II single-arm n=185 pts. CR 32% (95% CI, 26%-40%); Median DOR 6.7 m (95% CI, <0.1-16.5 months); MDR to $<10^{-4}$ 31% (95% CI, 25%-39%)	Ph II single-arm n=189 pts. CR/CRh 42.9% (33% CR, 9.5% CRh) RFS 5.9 m (95% CI, 4.8-8.3)
Tagrisso	treatment of patients with T790M mutation-positive NSCLC, who have progressed on or after EGFR TKI therapy	5m	8m	Two Ph II single-arm N=411 pts. ORR 59% Median DOR not reached (Ph I: 12.4m)	Two Ph II single-arm N=411 pts. ORR 66% DOR not reached (app. 8.5m)
Zykadia	treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib	4m	13m	Ph I single-arm N=163 pts. ORR 44% Median DOR 7.1m	Two single-arm N=303 pts. in total: Study A (N=163 pts.); ORR 56% and DOR 8.3m Study B (N=140 pts.) ORR 37% and DOR 9.2m

Case studies: accelerated approval in US vs. standard approval in EU

Even though the CMA by the EMA is a similar tool as the AA by the FDA, the interpretation and implementation of this expedited program showed discrepancy by both agencies. Three approved BTD drugs from oncology indication, Imbruvica, Keytruda, and Opdivo, received AA by the FDA, while approved as standard type by the EMA (Table 7). In the US the submissions of NDAs for different indications were approached subsequently, while in EU all were in one submission package. The data evaluated by the EMA were therefore more comprehensive at the time of filing as compared to the data submitted to the FDA. While the AA by the FDA was based on single-arm non-randomized studies with ORR and DOR as endpoint, the full approval by the EMA was based on comparator-arm controlled studies with PFS or OS as endpoint. In case of Keytruda and Opdivo to treat melanoma, the full approvals granted by the EMA had broader patient population as first line treatment, while the conditional approvals granted by the FDA only as second line treatment.

Table 7 Comparison of approval basis in US (accelerated approval) vs. EU (standard approval) based on case studies of Imbruvica, Keytruda and Opdivo

	Indication		**Approval basis**	
	US	**EU**	**US AA**	**EU full approval**
Imbruvica	MCL (CLL as sNDA)	MCL and CLL	Ph II for MCL N=111 pts Single-arm ORR 65.8% DOR 15.8 m	The same Ph II for MCL Additional CLL Phase III Imbruvica vs. ofatumumab PFS
Keytruda	2nd line melanoma	1st and 2nd line melanoma	Ph Ib Single arm, multiple-cohort, randomized (1:1) N=173 pts ORR 24% DOR 8m	2nd line melanoma study: Keytruda vs chemotherapy N=540 pts, PFS (34% Keytruda vs. 16% Chemotherapy)
				1st line melanoma study: Keytruda vs ipilimumab N=834 pts, PFS and OS 5.5 m (PFS) and 71% (OS) Keytruda vs. 2.8 m and 58% (OS) ipilimumab
Opdivo	2nd Line melanoma	1st line Melanoma and 2nd line NSCLC	Ph III Randomized (2:1) interim analysis: N=120 pts ORR 31.7%	1st line Melanoma study: N=418 pts Opdivo vs dacarbazine OS (73% Opdivo vs. 42% Dacarbazine)
				2nd line NSCLC: N=405 pts Opdivo vs SOC ORR (32% Opdivo vs. 11% SoC)

As shown in retrospective analysis based on 22 BTD drugs, a delay of availability of those breakthrough therapies in EU was observed as compared to US. On the one hand, this is resulted from different submission timelines in different regions triggered by the sponsor. On the other hand, it is resulted from different regulatory procedure as well as from the different fundament of decision making in different agencies. In Japan, the reason of ``drug lag´´ is also multiple factorial, e.g. clinical trials starting later in Japan, and a longer time taken to conduct clinical trials and review new drugs[xx]. The PMDA has made various efforts to resolve this issue, e.g. increased the number of reviewers, and enhanced and improved the review system. To shorten the pre-application lag, the quality and quantity of consultations have improved, and global drug development has been promoted. A prior assessment consultation, conducted six-month prior to NDA submission, has been introduced since 2009 by PMDA's scientific consultation. Under product reviews, the PMDA offers a variety of consultation opportunities[xxi].

