A retrospective landscape assessment of the use of real-world data in the FDAs recent (Jan 2019-Jun 2022) regulatory decision making for the pharmaceutical products.

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List of Abbreviations

Abbreviations	Full Form
AACR	American Association for Cancer Research
AC	Advisory Committee
ACH	achondroplasia
AE	Adverse Event
AGV	Annualized growth velocity
BLA	Biologic license application
BTD	Breakthrough therapy designation
CBER	Centre for biologics evaluation and research
CDC	Centers for Disease Control and Prevention
CDER	Centre for drug evaluation and research
CINRG	The Cooperative International Neuromuscular Research Group
CNI	calcineurin inhibitor
CRF	Case report form
CUP	Compassionate Use Program
DEPI	Department of Epidemiology
DLBCL	diffuse large cell B cell lymphoma
DPV	Division of Pharmacovigilance
EAP	Expanded Access Program
EDC	electronic data capture
EDS	excessive daytime sleepiness
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ES	epithelioid sarcoma
EUA	Emergency use authorization
FDA	Food and drug administration
FEARS	FDA Adverse Event Reporting System
FGFR	Fibroblast growth factor receptors
FHAD	Flatiron Health Analytic Database
GCP	good clinical practice
GIST	gastrointestinal stromal tumor

GM-CSF	Granulocyte-macrophage colony-stimulating factor
ICH	International Conference on Harmonization
IIT	Investigator-initiated trial
IO	Immunotherapy
ISE	Integrated summary of effectiveness
ISS	Integrated summary of safety
ITT	intent to treat
LOT	Line of Therapy
MAA	Marketing authorization application
MBC	metastatic breast cancer
MDR	Multi-discipline review
MDR-TB	Multi-drug resistant tuberculosis
MET	Mesenchymal-epithelial transition factor
MMF	mycophenolate mofetil
MMF	Multiple myeloma
MSK	Memorial Sloan Kettering Cancer Center
NCI	National Cancer Institute
NDA	New Drug Application
NH	Natural history
NME	New molecular entitiy
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine receptor kinase
ODAC	Oncologic Drugs Advisory Committee
OSE	Office of Surveillance and Epidemiology
PASS	Post-Authorization Safety Study
PBRER-4	Periodic Benefit Risk Evaluation Report, Number 4
PK	pharmacokinetics
PNCR	Pediatric Neuromuscular Clinical Research database
PROS	PIK3CA related overgrowth spectrum
PSUR	Periodic Safety Update report
rcPMP	Recombinant Escherichia coli-derived Cyclic Pyranopterin Monophosphate
RCT	Randomized controlled trial

ROS-1	ROS proto-oncogene
RRMM	relapsed refractory multiple myeloma
RWD	Real world data
RWE	Real world evidence
SAEs	Serious Adverse Events
SAP	Statistical analysis plan
sBLA	supplemental BLA
SCRIH	Scientific Committee for Research in Human Subjects
SMA	Spinal Muscular Atrophy
sNDA	supplemental NDA
STS	soft tissue sarcoma
TB	Tuberculosis
TCBZ	Triclabendazole
TI/NR MDR-TB	treatment-intolerant/non-responsive multidrug-resistant tuberculosis
US	United States
VVC	vulvovaginal candidiasis
WHO	World Health Organisation
XDR-TB	Extensively drug resistant Tuberculosis

1. INTRODUCTION

The United States Food and Drug Administration's (FDA's) drug approval standard requires substantial evidence of effectiveness from adequate and well-controlled investigations including clinical investigations that incorporate, a valid comparison to a control, to "distinguish the effect of a drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or a biased observation". [1] As per the regulations (21 CFR 314.126) and ICH E10 guidance, US-FDA also considers internally controlled study designs (placebo, active treatment, dose comparison, no-treatment) where "the control group and test groups are chosen from the same population and treated concurrently". [1] In the case of diseases with high unmet medical need reliance on external control is also acceptable as it would be unethical to use placebo control in such cases and active comparators don't exist. When a trial is externally controlled, the results of treatment with the test drug may be compared with experience derived from the adequately documented natural history of the disease or condition, a registry, published literature, or patient medical records. [2] This type of evidence falls under the real-world evidence where the real-world data collected as a part of usual course of disease involving use of medication under usual clinical practice not following a pre-specified investigation plan. The ICH E10 guidance defines an externally controlled trial as "one in which the control group consists of patients who are not of part of the randomized study as the group receiving the investigational agent i.e., there is no concurrently randomized control group" [1]

So, even though randomized clinical trials (RCT) are the gold standard for providing evidence for regulatory approval of new medicines, insights derived from real-world data are also used to support the healthcare decisions. With rise in the development of novel drugs and therapy options (specifically targeted to act on a target receptor) for rare diseases or due to involvement of special population (target groups), the Sponsors often faces difficulties in the clinical trial recruitment due to narrow inclusion criteria. Also randomized clinical trials in case of high unmet medical need lead to time-consuming studies which by the end in some cases can lose relevance due to changing landscape of the rare disease conditions or due to shift in the therapy goals. In such cases evidence from real-world data (RWD) can be used to supplement and expedite evidence generation though it's not the only utility of the real-world data.

There is a rise in the use of real-world data in the submission of the marketing authorization. This shift is seen since real-world data is now more accessible than ever due to the rising digitalization of the healthcare industry and use of medical applications and wearable devices which can be used for continuous monitoring. This has also increased the availability of large and better curated data sets. The use of RWD has moved beyond post-marketing surveillance (for safety and efficacy) to its use in development & clinical application. It has the potential to help improve the design and conduct of the clinical trials and provide answers to questions which were earlier thought to be impractical. Often it is used to supplement the clinical evidence and in some cases is the sole basis of indication extension by the health authority.

Initiatives and guidance by the US FDA on the use of real-world evidence:

The utilization of real-world evidence (RWE) has increased in the recent years also due to increasing support by the health agencies across the globe starting with the US FDA which has published several draft guidance (as shown Figure 1). It all started with the Sentinel initiative back in 2008 followed by the passage of the United States' 21st Century Cures Act in 2016 and the use of RWD has advanced significantly from post authorization safety and effectiveness studies to its use in design of clinical studies, characterizing patient population, market utilization of the medicines and supporting the benefit-risk assessment for regulatory decision making. Also, the PDUFA VII which came in effect in September 2022 has facilitated use of RWE in submissions of marketing authorization. [3] One such program is the Advancing Real-World Evidence (RWE) Program, an initiative by the US FDA under PDUFA VII which seeks to improve the quality and acceptability of RWE-based approaches in support of new intended labeling claims, including approval of new indications of approved medical products or to satisfy post-approval study requirements. [4] The Advancing RWE Program provides sponsors who are selected into the Program the opportunity to meet with Agency staff—before protocol development or study initiation—to discuss the use of RWE in medical product development. The Advancing RWE Program is an optional pathway for sponsors submitting RWE proposals; established procedures to engage with the Agency and will continue to be available. [4] Also recently US-FDA has announced new funding opportunities for using RWD to generate RWE in regulatory decision making to address topics related to FDA's Real-World Evidence (RWE) Program

and to enable FDA to assess the potential utility of real-world data (RWD) in generating RWE. [5]

Other FDA initiatives supporting the deployment of RWD and RWE in product development include various demonstration projects aimed at improving the usefulness of RWD, exploring methods of designing studies and analyzing data to generate RWE, or developing specific tools and techniques to assist in this process. An example is the OneSource Project which is developing approaches for automating the flow of structured data from electronic health records into external systems to facilitate research and narrow the divide between patient care and clinical investigations. [6]

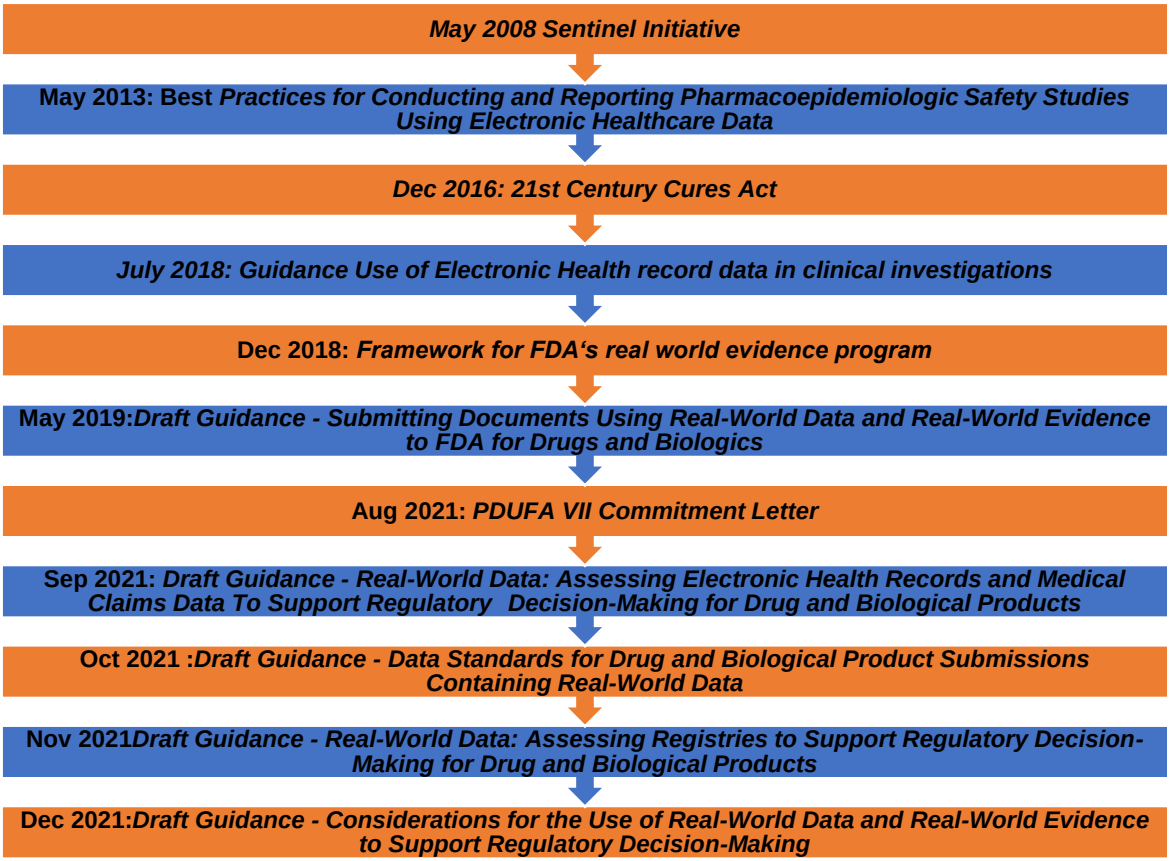

Figure 1:US FDAs Guidance and Framework which support use of real-world evidence submission. [7]

All the initiatives shown in Figure 1 were intended to accelerate medical product development and bring innovations faster to the patients who need them.

1.1 Real World Data (RWD)

Real-world data are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. [8] US FDA cites several potential sources of RWD, like:

- Electronic health records (EHRs)
- Claims and billing activities.
- Product and disease registries
- Patient-generated data including in home-use settings.
- Data gathered from other sources that can inform on health status, such as mobile devices.

In relation to the use of RWD in the marketing authorization application it is important to mention the non-interventional studies (observational) and externally controlled trials (including historically controlled trials).

Non-interventional studies: A non-interventional study (also referred to as an observational study) is a type of study in which patients received the marketed drug of interest during routine medical practice and are not assigned to an intervention according to a protocol. Non-interventional studies analyze data reflecting the use of a marketed drug administered in routine medical practice, according to a medical provider's clinical judgment and based on patient characteristics, rather than assignment of a participant to a study arm according to a research protocol. As such, non-interventional studies are not clinical investigations as defined under § 312.3 and do not require an IND. [9]

Externally Controlled Trial: A clinical trial that compares outcomes in a group of participants receiving the test treatment with outcomes in a group of people external to the trial, rather than to an internal control group consisting of participants from the same trial population assigned to a different treatment or no treatment. The external control arm can be a group of treated or untreated patients from an earlier time in a historically controlled trial or a group of treated or untreated patients during the same time period but in another setting. [9]

A wide spectrum of study designs rely on the RWD in some form as is seen in Figure 2.

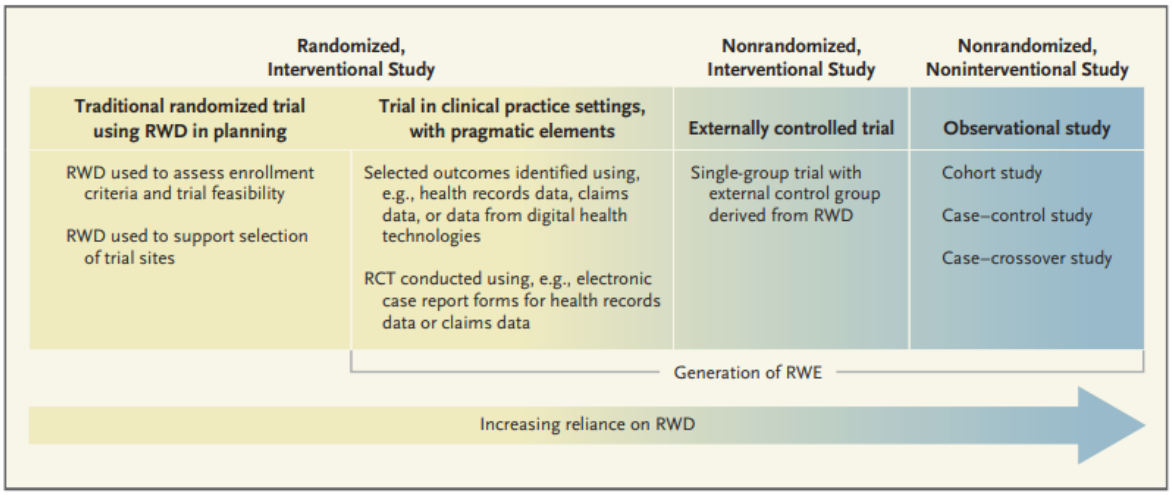

Figure 2: From left to right in the above figure shows increase in reliance on real-world data (RWD) and real-world evidence (RWE) to supplement the data for a positive assessment [6]

On moving from left to right the reliance of study designs increases on the RWD. Even for planning the traditional randomized clinical trials there is need of real-world data which helps in deciding the inclusion criteria, the demography of the population to be included (high risk patient population) and to know about the therapeutic agents used in the usual clinical practice (to show effectiveness) against which the comparison need be performed. Then there are pragmatic clinical trials (example with a broader patient inclusion covering almost all patients who will receive treatment in routine care) which have always been seen to provide answers about the real-world effects of the treatment decisions. [10] Followed by the externally controlled and non-interventional studies where the reliance on real-world data increases.

1.2 Real-world evidence (RWE):

Real-World Evidence (RWE) is the clinical evidence about the usage and potential benefits, or risks of a medical product derived from analysis of RWD. [8] Section 505F(b) of the FD&C Act defines RWE as “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than traditional clinical trials” (21 U.S.C. 355g(b)). [8]

1.3 Differentiation between real-world data from real-world evidence

Real-world evidence can be understood as the insights and findings derived from the analysis of real-world data. RWE can be generated by different study designs or analyses,

including but not limited to randomized trials, including large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective) as seen above. [7]

The basic utility of RWE is to fill the gap in the evidence for efficacy or safety. Whenever a gap in the evidence is seen then through hypothesis generations relevant RWD sources can be identified which my provide data for answering the research question then using appropriate curation and data transformation technique fit-for purpose RWD set can be obtained. After appropriate statistical analysis the real-world data can provide real-world evidence to supplement the benefit-risk assessment for a medicinal product.

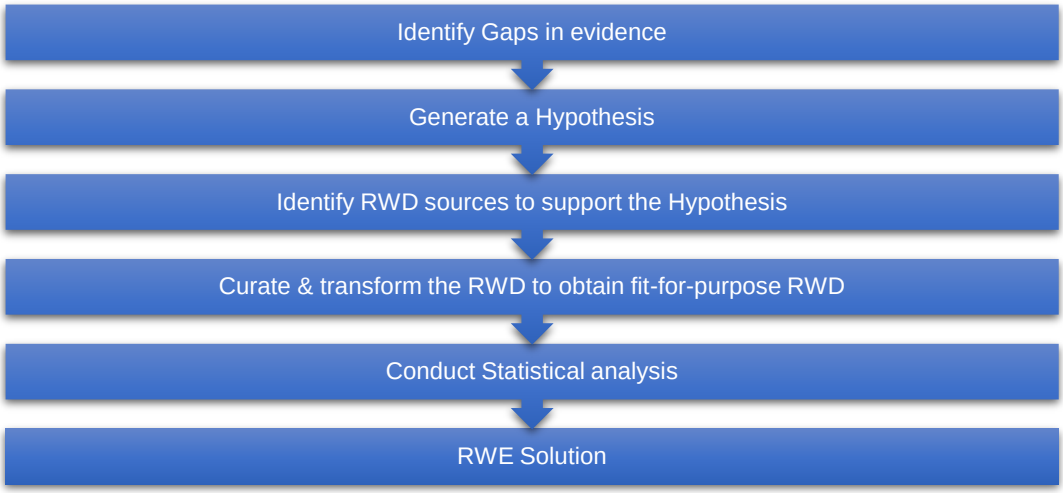

Figure 3: Transformation of RWD to RWE

In short after processing of the raw real-world data one can obtain real-world evidence which can provide insights on benefit-risk association for a medicinal agent (refer Figure 3).

From FDA´s initiatives in the field of real-world evidence (as seen in Figure 1) it is clear that FDA supports the use of real-world evidence because the real-world evidence has numerous applications across the entire product lifecycle which can be divided in to following stages:

Early development:

- Biomarker assessment: EHR-derived RWD, coupled with genomic information, is a powerful combination for generating hypotheses regarding new biomarker-mediated therapies. [11]
- For selection of molecular targets for treating rare conditions based on the published scientific literature.

- Understand the disease progression and response to available treatment options.
- Assess the therapeutic areas of unmet medical need.

Clinical development:

- Assess the efficacy and safety of the available treatment options, analyze the disease epidemiology.
- Selection of appropriate comparator population for clinical trial (clinical trial recruitment).
- Selection of appropriate clinical endpoints for the clinical study based on evaluation from the physician's needs.
- Design of external control studies or historical control studies.

Regulatory Assessment:

- Natural history data to provide therapeutic context.
- Unmet medical need.
- RWD for Indirect treatment comparison.

Market access:

- Long term survival extrapolation: post marketing efficacy data.
- Health technology assessment: To demonstrate the real-world benefits for HTAs and payers and gain leverage in pricing negotiations by understanding real-world treatment patterns and risks of outcomes.

Post Approval

- Real-world studies can be used to fulfill the post-marketing commitment and to generate patient data in routine clinical practice.
- Long term safety data generation.
- Extension of indication: The efficacy and acceptability of the approved drugs and biologics in new patient population using the RWE can help in extension of label and reassure clinicians that it is acceptable for new populations.

1.4 Applications of RWE: [11]

Based on the use cases and gap in evidence the applications of RWE can be summarized as below:

1) Characterizing natural history or unmet medical need.

2) Analysis of conditions in terms of available treatment options and their real-world response for comparison.
3) As an external comparator to a single arm trial for benchmarking in conditions where use of placebo control is unethical. Also, the use of hybrid designs where, for example, we have two to one randomization, and the control arm is complemented with some real-world data.
4) Satisfying post-marketing requirements or commitments especially for accelerated approval e.g., efficacy and safety in special populations like pregnancy.
5) To expand a label into new indications based on the off-label use of the medicinal product in patient population which is not covered by the approved label.
6) For the global market access including Health Technology Assessments (HTA)

2. METHODS

To identify the submissions where RWE was used in a submission between Jan-2019 and Jun-2022, the assessment reports and the drug approval packages available from the www.drugs@FDA were reviewed and the information regarding the source of RWE, its purpose, Agency´s decision and communications between the FDA and the Applicant were analyzed.

- To determine the cases where the probability of acceptance of RWE is higher.
- To understand the mistakes made by the Sponsors with the submission of RWE.

To analyze the RWE based submission and to devise an ideal strategy for submission of the RWE in support of Benefit-Risk assessment.

2.1 Extraction of List of Approvals

To determine which FDA approvals used RWE, first a list of small molecules and large biologicals approved by the CDER and CBER was obtained.

The list of medicinal products approved by CDER was obtained using www.drugs@fda. The obtained list was filtered for Submission Type 1 (New Molecular entity), Type 10 (New indication submitted as distinct NDA), BLA original submissions (Approved by CDER & CBER) and Efficacy supplements for the BLA approved by CBER. Following Table 1 shows the number of approvals between Jan 2019 till Jun 2022.

Table 1: List of approvals from Jan 2019 till Jun 2022 with Type 1 NDA, Type 10 NDA, BLA submissions and s-BLA

Year	Total Approvals (Type 1, Type 10, BLA, s-BLA)
2019	59
2020	66
2021	75
2022	19

The Figure 4 is a diagrammatic representation of the shows the entire methodology used for writing this master thesis and to ease the understanding.

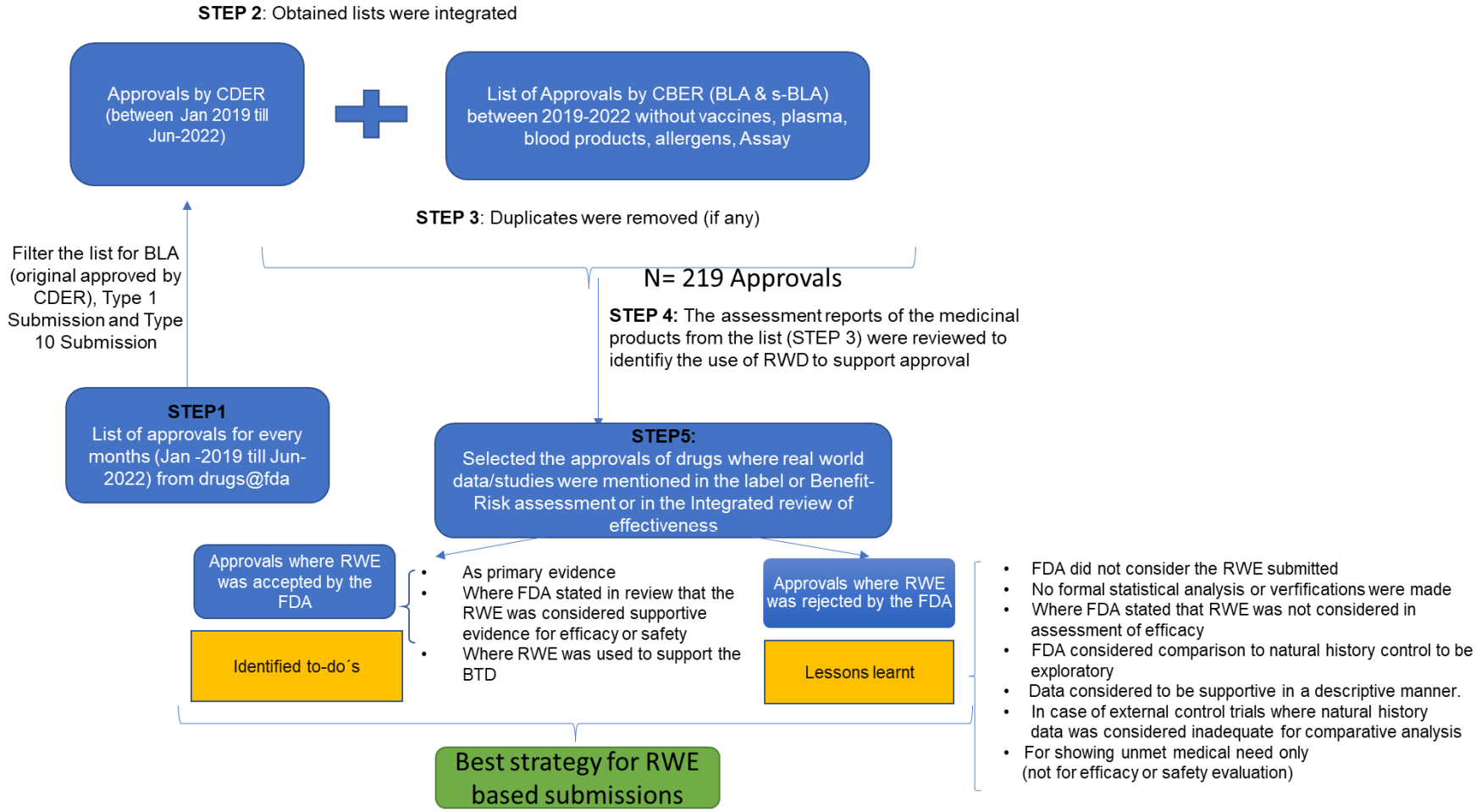

Figure 4: Flow chart to represent the methodology used for the writing of this master thesis

2.2 Inclusion Criteria

From the obtained approvals from Table 1 only those applications (NDA, BLA and s-BLA) using RWE were considered which fulfilled one of the following inclusion criteria.