7. Discussion and conclusions

7.1. Opportunity and challenges of BTD to accelerate drug development

Since the inception of BTD program in September 2012, the number of requests to the FDA has been continuously increased over the years, showing its popularity for pharmaceutical industry. The 22 NMEs have received first-ever approvals as novel drugs by the FDA with previous designation as Breakthrough Therapy and have been collected as case studies to represent the impact of BTD program on innovative drug development. Based on retrospective analysis of those 22 NMEs, the opportunities and challenges of BTD program for innovative drug development are illustrated in this master thesis.

Key outcomes from analyzed case studies:

To evaluate the impacts of BTD on drug development, some key measures were pre-defined: The grade of combination with other expedited tools, the review time, and the development time.

- All of the 22 approved BTD drugs received at least one additional expedited tool. Some of them received all four available expedited tools by the FDA to maximize the acceleration of development program. As compared to 91 non-BTD NMEs approved from 2013 to 2015, the BTD drugs demonstrated to combine much more frequently with other expedited tools and benefit from those tools to accelerate their development program.
- All of the 22 approved BTD drugs were evaluated as priority review by the FDA: the average review time is shortened significantly by up to 1.4 months faster than the PDUFA due date of priority review. The retrospective analysis to compare review time with 37 non-BTD NMEs which received priority review and approved as novel drugs from 2013 to 2015 has demonstrated an average of 3.3 months' review time as additional benefit for BTD drugs.
- The drugs which were granted as BTD in their early development, typically as the first evidence on efficacy shown in early PoC study, have shown very fast pre-market development path: in some cases it took less than 4 years from IND until the approval. All of those novel drugs of which the BTD was granted at the early development received

accelerated approval, some only based on a single-arm non-randomized pivotal study by using scientific tools (e.g. adaptive design, using biomarker) in fewer numbers of patients.

- Also drugs which the BTD was granted in the late development stage, especially some cases during or after NDA/BLA filing, could also expect additional benefit from the BTD program, e.g. potential of expedited review, possibility of extended resources by the FDA to review additional data or flexibility of CMC readiness supported by the FDA through intensive guidance.

Taken all together, the retrospective analysis based on case studies indeed demonstrates the positive impact of BTD on innovative drug development, as committed by the FDA. Rather than a separate new regulatory tool, the BTD builds on existing regulatory tools, e.g. based on the use of accelerated approval tool to enable ``conditional`` approval to reduce development time, use of priority review tool to reduce review time after filing. Moreover, the BTD offers some unique additional benefits beyond other expedited programs, e.g. organizational commitment and procedural commitment by the FDA. In terms of organizational commitments, the FDA involves senior managers from various disciplines for a proactive, collaborative and cross-disciplinary review. A cross-disciplinary project lead will be appointed as a scientific liaison between members of the review team to facilitate the coordination of internal interactions as well as communication with sponsor through the review division's regulatory health project manager. In terms of procedural commitments, the FDA provides timely advice and interactive communication with the sponsor and intensively guides drug development. The FDA encourages the use of modern scientific tools to shorten drug development time and minimize the number of patients exposed to less efficacious treatment (placebo or SoC). Rather than a separate expedited regulatory tool, the BTD creates an entire regulatory environment to facilitate the early availability of therapeutic breakthroughs to patients with serious disease with a high unmet medical need.

Some considerations on challenges associated with BTD program:

The risks for sponsors: the sponsor should be aware that BTD is not a guarantee for approval and a granting of BTD could still be associated with certain risks. For example, the Serelaxin was developed by Novartis to treat patients with acute heart failure and was granted as BTD in June

2013 shortly after BLA submission. The reason for the FDA to grant BTD was based on data from pivotal Phase III trial showing substantial improvement of 37% reduction in mortality. However, the single pivotal Phase III trial was actually designed using the dyspnea or shortness of breath as primary endpoint whereas using reduction in mortality as secondary endpoint (safety endpoint). There was a gap in evaluating the importance of endpoints between the FDA and the sponsor. Indeed, due to the modest improvement on the primary endpoint, the FDA did not grant priority review to Serelaxin, but rather standard review. And based on the outcome from an advisory committee meeting, the FDA finally issued the complete response to Serelaxin[xxii]. Until today, the second Phase III study RELAX-AHF-2 with primary endpoint of cardiovascular mortality for Serelaxin is still ongoing.