- Where RWD and real- world evidence has been used for benefit-risk assessment and has been discussed
    a) in Section 1.3 of Multi-discipline review,
    b) in Statistical and clinical evaluation (Section 8 of Multi-discipline review) for selection of a surrogate endpoint for accelerated approval, or
    c) for selection of target patient population which supplement information about the demographic and clinical characteristics which help in designing the confirmatory clinical studies, or
    d) in the integrated review of effectiveness (Section 8.1.5 Integrated Assessment of Effectiveness) in the multi-discipline review,
    e) in Clinical review memorandum (in case of BLA),
    f) in Section 1.2 Conclusions on the Substantial evidence of Effectiveness to show based on the real-world data that the new therapy brings advantage in comparison to the available therapy options,
    g) support the safety.
- When RWE is used to provide therapeutic context by serving as external or historical control for the single arm clinical studies (as mentioned in Section 9 Summary and Conclusions of Multi-discipline review), as use of placebo control would be deemed unethical.
- For providing substantial evidence of efficacy and safety. In cases, where real-world data provided major evidence of efficacy or safety.
- For extension of indication based on the real-world use of the medicinal product to provide evidence of safety and efficacy (in post-marketing setting from off-label use).
- BLA and sBLA approved by CBER were also included in the researching the RWE based submission.
- RWE from the Compassionate use program in EU and Expanded Access program in US.

- As proof of unmet medical need based on retrospective study analysis submitted by the Applicant to provide context on use of available non-targeted the standard of care which is then used by the Applicant for comparison and is discussed in the integrated assessment of effectiveness by the reviewer provides therapeutic context and ultimately translates into accelerated approval.
- Wherever the RWE was used to prove an unmet medical need or included in the clinical package and was discussed in the benefit-risk assessment.
- Only those submissions were considered where the RWD was used or mentioned in evidence in the analysis of condition and was then further discussed for benefit-risk assessment (in one of these sections of MDR; 7.0: Sources of clinical studies, 8.1.5 Integrated Review of Effectiveness, 8.1.6: Assessment of efficacy across trials, 8.1.7: Integrated Assessment of Effectiveness, 8.4: Conclusion & Recommendations)
- RWE in the form of post-marketing data from foreign countries (eg, safety data from Eudravigilance) and post authorization safety studies.
- The data extracted from registries or clinical studies, or hospitals was also considered real-world evidence as it is data once generated and used again in a retrospective manner after transformation to provide relevant therapeutic context and fulfill gap in evidence.

2.3 Exclusion criteria

The exclusion criteria for not considering certain submissions were as follows:

- In cases where the RWE was used with the sole purpose of analysis of disease conditions using literature evidence to show an unmet medical need, information on background of the disease and was not discussed further in the benefit-risk assessment and had no significant bearing on the assessment of the efficacy and safety directly.
- Real world data serves the sole purpose of showing the rarity of the disease.
- Where use of real-world data collection was advised by the Agency for post-marketing surveillance.
- Where real world data was used for claiming safety in special populations like pregnant and lactating women (use in specific population).
- Blood product, approved as per 21 CFR 607.3(b) using RWE based submission eg, Kedrab rabies immune globulin (human)

- Vaccines using RWE data to supplement the efficacy and safety information eg, *COMIRNATY* COVID-19 Vaccine, mRNA, SPIKEVAX
- Allergens and assay tests were excluded.
- Type 2, Type 4, Type 5, Type and Efficacy supplements (s-NDA). (Note: Ibrance & Prograf were the only exceptions of s-NDA included in the results and discussion as examples of indication extension based on off-label use.)
- Combination products

2.4 Identification of Submissions with RWE

For identifying the submissions incorporating RWE, FDA's public resources were then systematically examined as per the inclusion & exclusion criteria mentioned above. The FDA resources used included the review documents like multi-disciplinary review documents, approved label (section 1: and section 14 Clinical studies), administrative correspondence, Regulatory history, data on the Advisory committee meetings (wherever applicable), Clinical review, Statistical review, Integrated review, Summary review and Other reviews were taken from CDER´s Drugs@FDA for analysis.

The data sources for products approved by CBER include Approved label, BLA Clinical review memoranda, Statistical review, Team meeting summaries, Summary basis for regulatory action. Additionally, the FDA´s press releases were examined for the drug approvals and information about use of real-world data. All available information on RWE use from research databases like Flatiron and seminars on RWE use by pharmaceutical companies were analyzed in order to gather all data on FDA approvals utilizing RWD in some capacity.

2.5 Abstraction of data and the review of the assessment reports by the FDA

The approvals were analyzed to find the list of approvals where the real world-data was discussed by the Agency in the benefit-risk assessment or in the assessment of effectiveness. Also, wherever the use of real-world studies was mentioned in the product label.

Whenever real-world evidence in a submission application was accepted by the Agency, its purpose and source were determined, and the limitations encountered by the reviewer were also listed along with the strategies the applicant undertook to overcome the issues. The discussion between the Applicant and US-FDA pre-submission and post-submission wherever found were also listed. The approvals for which the Agency approved the RWE and the grounds behind that acceptance were identified. It was also assessed for which

indications real world evidence is often used and the likelihood that real-world evidence will be accepted. From all cases a list of lessons learnt is made.

To better understand the different terminologies used in the assessments in the Results section 3.1, about whether RWE was accepted or not accepted by the US-FDA for the evaluation of benefit-risk following Table 2 provides brief explanation under categorize the cases in to two categories. The final conclusion of US-FDAs assessment was considered to be positive if the assessment included terms like considered as primary evidence, accepted or accepted as supportive evidence. In cases where US-FDA assessment includes partly considered, inconclusive, not addressed or not considered were considered to be negative cases.

Table 2: Classification and explanation of the terms accepted and not accepted (with respect to RWE)

Agency Judgement	Terms used in Result table	Explanation
Accepted	Accepted as primary evidence	RWE provided major evidence for efficacy
	accepted as Supportive evidence	contributed to the totality of evidence or not independently verified and considered supportive by the FDA
	accepted	accepted for supporting break through designation or for selection of surrogate endpoint
Not Accepted	partly considered	as evidence for trial design, epidemiology comparison, or for something other than safety and efficacy
	inconclusive	FDA performed review and found issues and did not accept the data from safety/efficacy (or had limitations due to lack of comparability or misleading estimates)
	not addressed	FDA did not consider for efficacy, safety or effectiveness or detailed review was not conducted
	Not considered	FDA found the evidence not satisfactory or exploratory

Finally, to better comprehend the FDA's requirements for RWE-based submissions, an example of the best strategy for the pharmaceutical companies is presented for a regular approval using supportive evidence from real-world data.

3. RESULTS

All the submissions where real world data was used by the Applicant and was discussed either for supporting unmet medical need, providing context for assessment of clinical benefit, benefit-risk assessment, comparability of demography of patient population included in the clinical studies or selection of clinical endpoints or to support the integrated assessment of effectiveness are summarized in the Section 3.1 as case studies (Section 3.1.1 including NDA and Section 3.1.2 including BLA). The information about source of real-world data, its purpose and whether the RWE was accepted or rejected by the Agency is also included along with date of approval, sponsors name and whether use of RWE was mentioned in the label. It is important to mention that two s-NDA Efficacy supplements Ibrance and Prograf are included as additional examples in the results. For more details on the submissions Appendix can be consulted.

3.1 Case studies of submissions to US FDA with real world evidence

3.1.1 NDA submissions to US FDA employing real-world evidence.

In this section, case studies of NDA (initial marketing authorization) assessed by CDER between Jan 2019- Jun 2022 where the Applicant included RWE to support benefit-risk assessment in accordance with the inclusion criteria mentioned in section 2 methods.

*Please note that wherever FDA or Agency is mentioned it refers to US FDA.

Also note that only 2 s-NDA applications Ibrance and Prograf are included in this section as examples of off-label use).

1) EGATEN (triclabendazole) NDA 208711

- **Sponsor:** Novartis Pharmaceuticals Corporation
- **Approval date:** 13-Feb-19
- **Indication:** For the treatment of fascioliasis in patients 6 years of age and older.
- **Source of RWD:** Novartis Global Safety Database and literature reports. Named Patient Program conducted by CIBA/Novartis Publications referenced by the Applicant, Egyptian government sponsored studies for fascioliasis, paragonimiasis studies. Most of the data presented in the NDA was already generated from disparate published and unpublished studies which were not all performed under GCP. [12]
- **Purpose:** The RWD provided supporting evidence for absence of risks and any new safety signals and to evaluate the effectiveness and safety of Egaten in humans. [12]
- **FDA´s decision:** Agency accepted the RWE as supporting evidence for safety.
- **RWE mentioned in Package insert:** Yes.

2) **IBRANCE sNDA (Efficacy supplement)**
   - **Sponsor:** Pfizer, Inc.
   - **Approval date:** 4-Apr-19
   - **Indication:** For the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in women and in men (extension of indication for men). [13]
   - **Source of RWD:**
     - Flatiron Health study (retrospective analysis of EHR),
     - IQVIA study data (retrospective analysis of claims data). It included analysis of claims data for Males Treated for Metastatic Breast Cancer (MBC).,
     - Post marketing reports and the review of cases in Pfizer global safety database. [13]
   - **Purpose:** The efficacy as well as safety analysis was carried out using real world evidence. The Agency considered the RWE as supportive evidence for safety profile in men for the use of palbociclib. [13]
   - **FDA´s decision:** Accepted as evidence of safety in men and efficacy from the off-label use in men.
   - **RWE mentioned in Package insert:** Yes.

3) **BALVERSA (erdafitinib) NDA 212018**
   - **Sponsor:** Janssen Biotech Inc
   - **Approval date:** 12-Apr-19
   - **Indication:** Anti-cancer, for the treatment of locally advanced and metastatic urothelial carcinoma.
   - **Source of RWD:** Real world evidence from retrospective study using the Flatiron-FMI and the Bladder Cancer Research Initiative for Drug Targeting in Germany (BRIDGE) databases was conducted by the Applicant. [14] The BRIDGE dataset was more recent than the Flatiron-FMI dataset.[14]
   - **Purpose:** Natural history data to serve as external control data for comparison of results and to show that the patients with FGFR mutations would be a special subset of patients who would benefit with Balversa in comparison to the available therapy options. Also, to determine the prognosis of the patients with metastatic urothelial malignancies that have FGFR mutations. [14]
   - **FDA´s decision:** Not considered. Due to methodological problems with the presented RWE, no conclusive proof could be provided. [14]
   - **RWE mentioned in Package insert:** No

4) **XPOVIO (Selinexor) NDA 212306**
   - **Sponsor:** Karyopharm Therapeutics
   - **Approval date:** 3-Jul-19

- **Indication:** For the treatment of patients with relapsed refractory multiple myeloma (RRMM).
- **Source of RWD:** A retrospective observational study (KS-50039) using electronic health record data as supportive evidence was submitted by the applicant in the NDA. This data was collected from Flatiron Health Analytic Database (FHAD) with n=64 subjects with primary endpoint of overall survival. [15]
- **Purpose:** To serve as an external control arm and to show agreement with results in the literature about the use of other anti-myeloma therapies. [15]
- **FDA´s decision:** Not considered for evaluation of efficacy due to comparability issues of the two cohorts. Also, the protocol and SAP were not communicated earlier to the FDA which led to consideration of post-hoc analysis. [15]
- **RWE mentioned in Package insert:** No.