Moreover, even if BTD status is granted, the FDA still reserves the right to rescind the designation if subsequent evidence demonstrates that the therapy no longer meets the criteria or the program is no longer being pursued. In case that the designated drug no longer demonstrates substantial improvement over a new available therapy, the FDA holds the authority to withdraw the BTD. For example, both Merck's once-daily hepatitis C regimen and Bristol-Myer Squibb's hepatitis C regimen had their BTD rescinded by the FDA in February 2015, after the recent approvals of Solvadi and Viekira Pack, which dramatically changed the SoC in this indication landscape[xxiii,ix]. After announcing the rescinding, Merck`s shares fell by 3.5%, showing the perceived values investors attach to BTD status.

The flexibility and resources attached with the BTD program: Once the BTD is granted, the FDA commits to intensively guide the sponsors for an efficient drug development program. This requires the sponsor to have certain flexibility to change and adapt their development plan to FDA`s guidance. If appropriate, the FDA will involve their senior managers in BTD drug development program, which also requires the sponsor to involve their senior experts or managers into their internal BTD drug development team in a similar way. As shown in some case studies, the FDA-Sponsor meetings and communication after granting BTD could be very frequent and flexible. The sponsors should be aware that many resources will need to be added for BTD drugs. Particularly in the big pharmaceutical companies, due to the complex internal procedure and long decision making process in the top management, a more dynamic and

fostering model is needed, adapted to the accelerated development of the BTD pathway. The sponsors should be selective about their candidates and be ready to adapt the internal company process accordingly to the dynamic BTD pathway.

The CMC challenges: In average after 2-3 years after having been granted BTD, the sponsors of the 22 BTD drugs are ready for filing their NDA/BLA. This short-cut of development time could be very challenging for the CMC readiness and require intensive resources by the sponsor. In the past, the FDA certainly showed some flexibility to negotiate with sponsors to complete some of the development steps as post-marketing commitments or requirements. In my observation, those CMC related post-marketing activities are all related to process optimization, process validation and completion of real-time stability testing, but until the submission the CMC development was expected to be complete in a level that a supply of safe drugs to patients should be ensured. The FDA retained their approval standard for BTD and it is still the sponsor`s own responsibility to complete CMC readiness within a short-cut of development time.

The safety concerns: Although the BTD demonstrated positive benefit-risk evaluation at the time of approvals, the identification of serious tolerability issues might only be possible after exposing a larger patient population[xxiv]. Solvadi could be illustrative as of importance of safety monitoring after exposure in a wider patient group[xxv]. Nine post-marketing cases caused by drug-drug interaction with amiodarone were reported, with one patient having a fatal outcome, which prompted the addition of symptomatic bradycardia to the warnings and precautions in the label. Since the approval of drugs under BTD was based on significant therapeutic efficacy and positive benefit-risk evaluation in a small patient population, the importance of safety concern should be noted for the BTD drugs, similarly to the other drugs which were developed under accelerated program.

7.2. Impact of BTD on global regulatory environment

Key outcomes from analyzed case studies:

Even though the BTD program is a regulatory pathway initiated only by the US, for the global drug development it also needs to be considered in other major markets in ICH regions. As shown in the retrospective analysis on 22 approved BTD drugs, a delayed access of breakthrough therapy in the EU as well as the ``drug-lag`` in Japan with delayed and fewer approvals were observed.