5) PRETOMANID (pretomanid) NDA 212862

- **Sponsor:** Global Alliance for TB Drug Development (MYLAN IRELAND LTD)
- **Approval date:** 14-Aug-19
- **Indication:** Treatment of pulmonary extensively drug-resistant (XDR) and treatment-intolerant/nonresponsive multidrug-resistant (MDR) tuberculosis in adults. [16]
- **Source of RWD:**
  - Literature review: Literature analysis of 16 peer-reviewed articles which reported treatment outcomes in patients with extensively drug-resistant tuberculosis (XDR-TB) excluding articles where the treatment included any of the Nix-TB regimen drugs (pretomanid, bedaquiline, and linezolid) or delamanid (delamanid is in the same drug class as pretomanid). [16]
  - Historical control: To supplement the data from literature review, a matched historical control group of patients from Brooklyn Chest Hospital in Cape Town, South Africa was used as an external control. [17].
- **Purpose:** TB Alliance provided a literature summary and case matched analysis of historical control data for XDR-TB patients to support efficacy outcomes. [16]
- **FDA´s decision:** FDA accepted the matched historical control data for comparison. [16]
- **RWE mentioned in Package insert:** Yes.

6) WAKIX (pitolisant) NDA 211150

- **Sponsor:** Bioprojet Pharma
- **Approval date:** 14-Aug-19
- **Indication:** Treatment of excessive daytime sleepiness (EDS) in adult patients with narcolepsy. [18]

- **Source of RWD:** The European Compassionate Use Program, and the U.S. Expanded Access Program, publicly available European post marketing data (Eudravigilance), data from WHO´s Vigibase, European post-marketing safety data from FAERS, Off-label use and literature report on the use of the drug in all possible indications. [18]
- **Purpose:** The drug was intended for chronic administration and the Agency required long term-safety data which came from the above-mentioned sources. [18]
- **FDA´s decision:** The Agency considered the real-world safety data as supportive evidence to ensure that no new risks were associated with the use of pitolisant. [18]
- **RWE mentioned in Package insert:** No.

7) ROZYLTREK (entrectinib) NDA21275

- **Sponsor:** Genentech, Inc.
- **Approval date:** 15-Aug-19
- **Indication:** Lung cancer;
  Indication 1: ROS1-Positive Non-Small Cell Lung Cancer NDA 212725.
  Indication 2: NTRK Gene Fusion-Positive Solid Tumors-(adult and Pediatric patients) NDA 212726. [19]
- **Source of RWD:** RWD submitted (from Flatiron Health Analytic Database of 69 patients) for NDA 21275 for indication ROS1-Positive Non-Small Cell Lung Cancer. [18]
- **Purpose:** To serve as external control data for comparative analysis of time to treatment discontinuation (TTD), progression free survival (PFS), and overall survival (OS) between the time period of Jan 2011 to Jun 2018. [19]
- **FDA´s decision:** DEPI performed review of the submitted RWE but due to limitations of the data and comparability issues did not consider the RWE further. (Not accepted.) [18]
- **RWE mentioned in Package insert:** No.

8) AYVAKIT (avapritinib) NDA 212608

- **Sponsor:** Blueprint Medicines Corporation
- **Approval date:** 9-Jan-20
- **Indication:** Treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation. [20]
- **Source of RWD:** BLU-285-1002: a multi-center, retrospective, observational, natural history study obtained by extraction of data from chart review and entered on prespecified electronic case report forms (CRFs). [20]
  Data from retrospective analyses of the published literature.

- **Purpose:** To support the lack of activity of the approved therapies in the unique subset of patients with GIST harboring a specific mutation (PDGFRα D842 mutant). The results of this natural history study also served to act as an external control (the advantage over the natural history and patients treated with approved non-targeted TKIs). [20]
- **FDA´s decision:** Accepted as supportive evidence to show the unmet medical need and lack of effectiveness of available therapies (tyrosine kinase inhibitor therapies (TKIs)) in the target population. [20]
- **RWE mentioned in Package insert:** No.

9) TAZVERIK (tazemetostat) NDA 211723

- **Sponsor:** Epizyme, Inc.
- **Approval date:** 23-Jan-20
- **Indication:** Anticancer for Epithelioid sarcoma for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection. [21]

- **Source of RWD:**
  - Natural history study carried out by the Applicant.
  - Four small, retrospective case studies in patients with advanced epithelioid sarcoma who were administered anthracycline as a single-agent and in combination with ifosfamide, and pazopanib. [21]
- **Purpose:** To use natural history data as external comparator arm and to support the efficacy findings in study EZH-202 (Cohort 6). [21]
- **FDA´s decision:** FDA did not consider the design of the study adequate to provide direct or relevant comparison of any aspect of efficacy reviewed in this application. As a result, the results of the natural history study were not considered in the FDA´s assessment of the efficacy. [21]
- **RWE mentioned in Package insert:** No.

10) KOSELUGO (selumetinib) NDA 213756

- **Sponsor:** AstraZeneca Pharmaceuticals
- **Approval date:** 10-Apr-20
- **Indication:** For the treatment of pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1). [22]
- **Source of RWD:** A natural history study of NF1 conducted by the NCI POB was submitted with the application.
  Expanded access program: for safety analysis [22].
- **Purpose:** To provide external control data for comparisons with the results of the Phase 2 Clinical studies however, no formal statistical comparisons were made by

the FDA. [22] Also, to demonstrate that a key characteristic of NF1 PN is the uncommon occurrence of spontaneous regression. This proved that the observed tumor responses in SPRINT trial were an effect of the drug.

- **FDA´s decision:** For the Breakthrough designation the NCI natural history data was considered by the FDA. But the external control data for the comparisons of efficacy endpoints in SPRINT Phase II Stratum 1 was considered exploratory by the Reviewers due to several statistical issues. In conclusion, the FDA reviewer considered the findings of the natural history study that occurrence of spontaneous regression was uncommon in the NF1 patients. [22] (Partly considered)
- **RWE mentioned in Package insert**: No.

11) TABRECTA (Capmatinib) (NDA) 213591

- **Sponsor:** Novartis Pharmaceuticals Corporation
- **Approval date:** 6-May-20
- **Indication:** For the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have a mutation that leads to mesenchymal-epithelial transition (MET) exon14 skipping. [23]
- **Source of RWD:** Study X2401 (Study CINC280X2401), in which Novartis conducted a retrospective chart-review of 211 patients with MET dysregulated NSCLC. This study provided an estimate of MET dysregulated NSCLC natural history via a global retrospective chart collection. [23]
- **Purpose:** To describe the natural history of advanced MET -dysregulated NSCLC, including data from 157 patients with MET-mutated advanced NSCLC. [23] (Helped in clarifying the unmet medical need and providing evidence for lack of efficacy of the available therapies).
  Novartis did not submit this data, and thus FDA could not independently verify these results.
- **FDA´s decision:** The study X2401 provided estimate of MET dysregulated NSCLC natural history via a global retrospective chart collection. [23]
  But the Applicant did not submit the data for the FDA to carry out their own statistical analysis. Thus, it was not considered for efficacy evaluation.
- **RWE mentioned in Package insert:** No.

12) LAMPIT (nifurtimox) NDA 213464

- **Sponsor:** Bayer HealthCare Pharmaceuticals Inc.
- **Approval date:** 6-Aug-20
- **Indication:** For the treatment of Chagas disease caused by Trypanosoma cruzi in pediatric patients (birth to less than 18 years of age and weighing at least 2.5 kg). [24]

- **Source of RWD:** Published literature: Historical placebo control data.
  - Patient level data from study by Andrade et al 1996: Data of placebo treated group from a randomized, double-blind, placebo-controlled trial (between 1991 and 1995) in a rural area of Brazil with endemic Chagas' disease. [25]
  - Patient level data from study by Sosa Estani et al 1998: [26] Data of placebo treated group from a double-blind, randomized, clinical field trial was designed to test the efficacy and tolerance of a specific drug treatment in children in the indeterminate phase of infection by Trypanosoma cruzi. [24]
- **Purpose:** Historical control data was used to assess the superiority of the 60-day nifurtimox regimen and helped in selection of the surrogate endpoint of 20% decrease in optical density corresponds to decrease in the antibody titer. [24] [25]
- **FDA´s decision:** The historical placebo control data was accepted by the FDA as supportive evidence.
- Published literature studies provided supportive evidence for the efficacy of nifurtimox in the treatment of Chagas disease in the pediatric patient population. [24]
- **RWE mentioned in Package insert:** Yes.

13) EVRYSDI (risdiplam) NDA 213535

- **Sponsor:** Genentech Inc
- **Approval date:** 7-Aug-20
- **Indication:** For the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older. [27]
- **Source of RWD** [27]**:** five natural history studies of Type 1 SMA (CARNI-VAL Type I, PNCR Network, NeuroNEXT SMA Infant Biomarker Study, Oskoui et al. 2007 [28], Rudnik-Schoeneborn et al. 2009 [29]).
- **Purpose:** Natural history data for comparison of the primary end point from the FIREFISH clinical study. [27]
- **FDA´s decision:** Clinical reviewer considered the natural history data as external control for the FIREFISH study. Accepted as supportive evidence of efficacy.
- **RWE mentioned in Package insert:** Yes.

14) VILTEPSO (viltolarsen) NDA 212154

- **Sponsor:** Nippon Shinyaku
- **Approval date:** 12-Aug-20
- **Indication:** for the treatment of Duchenne muscular dystrophy (DMD).

- **Source of RWD:** The applicant carried out a comparison of functional endpoints to natural history using a total of 65 Natural history patients from CINRG (The Cooperative International Neuromuscular Research Group) network. [30]
- **Purpose:** To compare the functional endpoints, to demonstrate an effect on a surrogate or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit.
- **FDA´s decision:** Clinical reviewer concluded that" the data do not support whether the amount of dystrophin produced after 24 weeks of treatment is reasonably likely to predict clinically meaningful benefit." [30] Not accepted.
- **RWE mentioned in Package insert:** No.

15) VEKLURY (remdesivir) NDA 214787

- **Sponsor:** Gilead Sciences
- **Approval date:** 22-Oct-20
- **Indication:** For adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. [31]
- **Source of RWD:** Safety data from the Expanded access program (EAP) and Emergency use authorization (EUA). [31]
- **Purpose:** To provide information on all the medication errors and adverse events collected under Emergency use authorization and expanded access program to support the safety profile of the drug. [31]
- **FDA´s decision:** The safety information provided by the EUA supplemented the adverse events profile and was accepted as supportive evidence by the Agency.
- **RWE mentioned in Package insert:** Yes.

16) ZOKINVY (lonafarnib) NDA213969

- **Sponsor:** Eiger BioPharmaceuticals Inc.
- **Approval date:** 20-Nov-20
- **Indication:** In patients 12 months of age and older to reduce the risk of mortality in Hutchinson-Gilford Progeria Syndrome (HGPS). [32]
- **Source of RWD:** A natural history cohort identified and maintained from the Progeria Research Foundation International Progeria Registry (reliable source of real-world data). [32]
- **Purpose:** Natural history control was used to compare the survival of untreated patients with the treated patients.
- **FDA´s decision:** Agency provided guidance on how to address the review issues and the natural history data was accepted as external control.
  Provided substantial evidence for effectiveness.
- **RWE mentioned in Package insert:** Yes.