One reason for this delay could be the longer review time needed by the EMA and PMDA as compared to the FDA approval time due to procedural difference. Differing to FDA, the EMA and PMDA issue the deficiency letters only at fixed procedural date as full package. All the deficiency letters need to be answered at the same time by sponsors, before the review restarts. In certain cases, the quantity and complexity of deficiency letters could be the time-limiting step for the approval timeline. In the US, the FDA reviewers have become familiar with the product due to interactions with sponsors and reviewing dossier during IND and rolling NDA, which allowed reviewing parts of dossiers prior to final submission. This could be an efficient step to shorten review time starting from submission. In EU, the sponsors have the chance to present their investigational products during scientific advice meetings. However, the appointed rapporteur and their advice might not always be consistent at the time of submission. Moreover, the less popularity of using the accelerated review tool in EU and Japan could be the additional reason for longer review time. While all BTD approved drugs received priority review by the FDA, accelerated review was given only to 40% by the EMA respectively to 30% by the PMDA.

The second reason to cause the delay could result from the different approval basis shown by the EMA and the FDA. Due to the concern on the safety of products prevailing over benefit in EU, the EMA trends to require more comprehensive data to make a positive approval decision. Even though the CMA intended to approve drugs based on promising therapeutic effects but for which only less comprehensive data are available, this expedited tool was less used in EU as the similar approval type used in the US, the accelerated approval. Of the 22 approved BTD drugs, 45% (10/22) received the accelerated approval in the US and of 12 approved oncology BTD

drugs, 83% benefitted from this expedited tool. In contrast, only 18% (3/17) were approved as conditional approval by the EMA and all three were distributed for oncology indication. As shown in a historical analysis from 2006 to 2013[xxvi], the CMA was often accompanied by significantly longer assessment times and less consensus among regulators about marketing authorization. Sponsors trend to use CMA in EU as ``rescue option`` instead of as a prospectively planned pathway to obtain early access.

The third consideration is the delayed submission by sponsors to EMA and PMDA. The procedure in the US allows the parallel assessment on separate NDAs of the same drug under the same trade name but for different indications. Differently, the procedure in EU only allows the subsequent assessment in case of different indications for the same drug under the same trade name. As shown in the retrospective analysis, the applicant trend to submit broader or multiple indications at the same time to EMA, with a more comprehensive data basis during review. Thus, some of breakthrough therapies were submitted by sponsor later in EU and Japan as compared to in the US.

Additional challenge in EU to consider is the current European health care reimbursement landscape.[xxvii] Even though the breakthrough therapy is approved by the EC, the national Health Technology Assessment (HTA) body will independently assess the effectiveness and in some situations the parameters could differ far from the authority assessment. A report[xxviii] comparing acceptance on clinical endpoints for oncology drugs approved by the EMA and evaluated by the G-BA (the German HTA): while the mortality endpoints are accepted by EMA and G-BA, the PFS and ORR which are well established and clinically relevant morbidity endpoints accepted by the EMA accepted were mostly excluded by G-BA from their evaluation. This could lead to additional delay for patients who are urgently under unmet medical needs conditions to access those innovative therapeutics in the EU countries.

Trends on developing expedited tools in EU and Japan to harmonize with BTD program:

To overcome those shortages which lead to delayed access of breakthrough therapy to patients in EU and Japan, EMA and PMDA have been recently developing similar concepts to expedite drug development to treatments in areas of high medical needs. In EU, the adaptive licensing

was launched in 2015 and the PRIME scheme launched in 2016, while the ``Sakigake`` has been introduced in Japan since April 2015.

EU Adaptive Licensing: The approach of adaptive licensing is to establish a prospectively planned process beyond the traditional pathway by attempting to two scenarios: 1) either an initial approval in a well-defined patient subgroup with a high medical need and subsequent widening of the indication to a larger patient population, or 2) an early regulatory approval (e.g. conditional approval) which is prospectively planned, and where uncertainty is reduced through the collection of post-marketing data on the medicine's use in patients. The Adaptive Licensing encourages early dialogue between all stakeholders, including the EMA, the industry, HTA bodies, organizations issuing clinical treatment guidelines and patient organizations. The adaptive licensing builds on existing regulatory framework, including scientific advice, compassionate use, the conditional marketing authorization mechanism, patients' registries and other pharmacovigilance tools that allow collection of real-time data and development of risk management plans. In the pilot stage, the agency calls for ongoing experimental medicine development programs in the early stage of clinical development to enable actionable input from relevant stakeholders[xxix].

EU PRIME scheme: Most recently, a scheme PRIME has been developed and launched by EMA to enhance support for the development of medicines that target an unmet medical need[xxx] since March 2016. The scheme focuses on ``*PRIority MEdicines*`` considered by the EMA that may offer a major therapeutic advantage over existing treatments, or benefit patients without treatment options. This regulatory tool is the most similar tool as compared to breakthrough designation launched by the FDA. As the eligible criteria for PRIME[xxxi], a medicine has to show its potential to benefit patients with unmet medical needs based on early clinical data. However, for micro-, small- and medium-sized enterprises (SMEs) and applicants from the academic sector, the application could be earlier based on compelling non-clinical data and tolerability data from initial clinical trials[xxxi]. The PRIME builds on the existing regulatory framework such as early dialogue, scientific advice and accelerated assessment. Once a candidate medicine has been selected for PRIME, the agency will appoint a rapporteur from the scientific committee CHMP or Committee for Advanced Therapies (CAT). The unique organizational commitment is

that the same rapporteur will provide continuous and consistent support to build knowledge ahead of a marketing authorization application. The agency will organize a kick-off meeting with the CHMP/CAT rapporteur and a multidisciplinary group of experts, so that they provide guidance on the overall development plan and regulatory strategy. A dedicated contact point will be assigned for the candidate medicine. The scientific advice will be provided at key development milestones, involving additional stakeholders such as HTA bodies, to facilitate quicker access for patients to the new medicine[xxxi]. After one month of inception of the PRIME Scheme, the EMA has received several requests. Since PRIME scheme is a very similar tool to BTD, it will be very interesting to analyze the final implementation of this tool in EU after two or three years after its launch.

Japan ``Sakigake``: In recent years, Japan has been encouraging pharmaceutical companies to get new products approved first there, or at the very least, parallel to the US and EU. Since April 2015, Ministry of Health, Labour, and Welfare (MHLW) in Japan launched a most recent regulatory tool ``Sakigake`` as a process to provides faster access to new therapies responding to high medical needs. Once a product is designated for the Sakigake fast track, all priority review designation features will also be applied, the prioritized clinical trial and pre-application consultation will be conducted, a PMDA manager will be assigned as a concierge throughout entire development, and post-marketing safety measures will be considered to compensate early launch of innovative therapy in Japan. Review time will be shortened from 9 to 6 months and the regulators in Japan hope the Sakigake approval pathway will potentially cut pharmaceutical review times by half[xxxii]. The eligibility for Sakigake designation seems very similar to BTD, and relies on the novel mechanism of action, the desirability of early commercialization, and the demonstration of prominent effectiveness. However, Sakigake is only applied to a candidate therapy that has been developed in and received targeting approval in Japan prior to other countries (including global simultaneous submissions), which in my opinion could be a limiting criterion for global pharmaceutical industry. Starting in April 2015, the first six innovative drugs were selected and announced for Sakigake as a pilot project[xxxiii]: almost all were domestically developed and only Keytruda was developed and registered by international pharmaceutical industry.

7.3. Conclusion and Outlook

Taken all together, the BTD created a regulatory environment offering unique benefits from the FDA to expedite access of breakthrough therapy to patients with serious diseases with high unmet medical needs. The FDA provided intensive resources, intensive guidance and significant flexibility to breakthrough therapy development. But it is important to understand that the BTD is not a guarantee for success but is correlated with certain risks for sponsors, and it is still the sponsor`s own responsibility to overcome all challenges associated with the expedited development pathway. The breakthrough therapy development is certainly very dynamic, resource intensive and cost intensive for sponsors, thus the sponsors should be selective about their candidates and be ready to adapt the internal company process accordingly to the BTD pathway.