17) OXLUMO (lumasiran) NDA 214103

- **Sponsor:** Alnylam Pharmaceuticals Inc.
- **Approval date:** 23-Nov-20
- **Indication:** For the treatment of primary hyperoxaluria type 1 (PH1) to lower urinary oxalate levels in pediatric and adult patients. [33]
- **Source of RWD** [33]**:** Literature publications based on real world data:
  - Lawrence J, Wattenberg DJ: Primary hyperoxaluria: The patient and caregiver perspective. Clin J Am Soc Nephrol 15: 1056-1065, 2020.PMID 321654412. [34]
  - Milliner DS, McGregor TL, Thompson A, et al: Endpoints for Clinical Trials in Primary Hyperoxaluria. Clin J Am Soc Nephrol 15: 909-911, 2020.PMID 321654401, 2. [35]
- **Purpose:** Justify selection of the clinical endpoint.
- **FDA´s decision:** The clinical end-point selection was based on real-world observational data and was accepted by the Agency. (Partly considered)
- **RWE mentioned in Package insert:** No.

18) TEPMETKO (tepotinib) NDA 214096

- **Sponsor:** EMD Serono
- **Approval date:** 3-Feb-21
- **Indication:** For the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.
- **Source of RWD:** Natural history study (with 30-40 patients) and published literature. [36]
- **Purpose:** The epidemiology of the natural history population was compared to the population included in the clinical studies and it was proposed to serve as external control for evaluation of efficacy. [36]
- **FDA´s decision:** In the FDA´s assessment the epidemiology of the natural history population and the population for safety were comparable. But FDA did not accept the comparison with natural history data due limitation of the approaches used to collect this data (methodological limitation). [36].
- **RWE mentioned in Package insert:** No.

19) NULIBRY (fosdenopterin) NDA 214018

- **Sponsor:** Origin Biosciences Inc.
- **Approval date:** 26-Feb-21

- **Indication:** To reduce the risk of mortality in patients with molybdenum cofactor deficiency (MoCD) Type A. [37]
- **Source of RWD:** An Observational Natural History Study of Molybdenum Cofactor (NCT 01735188) with n=37 subjects from 27 centers across 14 countries to characterize the natural history of the disease and determine the overall survival of untreated patient population. [37]
- **Purpose:** Natural history data was used as historical control to provide evidence of survival benefit. (Mentioned in the label.)
- **FDA´s decision:** FDA accepted the natural history data for evaluation of efficacy.
- **RWE mentioned in Package insert:** Yes.

20) LUMAKRAS™ (sotorasib) NDA 214665

- **Sponsor:** Amgen Inc
- **Approval date:** 28-May-21
- **Indication:** For the treatment of adult patients with KRAS G12C-mutated (Kirsten rat sarcoma proto-oncogene (KRAS) G12C) locally advanced or metastatic non-small cell lung cancer (NSCLC). [38]
- **Source of RWD:** 3 Retrospective natural history (Studies 20180277, 20200097, and 20200132) using data from Flatiron Health-Foundation Medicine Clinico-Genomic Database and AACR (American Association for Cancer Research) Project GENIE databases in the United States using data from n=743 patients. [38]
- **Purpose:** As historical control to benchmark the outcomes in a rare biomarker defined patient population and to prove unmet medical need based on poor prognosis with available therapies regardless of the line of therapy.
- **FDA´s decision:** The RWE has been discussed in the Integrated assessment of effectiveness to prove poor prognosis with available therapies in any line of therapy (rwPFS ~ 2.6 - 4 months). [38] Thus, considered as supportive evidence.
- **RWE mentioned in Package insert:** No.

21) TRUSELTIQ (infigratinib) NDA214622

- **Sponsor:** QED Therapeutics, Inc.
- **Approval date:** 28-May-21
- **Indication:** For the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or other rearrangements. [39]
- **Source of RWD:** Applicant performed retrospective analysis of the natural history of cholangiocarcinoma using real-world data from Flatiron Health and Foundation Medicine. [39]
- **Purpose:** To provide therapeutic context and evaluate the natural history of cholangiocarcinoma and the prognostic power of the FGFR2 alterations.

- **FDA´s decision:** Rejected. FDA acknowledges QED's interpretation of the literature and RWE data but notes that the prognostic value of FGFR rearrangements is somewhat controversial due to improper adjustment for baseline characteristics. [39]
- **RWE mentioned in Package insert:** No.

22) BREXAFEMME (ibrexafungerp) NDA 214900

- **Sponsor:** SCYNEXIS, Inc.
- **Approval date:** 1-Jun-21
- **Indication:** For the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC).
- **Source of RWD:** Natural history data in the form of retrospective published studies on vulvovaginal candidiasis (VVC) in Pre-Pubertal Girls: [40] Following literature publications were mentioned in the multi-discipline review document:
  - Jaquiery, A., et al. (1999). "Vulvovaginitis: clinical features, aetiology, and microbiology of the genital tract." Arch Dis Child 81(1): 64-67. [41]
  - Pierce, A. M. and C. A. Hart (1992). "Vulvovaginitis: causes and management." Ibid. 67(4): 509-512. [42]
  - Banerjee, K., et al. (2004). "Low prevalence of genital candidiasis in children." Eur J Clin Microbiol Infect Dis 23(9): 696-698. [43]
  - Agana, M. G., et al. (2019). "Vulvovaginitis in adolescents." Pediatric Medicine. [44]
- **Purpose:** The natural history data formed the basis for waiving the pediatric studies involving girls <12 y. The natural history data showed similarities in disease characteristics for adult women and post-pubertal girls (>12 y) which enabled extrapolation of efficacy and safety to post-pubertal girls without enrollment in the clinical studies. [40]
- **FDA´s decision:** FDA accepted the natural history comparison showing similarities in disease characteristics for adults and post-pubertal girls which enabled extrapolation of efficacy data from adults to pediatric population (>12y). [40]
- **RWE mentioned in Package insert:** No.

23) PROGRAF (tacrolimus) sNDA 210115/005 (Efficacy supplement)

- **Sponsor:** Astellas Pharma US Inc.
- **Approval date:** 16-Jul-21
- **Indication:** For the prevention of rejection in lung transplantation.
- **Source of RWD:** Non-interventional observational study using data from Scientific Registry of Transplant Recipients (SRTR) which captures off-label use of Prograf in combination with immunosuppressant and published literature. [45]
- **Purpose:** RWE was used to provide evidence of efficacy and safety for use of Prograf in lung transplantation.

- **FDA´s decision:** FDA accepted the RWE from the observational study as an adequate well-controlled study showing efficacy and safety of Prograf for extension of labelling information for its use in lung transplantation.
- **RWE mentioned in Package insert:** Yes.

24) EXKIVITY (mobocertinib) NDA 215310

- **Sponsor:** Takeda Pharmaceuticals USA Inc.
- **Approval date:** 15-Sep-21
- **Indication:** For the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR). [46]
- **Source of RWD:** TAK-788-5002 (Natural history study): A Retrospective Observational Study of Non-small Cell Lung Cancer (NSCLC) patients with EGFR Exon 20 insertion mutations: This study used data from Flatiron Health Research Database.
- As well as literature review of RWD: RWD from China, German Chart Review from Study 5008, Docetaxel as Standard of Care, Comparison between immunotherapy and mobocertinib. [46]
- **Purpose:** As external control to benchmark the clinical results. To show unmet medical need. To provide supportive evidence for efficacy by comparison to natural history and published literature results on the therapy options. [46]
- **FDA´s decision:** The analysis of condition and selection of efficacy population with appropriate representation of vulnerable population has been accepted by the FDA. FDA acknowledges the Applicant's description of Study TAK-788-5002 and these data are considered supportive but was not independently verified by the FDA. Thus, the submitted RWE was partly considered by the US FDA. [46]
- **RWE mentioned in Package insert**: No.

25) VOXZOGO (vosoritide) NDA 214938/

- **Sponsor:** BioMarin Pharmaceutical Inc.
- **Approval date:** 19-Nov-21
- **Indication:** To increase linear growth in pediatric patients with achondroplasia who are 5 years of age and older with open epiphyses. [47]
- **Source of RWD:** Retrospective, observational natural history data from 4 studies namely, [47]
  - AchNH: Observational, retrospective, Achondroplasia natural history study (n= 1374 from 4 centers)

- Study 111-901: observations, prospective, non-interventional study with pediatric subjects suffering from ACH (from birth to ≤17 y). (n=352 from 27 centers)
- LIASE: Observational, retrospective, non-interventional study (n=128 from 11 centers)
- KAISER: Observational, retrospective, non-interventional study (n=114 from 1 center).

- **Purpose:** Natural history data was used as external control for confirmatory evidence of efficacy for single arm trial (Studies 111-202/205 and 111-302). [47]
- **FDA´s decision:** FDA suggested use of natural history data due to non-feasibility of long-term placebo studies. FDA performed their own exploratory analysis and accepted the natural history data submitted by the applicant. [47]
- **RWE mentioned in Package insert:** No.

26) VIJOICE (Apelisib) NDA 215039

- **Sponsor:** Novartis Pharmaceuticals
- **Approval date:** 5-Apr-22
- **Indication:** for adult and paediatric patients >2 with severe manifestations of PIK3CA- Related Overgrowth Spectrum (PROS) who require systemic therapy. [48]
- **Source of RWD:** A retrospective chart review study (NCT04285723) to serves as a single-arm clinical study in patients two years of age and older with *PIK3CA*-related overgrowth spectrum (PROS)who received alpelisib as part of an expanded access programme for compassionate use. [49]
- **Purpose:** To provide proof of efficacy for accelerated approval. [49]
- **FDA´s decision:** Approval is based on real-world data from EPIK-P1 study. Primary evidence of efficacy. Accepted by the FDA.
- **RWE mentioned in Package insert:** Yes.

3.1.2 BLA submissions to US FDA employing real-world evidence.

In this section, case studies of BLA assessed by either CDER or CBER between Jan 2019- Jun 2022 where the Applicant included RWE to support benefit-risk assessment in accordance with the inclusion criteria mentioned in section 2 methods.

*Please note that wherever FDA or Agency is mentioned it refers to US FDA.

1) ZOLGENSMA (onasemnogene abeparvovec) BLA

- **Sponsor:** AveXis, Inc*\Novartis Gene Therapies,
- **Approval date:** 24-May-19

- **Indication:** Treatment of Spinal Muscular Atropy (Type I) for pediatric patients less than 2 years of age. [50]
- **Source of RWD:** Natural history data obtained from the Pediatric Neuromuscular Clinical Research database (PNCR) and the NeuroNEXT [51] [52] [53] [50] natural history datasets. Data from expanded access program and the publications submitted by the applicant. [50] As well as the publications submitted by the applicant. [50]
- **Purpose:** Historical control, Comparison of the results of the ongoing clinical trial to available natural history data of patients with infantile onset SMA provides primary evidence of the effectiveness of ZOLGENSMA.
- **FDA´s decision**: Accepted as evidence of effectiveness.
- **Inclusion of RWE in Package insert:** Yes.

2) Enhertu (fam-trastuzumab deruxtecan-nxki) BLA 761139

- **Sponsor:** Daiichi Sankyo, Inc
- **Approval date:** 20-Dec-19
- **Indication:** For the treatment metastatic HER2-positive breast cancer who have received two or more prior anti-HER2-based regimens [54].
- **Source of RWD:** Matched historical cohort from French Unicancer database and a literature-based analysis of 37 studies requiring only prior trastuzumab and chemotherapy for inclusion. [54]
- **Purpose:** To serve as external control for single arm trial and provide data for comparison of results from the clinical study to supplement the efficacy information.
- **FDA´s decision**: RWE not discussed by the FDA for efficacy assessment. (No comments were found for considering RWE studies for comparison of efficacy results.) Not considered.
- **Inclusion of RWE in Label:** No.