The BTD encouraged the use of modern scientific tools to shorten pre-market development time and minimize number of patients in pivotal trials, especially the patients exposed to less efficient therapy. This approach is of importance to treat serious life-threatening disease with high unmet medical needs. Nevertheless, it is notable that the confirmatory clinical trials to compare the conditionally approved breakthrough therapy with the available therapy are still required as post-marketing requirements for BTD program. In terms of BTD program it will be important to investigate whether some post-marketing measures would be developed to reduce number of patients with serious disease conditions potentially exposed to less efficient therapy.

A lack of harmonization of those breakthrough therapies was observed in EU and Japan based on case studies, but both the EMA and the PMDA have been currently developing similar regulatory tools to achieve a harmonized global BTD concept. It will be interesting to analyze the PRIME scheme and Sakigake two or three years after their launch to evaluate the implementation of this global convergence concept of BTD programs.

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Annex: Overview of 22 approved BTD drugs (NMEs) in the year of 2013 to 2015

Trade Name	INN	BLA/ NDA	Sponsors	The first approved indication by the FDA
Alecensa	Alectinib	NDA	Genentech/ Roche	Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC), who have progressed on or are intolerant to crizotinib
Blincyto	Blinatumomab	BLN	Amgen	Treatment of Philadelphia chromosomenegative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
Darzalex	Daratumumab	BLN	Janssen	Treatment of patients with multiple myeloma (MM) who have received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or are double refractory to a proteasome inhibitor and an immunomodulatory agent
Empliciti	Elotuzumab	BLN	BMS	Treatment of patients with multiple myeloma who have received one to three prior therapies
Esbriet	Pirfenidone	NDA	InterMune	Treatment of idiopathic pulmonary fibrosis (IPF)
Gazyva	Obinutuzumab	BLN	Genentech/Roche	Treatment of patients with previously untreated chronic lymphocytic leukemia in combination with chlorambucil
Harvoni	Ledipasvir/ Sofosbuvir	NDA	Gilead	Treatment of chronic hepatitis C, genotype 1 infection
Ibrance	Palbociclib	NDA	Pfizer	Treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (BC) as initial endocrine-based therapy for their metastatic disease
Imbruvica	Ibrutinib	NDA	J&J/ Pharmacyclics	Treatment of patients with mantle cell lymphoma (MCL).
Kanuma	Sebelipase Alfa	BLN	Alexion	Treatment of patients with a diagnosis of lysosomal acid lipase (LAL) deficiency
Kalydeco	Ivacaftor	NDA	Vertex	Treatment of cystic fibrosis (CF) patients 2 years and older who have one of the following mutations in CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and R117H
Keytruda	Pembrolizumab	BLN	Merck	Treatment of patients with unresectable or metastatic melanoma & disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor
Ofev	Nintedanib	NDA	Boehringer Ingelheim	Treatment of idiopathic pulmonary fibrosis (IPF)
Opdivo	Nivolumab	BLN	BMS	Treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor
Orkambi	Lumacaftor / Ivacaftor	NDA	Vertex	Treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene
Praxbind	Idarucizumab	BLN	Boehringer Ingelheim	Treatment of patients treated with Pradaxa® when reversal of the anticoagulant effects of dabigatran is

Trade Name	INN	BLA/ NDA	Sponsors	The first approved indication by the FDA
				needed for emergency surgery/urgent procedures and in life-threatening or uncontrolled bleeding
Sovaldi	Sofosbuvir	NDA	Gilead	Treatment of chronic hepatitis C infection.
Strensiq	Asfotase Alfa	BLN	Alexion	Treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP)
Tagrisso	Osimertinib	NDA	Astrazeneca	Treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small-cell lung cancer (NSCLC), as detected by an FDA approved test, who have progressed on or after EGFR TKI therapy
Viekira Pak	Ombitasvir, Paritaprevir and Ritonavir	NDA	AbbVie	Treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis
Xuriden	Uridine Triacetate	NDA	Wellstat Therapeutics	Treatment of hereditary orotic aciduria
Zydelig	Idelalisib	NDA	Gilead	Treatment of relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities
Zykadia	Ceritinib	NDA	Novartis	Treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib

Eidesstattliche Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Dr. Qian Mao

Berlin, 30 June 2016