3) MONJUVI (tafasitamab-cxix) BLA 761163

- **Sponsor:** MorphoSys US Inc.
- **Approval date:** 31-Jul-20
- **Indication:** For the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified, including DLBCL arising from low grade lymphoma, and who are not eligible for autologous stem cell transplant (ASCT) in combination with lenalidomide. [55]
- **Source of RWD:** Observational, retrospective, comparative cohort study MOR208C206 (RE-MIND).

Published literature with Lenalidomide monotherapy in R/R DLBCL with best ORR ranging from 21-29%: (Wiernik et al., 2008 [56]; Witzig et al., 2011 [57]; Czuczman et al., 2017 [58])

- **Purpose:** To generate a matched control cohort for MOR208C203 (L-MIND) to isolate the contribution of tafasitamab to the combination. [55]
- **FDA´s decision:** Not considered by the Agency due to limitations associated with an observational study.
- **Inclusion of RWE in Package insert:** No.

4) BLENREP (belantamab mafodotin-blmf) BLA 761158

- **Sponsor:** GlaxoSmithKline
- **Approval date:** 5-Aug-20
- **Indication:** For the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent. [59]
- **Source of RWD:** Available published studies conducted in a similarly heavily pretreated RRMM patient population indicated an ORR of 10-18%. (Hájek, 2017 [60]; Kumar, 2012 [61]; Durie, 2012 [62]; Anderson, 2008 [63]) and published literature data from a single-arm trial of selinexor in combination with dexamethasone.
- **Purpose:** For comparison of the efficacy results from single arm trial with the historical control.
- **FDA´s decision:** Not considered by the FDA.
- **Inclusion of RWE in Label:** No.

5) DANYELZA (naxitamab-gqgk) BLA 761171

- **Sponsor:** Y-mAbs Therapeutics Inc.
- **Approval date:** 25-Nov-20
- **Indication:** For the treatment of pediatric patients 1 y & older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow. [64]
- **Source of RWD:** Retrospective, noninterventional, noncomparative, observational, single-site study 2PR01 (compassionate use), where EHR were reviewed for patients who received the drug between June 01, 2017 and November 30, 2018. [64]
- **Purpose:** To provide supporting evidence of efficacy and safety data.
- **FDA´s decision:** According to the FDA the data from the compassionate use program submitted by the FDA did not provide substantial evidence for efficacy and safety. FDA did not perform dedicated analysis for the retrospective study. (Not addressed)
- **Inclusion of RWE in Package insert:** No.

6) ABECMA (idecabtagene vicleucel) BLA 125736

- **Sponsor:** Celgene Corporation
- **Approval date:** 26-Mar-21
- **Indication:** For the treatment of adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. [65]
- **Source of RWD:** A real-world evidence study (NDS-MM003) was included in the submission which is a systematic literature review and matching-adjusted indirect treatment comparison (MAIC), which used aggregate summary data from published studies for selinexor/dexamethasone and belantamab and subject-level data from Study MM-001. [65]
- **Purpose:** To compare the outcomes of the clinical study (MM-001) with a real-world cohort who matched the study population and received available alternative therapies (comparison of effectiveness). [65].
- **FDA´s decision:** FDA did not consider the use of RWD acceptable due to lack of accepted standard of care. Single arm trial design without external control was considered reasonable.
- Issues with the RWE study include selection of a population which may not be comparable to subjects enrolled in Study MM-001 due to missing baseline patient characteristics, missing or absent data on efficacy assessments which may bias the outcomes and heterogeneity of real-world data from different databases that will be collated for analysis.
- **Inclusion of RWE in Label:** No.

7) RYBREVANT (amivantamab-vmjw) BLA 761210

- **Sponsor:** Janssen Biotech Inc.
- **Approval date:** 21-May-21
- **Indication:** For the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) exon 20 mutations. [66]
- **Source of RWD:** Two sources of RWD:

  1) data from a protocol-driven, retrospective cohort study of real-world data (Study NSC1002) collected between 01 January 2011 to 31 May 2020 from the Advanced NSCLC Flatiron Core Registry EHR-derived deidentified database.

  2) an analysis of 5 RWD datasets to provide insights on commonly used second-line regimens for EGFR Exon 20ins NSCLC (including ramucirumab-docetaxel combination). These evaluations utilized EHR and claims reimbursement data. [66]

- **Purpose:**
  - To evaluate the unmet needs and treatment patterns for patients with EGFR Exon 20ins-mutated NSCLC.
  - RWD also highlighted the demographic characteristics in real world setting.
  - To provide clinical context for interpreting the efficacy data of Rybrevant.
- **FDA´s decision:** FDA considered RWD for proving the unmet medical need. Asked the sponsor to demonstrate that patients with EGFR Ex20 ins mutations do not benefit from first-line immunotherapy. But RWD was not used for comparison of efficacy results from the Clinical study. Based on these RWD a PMC was agreed between the Agency and the applicant to include a representative proportion of Black /African American in the final post marketing clinical study to support the efficacy and safety.
- **Inclusion of RWE in Package insert:** No.

8) TIVDAK (tisotumab vedotin-tftv) BLA 761208

- **Sponsor:** Seagen Inc.
- **Approval date:** 20-Sep-21
- **Indication:** For the treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. [67]
- **Source of RWD:** A systematic review of the literature was conducted to describe the treatment landscape and the ORR and DORs.
- **Purpose:** Meta-analysis was performed to compare with the results of single arm clinical study.
- **FDA´s decision:** From administrative correspondence and regulatory history: FDA advised not to carry out any such comparisons. Such comparisons were deemed not to be appropriate. (While a systematic literature review can be useful to describe the treatment landscape and ORRs and DORs in the available therapy population, pooling of disparate ORRs is not appropriate.) Not considered.
- **Inclusion of RWE in Package insert:** No.

9) BESREMI (ropeginterferon alfa-2b-njft) BLA 761166

- **Sponsor:** Pharma Essentia Corporation
- **Approval date:** 12-Nov-21
- **Indication:** For the treatment of adults with polycythemia vera.
- **Source of RWD:**
  - A retrospective cohort study with 1213 patients who were followed for 20 y by the Gruppo Italiano Studio Policitemia (Gruppo Italiano Studio Policitemia. Ann Int Med 1995). [68]
  - The real-world analysis of the MPN registry & Study of the Study Alliance Leukemia. [69]

- **Purpose:** The real-world data showed that without intervention WBCs, PLTs and HCT increase along with thrombotic and cardiovascular events and that there are no spontaneous remissions in PV.
- **FDA´s decision:** The data from natural history study was considered as external control for the PEGNIVERA trials to provide evidence of efficacy of the Besremi.
- **Inclusion of RWE in Package insert:** No.

10) Kimmtrak (tebentafusp) BLA761228

- **Sponsor:** Immunocore Ltd.
- **Approval date:** 25-Jan-22
- **Indication:** For the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. [70]
- **Source of RWD:** In the integrated assessment of effectiveness: The control arm was generally consistent with historical reported trials confirming that tebentafusp provides substantial improvement over available therapies (Rantala, 2019 [71]; Piulats, 2021 [72]; Pelster, 2020 [73]). Tebentafusp is the first systemic treatment to demonstrate a statistically significant and clinically meaningful survival benefit in mUM, representing an essential treatment option for patients with this serious and life-threatening disease. Historical data from literature was mentioned for comparison. [70]
- **Purpose:** To provide supportive evidence of efficacy.
- **FDA´s decision**: Not considered by the FDA
- **Inclusion of RWE in Label:** No.

From the summarized case studies in Section 3.1.1 and 3.1.2, it is evident that acceptance of RWE whether for NDA or BLA is based on situation and is specific to the case. Out of the 36 marketing authorization applications (MAAs), 34 satisfied the inclusion criteria mentioned in the methodology. In the 36 marketing authorization applications (MAAs), two s-NDAs were intentionally included as examples of off-label use. Out of 34 MAA applications, 24 were NDA applications and 10 were BLA. The most often used real-word data type is natural history data from registries or patient level data from electronic health records which is used as external control to provide therapeutic context when use of placebo control or active control arm is not feasible.

RWE most often was used to supplement the evidence for efficacy and safety in case of medical conditions with high unmet medical need and no alternative therapy options. Cases where RWE provided major evidence were often the submissions where prior clinical studies were performed, or the drug was authorized in the past for some other indication (based on the classical clinical studies). So, the real-world evidence provided additional proof of efficacy in the new target population or indication along with the proof of safety

from the post-marketing experience. Thus, even though it seems that the RWE provided major evidence for efficacy for some medicinal products the totality of evidence also included data from randomized clinical study and post-marketing experience in a larger population to ensure safety.

3.2 Further Analysis of the RWE Based Submissions (Jan-2019 to Jun-2022)

In the following section the data from the case studies (from Section 3.1.1 & 3.1.2) is further analyzed to obtain insights on the various other factors associated with submission of RWE in the marketing authorization applications.

3.2.1 Analysis of number of approvals compared to the total number of submissions.

Following is a graph (refer Figure 5) showing the total number of submissions (fulfilling the inclusion criteria) from the Jan-2019 to Jun-2022 along with the US-FDA´s decision (Accepted or rejected). For the analysis the two s-NDAs were not considered as they do not fulfill the acceptance criteria described in section 2 Methods.

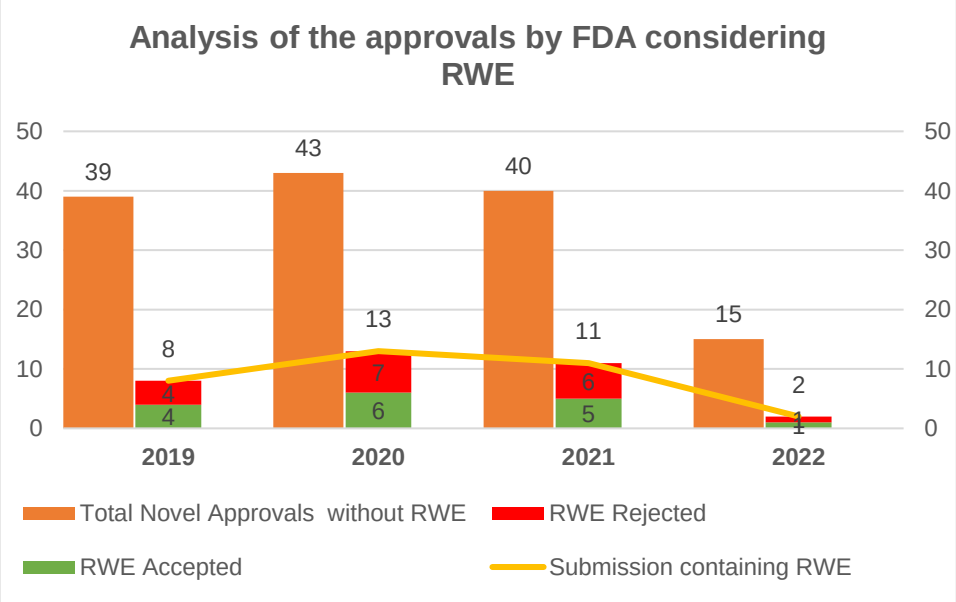

Figure 5: Graphical representation of yearly novel drug approvals by the US FDA and total no. of RWE based submissions (as per inclusion criteria for this master thesis) with decision status (accepted or rejected RWE data by the US FDA)

3.2.2 Data showing the total number of RWE based submissions and special status for those submissions (Orphan Designation, Break through Designation, Accelerated Approval)

Figure 6 in this section shows a graphical presentation of the number of submissions with RWE in the submission package and those which also received special designations and review status. Of the total of 34 marketing authorization applications (MAA´s) to US-FDA which fulfilled the inclusion criteria for this master thesis (included RWE in the submission

package as evidence for efficacy or safety or effectiveness) most received special designations.

- 25 MAA received orphan designation which shows that most applications were for medical conditions with no alternate treatment option.
- 20 MAA´s received break-through therapy designation which is a process designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy. [74]
- 19 MAA´s received accelerated approval based on a surrogate endpoint and a commitment of conducting post-marketing confirmatory clinical study.
- 16 MAA´s received fast track designation which is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. [74]
- 32 MAA´s received priority review designation means FDA's goal is to review an application within 6 months.

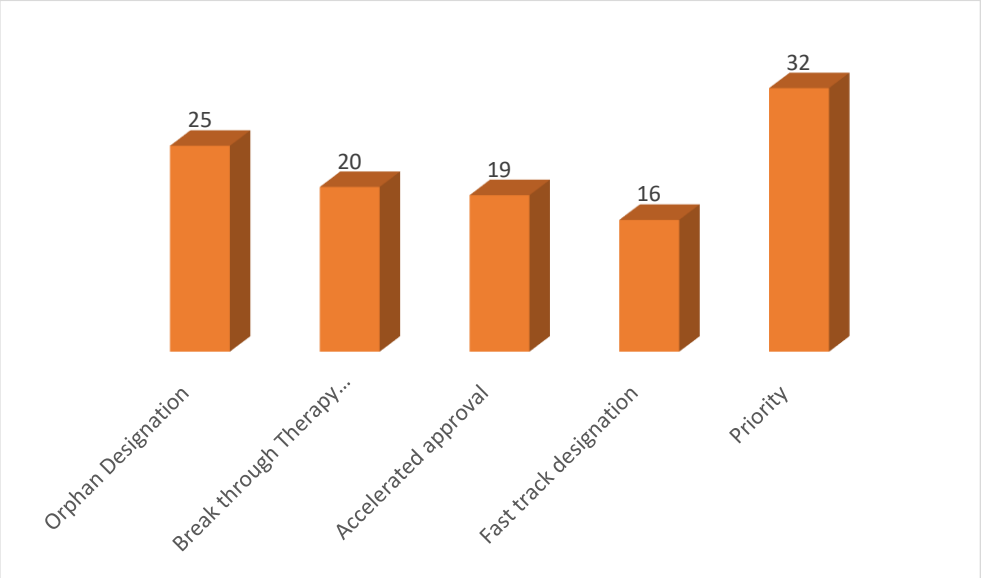

Figure 6: Number of different special designations granted to the submissions with RWE in the submission package (excluding Ibrance and Prograf s-NDA from this analysis)

The above graphical presentation shows the tendency of the pharma-companies to utilize RWE for supplementing the entire benefit-risk in areas of serious medical conditions with unmet medical need which would expedite the entire process of approval of marketing authorizations. Though not for all the marketing authorization applications the Agency decided to grant these special designations based on the RWE in the submission package but in some it did provide some supportive evidence. (Specially for orphan drug

designations where the Sponsor uses RWD to show lack of therapy options and high unmet medical need).

Other way around the health authority is also willing to accept the real-world evidence in such situation where classical randomized controlled clinical trials are either not feasible or would be too time-consuming to provide therapy options to patients with high unmet medical need suffering with fatal diseases.

3.2.3 Analysis of the various outcomes of the submissions with RWE

The outcomes of assessment by the US FDA for the submissions (the cases studies from Section 3.1) classified based on the classification mentioned in Table 2 are depicted in Figure 7. The figure shows the graphical representation of the percentage of applications with RWE which were accepted by the US FDA (as substantial evidence or supportive evidence).

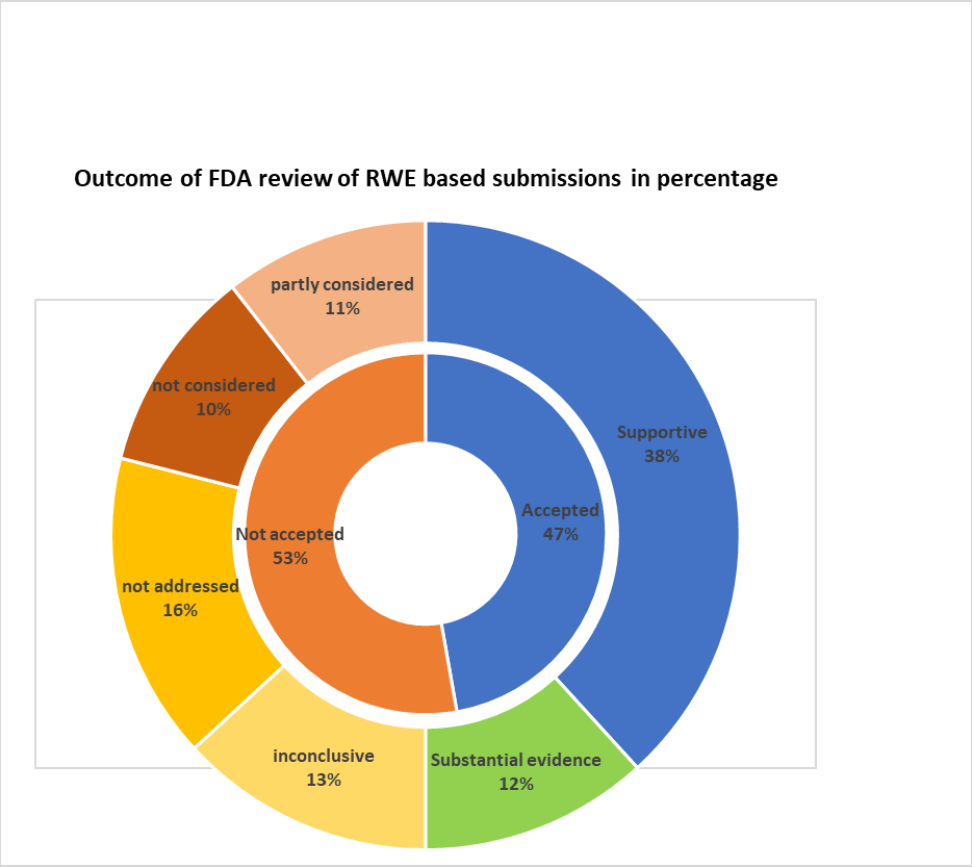

Figure 7: Graphical depiction of the percentage of submissions where the RWE was accepted versus not accepted by the US-FDA and their further categorization. (including Ibrance and Prograf s-NDA in this analysis)

3.2.4 An analysis of the indications where the sponsors used RWE

Figure 8 shows the most common indication for use of RWE was in oncological (with very specific targeting of a mutation type) followed by rare diseases (with no available therapy option, high unmet medical need). Indicating that innovations in the field of high unmet medical need are often supported by the RWE to supplement the evidence for efficacy and safety.

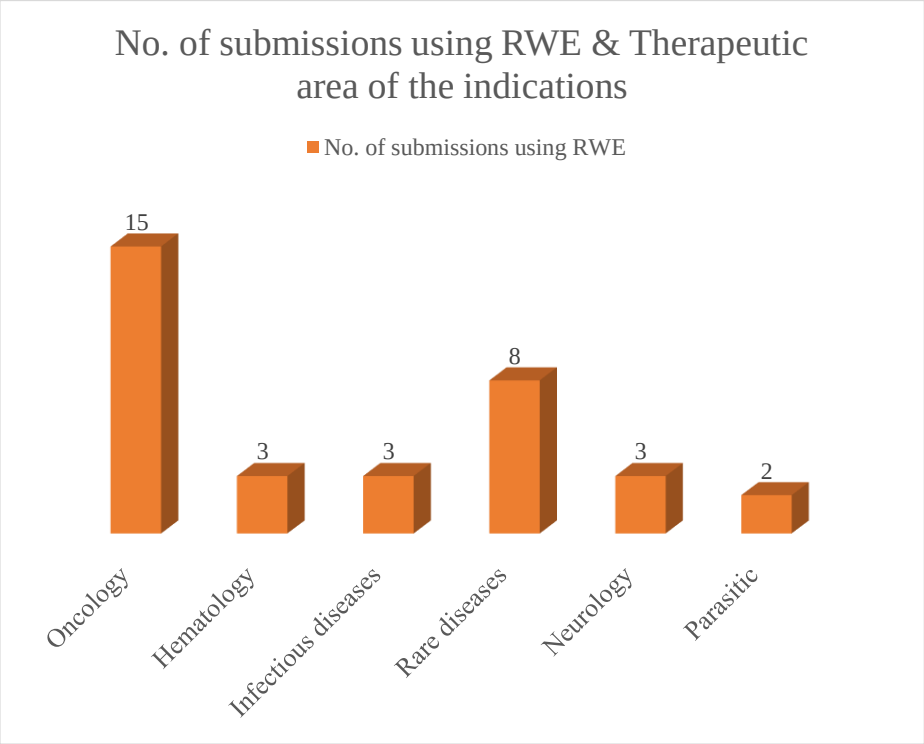

Figure 8: Graph showing the therapeutic area and the number of submissions using RWE submitted to the US-FDA between Jan 2019- Jun 2022 (excluding Ibrance and Prograf s-NDA in this analysis)

Table 3 provides the details of the disease conditions and their classification into different therapeutic areas which must be considered for assessing the graph from Figure 8.

Table 3: List of disease conditions and their classification into therapeutic areas

Therapeutic Areas	**Meaning**
Oncology	Breast Cancer, Lung Cancer, Prostate Cancer, Colorectal Cancer, Ovarian Cancer, and other Oncology indications.
Rare diseases	Hemophilia A & B, Von Willebrand Disease, Thrombocytopenia, Polycythemia Vera, Paroxysmal Nocturnal Hemoglobinuria (PNH).
Hematology	Multiple Myeloma, Lymphomas, Leukemias, and other onco-hematological indications.
Infectious diseases	Antimicrobial and Antifungal infections, antiviral and other ID.
Neurology	Genetic neurological disorders, Excessive daytime sleepiness, Alzheimers, Parkinsons & others
Parasitic	Anthelmintics, Anti-protozoal

4. DISCUSSION

Review of the assessment reports of the submissions using RWE as proof of either efficacy, safety or effectiveness from the Results Section 3.1, shows a general tendency of use of real-world data from registries or EHR or prior clinical studies from other countries as external control. Thus, real-world data in the form of external control is used most often by the sponsors. As seen from the Figure 6, it is evident that RWE is utilized often for rare and life-threatening diseases often associated with lack of available therapy options and poor prognosis for the patients. For most of these indications a single arm trial is the only option due to lack of an active comparator. Most such marketing authorization applications rely on the Phase-2 data and aim for accelerated approval for early market access. Since single arm studies with external controls have the potential to expedite the clinical development and aid in early market access by filling the gap in the evidence required to prove the benefit-risk balance in areas on high unmet medical need. They also provide a cost-effective option with limited and well understood impact on validity and generalizability of study results. Thus, instead of placebo control trial for benchmarking the treatment effect an external control is employed. However, there are also a number of risks or limitations associated with the use of external control trials which are pointed out by the FDA reviewers and summarized in the following section with examples.

4.1 Learnings from the individual cases

In the following Table 4, important learnings in the form of strengths of the data or the employed strategy and limitations of the real-world data are enlisted after review of the assessment reports (as referenced in the Appendix)

Table 4: Summary of learnings from each submission relying on RWD for both the NDA and BLA marketing authorization applications.

Name of drug (NDA/BLA)	Lessons learnt
EGATEN (triclabendazole):	Egaten was widely used for decades outside the US and there was a lot of robust literature to support the safety of the drug. Despite the limitations of missing data, differences in the study population, study designs and methodology to collect data which rendered cross-study comparisons challenging and poor data standards (as the studies were not performed under GCP) the Agency still accepted the RWE as supportive evidence.
Ibrance sNDA (Efficacy supplement)	Early and regular engagement with the Agency led to approval. It's an example of the use of off-label use for extension of indication. [12]
Balversa (erdafitinib):	Limitations of RWD like comparability issues, confounding, post-hoc analysis, missing/incomplete data, sample size issues and limitation of interpretation of real-world response led to non-acceptance of RWE.
ZOLGENSMA (onasemnogene abeparvovec):	Well-established natural history allowed for clear end-point comparison.

Name of drug (NDA/BLA)	Lessons learnt
Xpovio (Selinexor):	Limitations of RWD like index date issue, selection bias, confounding factors and post-hoc nature of the SAP lead to non-acceptance of RWE.
Pretomanid (pretomanid)	Despite comparability issue and lack of patient level data the historical control offered strong evidence of efficacy which was accepted by the US FDA due to lack of/poor available treatment alternatives.
WAKIX (pitolisant)	The submission relied on RWD from several sources. Sponsor aligned with FDA on use of foreign data & RWD. Data from Eudravigilance and European post-marketing surveilance was used. (NME was approved in EU but not in US).
Rozlytrek (entrectinib)	Lack of sufficient communication between the sponsor and Agency prior RWE submission along with limitations of comparability issues, post-hoc analysis, missing or incomplete real-world data and limitations with the interpretation of the real-world response led to non-acceptance of the RWE.
Enhertu (fam-trastuzumab deruxtecan-nxki)	Durable response from clinical study provided sufficient evidence to support accelerated approval. Lack of sufficient communication and other methodologic limitations with the use of RWD like comparability issue, absence of patient level data and interpretations issue with real-world response led to non-acceptance of the RWE.
AYVAKIT (avapritinib)	FDA proposed to use RWD for showing effectiveness over available therapy options. Regular discussions on the use of RWE were conducted. RWD strength includes measures to minimize confounding and use of high-quality data.
TAZVERIK (tazemetostat)	Even though there was frequent communication between the sponsor & the Agency but due to limitations and interpretation issues with the RWD, along with selection bias, confounding factors and sample size issues FDA did not accept the RWE. Also, the ORR observed in the single arm study was not durable. The drug got approval based on the positive outcome of Adcomm meeting.
Koselugo (selumetinib)	Sponsor had timely engagement with the FDA on the use of RWE, but RWD was not considered due to limitations (like selection bias, confounding factors, lack of patient level data and interpretation issues.)
TABRECTA (Capmatinib)	Applicant did not submit the patient level data for verification by the FDA due to which the RWE was not considered during review.
MONJUVI (tafasitamab-cxix)	Limitations of RWD like sample size issues and misinterpretation lead to non-acceptance of RWE.
BLENREP (belantamab mafodotin-blmf)	Limitations of RWD like selection bias and misinterpretation lead to non-acceptance of RWE.
LAMPIT (nifurtimox)	Early engagement with the FDA on use of RWE (Since pre-IND meeting) and applicant also provided patient level data to the Agency. Also, the sufficiency of clinical data package was discussed with the FDA before submission.

Name of drug (NDA/BLA)	Lessons learnt
EVRYSDI (risdiplam)	Early engagement, well-defined natural history of the disease (SMA), objective endpoint selection, patient comparability of natural history (NH) group was ensured, large treatment effect (ability to sit) and good covariate measurement.
VILTEPSO (viltolarsen)	The nature of disease condition rendered comparability difficult between natural history cohort and clinical study despite best efforts from applicant to control all known and unknown bias.
VEKLURY (remdesivir)	An exceptional case: given the rapidly emergent nature of the Covid pandemic and urgent need for medication the development of Remedesivir occurred rapidly and the Agency accepted the supportive evidence of safety from real-world sources.
Zokinvy (lonafarnib)	Applicant took efforts to adequately address all known confounders, selected appropriate clinical endpoint for comparison. Also, the applicant provided scientific justifications for all the Agency queries on time.
Oxlumo (lumasiran)	An example of integration of real-world evidence and patient needs in selection of relevant clinical endpoint.
DANYELZA (naxitamab-gqgk)	Results not verified by the FDA as according to FDA the nature of study may lead to incomplete data and thus misinterpretation. Strengths of the real-world data included: ➢ Data entry for this retrospective observational study followed the principles of the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines for data entry and monitoring, and with the laws and regulations in Spain. [54] ➢ The study populations considered to be sufficiently similar to allow comparison of the efficacy results across the trials. ➢ The SAP was signed before the statistical analyses of efficacy started.
TEPMETKO (tepotinib)	Due to methodologic issues the RWD was not addressed by the Agency for assessment of efficacy. FDA agreed with the demographic analysis of the safety population from the comparison to the natural history data.
NULIBRY (fosdenopterin)	Selection bias and detection bias were controlled by the genotype matching and the post-hoc nature of statistical analysis plan was also justified by the applicant. Strengths included well-defined inclusion & exclusion criteria and use of reliable and objective end-point of mortality to demonstrate the treatment effect.
ABECMA (idecabtagene vicleucel)	Due to methodologic issues like selection bias, confounding, missing data and misinterpretation of results (differences in the follow up and response assessment), heterogeneity of the RWE, the RWE was not addressed by the Agency for assessment of efficacy.
RYBREVANT (amivantamab-vmjw)	Large treatment effect of the drug formed the basis of approval. The strength of the submitted real-world data included prior communication with the FDA about the intent to use RWE and obtaining feedback from the FDA on the use of RWE. RWE submitted provided proof for unmet medical need and lack of effectiveness of

Name of drug (NDA/BLA)	Lessons learnt
	available therapy options. But RWE was not considered due to statistical issues associated with the real-world data.
LUMAKRAS™ (sotorasib)	Good quality real-world data with clear scientific intent supported approval.
TRUSELTIQ (infigratinib)	No information on communication between FDA & Sponsor.
BREXAFEMME (ibrexafungerp)	Regular communication with the FDA on use of the RWD for extrapolation of results of efficacy and safety supported a positive decision.
PROGRAF (tacrolimus) sNDA (Efficacy supplement)	Best example for the application of RWE for extension of indication. Applicant discussed early and frequently about the RWE submission. The Applicant also aligned on appropriateness of the SAP, the data source selection and on the content for submission. The non-interventional study satisfied the requirements of an adequate and well-controlled study under 21 CFR 314.126 and utilized reliable data source with fit for purpose data.
Exkivity (mobocertinib)	Due to limitations of the external control RWD was considered supportive but was not independently verified by the FDA.
TIVDAK (tisotumab vedotin-tftv)	The metanalysis conducted by the Sponsor was not acceptable for approval. Final approval was based on durable response from the clinical study.
BESREMI (ropeginterferon alfa-2b-njft)	Timely communication with the FDA about the plan to use RWE in the submission, use of fit for purpose real world evidence and the post-hoc analysis requested by the FDA were conducted by the Sponsor to ensure acceptance of RWE.
VOXZOGO (vosoritide)	RWE was fit for purpose and was reviewed by the RWE committee and timely communication with the FDA (3 years before submission the Sponsor obtained opinion from Pediatric Advisory Committee and FDA on the available natural history data in support of the application.). The applicant also performed the post-hoc analysis requested by the FDA to satisfy their doubts.
Kimmtrak (tebentafusp)	Durable and consistent response from the clinical study provided sufficient evidence for regular approval. Due to limitations of the RWD it was not considered for the assessment by the FDA. (Durable and consistent response from the clinical study provided sufficient evidence for regular approval. Due to limitations of the RWD it was not considered for the assessment by the FDA.
VIJOICE (Apelisib)	Applicant started discussing (early) during pre-IND the development program using data from expanded access program and aligned before submission on the data package with the US-FDA.

As seen from the summary of issues and the regulatory outcomes seen in above Table 4, it is clear that the outcomes of the assessment of marketing authorization applications differ on a case-to-case basis. In the following section the limitations of the use of RWE are discussed.

4.2 Limitations with the use of RWE in submission

A common set of limitations with the use of real-world data are as follows:

i. POST-HOC ANALYSIS: For evaluating the potential use of real-world evidence data (RWD) [75] the FDA´s published a guidance document on Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data in 2013 (FDA, 2013) [76] outlines the principles and considerations when observational studies are performed to generate evidence for regulatory decision-making. To enhance transparency, FDA requires submission of study protocols and statistical analysis plans (SAP) prior to study initiation. [75] Pre-specification of study protocols and SAPs can preclude unplanned multiple testing and analyses and reduce Type I error probability. Non-compliance often leads to consideration of the RWE as ad-hoc by the reviewers. Example: Rozyltrek, Xpovio.

ii. LACK OF PRE-SUBMISSION DISCUSSION AND FEEDBACK FROM US-FDA ON USE OF RWE: In some cases, the issues identified during review could have been addressed earlier if the Sponsor seeks additional meetings to discuss the RWE generation and its use in the data package. Example: Truseltiq and Rozyltrek.

iii. QUALITY OF THE REAL-WORLD DATA SOURCE: The data source employed affected the quality in terms of completeness of the data, its reliability and traceability.

iv. RWD ACCESS (Not providing patient level data to the reviewer): During review most FDA reviewers want to verify the results from the analysis performed by the Applicant. In the absence of patient-level data it is not possible and affects the transparency and reliability of the claims made in the study. Example in case of Koselugo & Tabrecta. In such cases the sponsor must ensure that they could be able to submit the patient level data (as per the 21 CFR 314.50 and 601.2). Sponsors should ensure that RWD and associated programming codes and algorithms submitted to FDA are documented, well-annotated, and complete, which would allow the FDA to replicate the study analysis using the same dataset and analytic approach. [9] Otherwise the reviewer cannot verify the data and thus the RWE analysis would be considered exploratory.

v. LIMITATIONS OF EXTERNAL CONTROL DATA: For regulatory agencies, it may be important that the external control population matches the actual trial population. The following types of issues may lead to non-comparability.

- SELECTION BIAS: Differences between study populations and RWD may come from institutions active in clinical research being different from other institutions or that patients enrolled in clinical trials frequently have better outcomes than patients not enrolled into trials. Some differences are explicit and intentional, i.e., through eligibility criteria such as legal age limits or laboratory value thresholds. [77] An example of adequately addressing selection bias is the case of Nulibry where the Sponsor performed genotype matching to show similarity between the control and the treatment groups.
- TEMPORAL BIAS: This bias originates from the differences in the standard of care in the past and the present. One mitigation step is to use concurrent control patients from a real-world data source along with a justification for the temporal bias in the non-concurrent control group. [77]
- REGIONAL BIAS: Patient outcomes may vary between different geographic regions due to differences in many factors, e.g., ethnicity, patient compliance or the health care system. The easiest way to avoid such bias is to use control patients from the same geographic regions as the clinical study. [77]
- ASSESSMENT BIAS: This assessment bias can be especially large for endpoints with a larger degree of subjectivity in their assessment. Choosing an objectively assessed endpoint, for example overall survival can drastically reduce assessment bias. Choosing an endpoint with highly subjective assessment could limit the applicability of external controls. [77] Eg. In the case of Zolgensma the use of objective endpoint of survival without ventilation and achieving motor milestone of sitting independently beyond 14 months helped in avoiding any such bias.
- DIFFERENT ENDPOINT BIAS: Endpoints in clinical trials may be different than endpoints in routine clinical practice or may not be even assessed in routine clinical practice. This may limit the applicability of external controls when using these endpoints, especially when external control relies on historical data (from EHR and registries). [77] Example use of real-world best therapy response in case of Balversa and the clinical study relying of RECIST V1.1.
- IMMORTAL BIAS: A relevant example is Nulibry where there was a potential for Detection Bias or a Spurious Mortality Benefit. An early onset of the disease implied a poorer prognosis than a late on-set. This could lead to spurious

mortality benefit. This was minimized by the genotype matching used for the selection of the natural history control group. [37]

- BETWEEN STUDY VARIABILITY: An important issue is also how variable and heterogeneous the outcome is across different studies. The reliance on external controls will be more critical if there is a high between study variability that cannot be explained, as this indicates that important factors affecting the outcome of an endpoint in a study cannot be controlled for. In such a situation, an RCT may be strongly recommended. [77]
- INTERCURRENT EVENT BIAS AFTER STUDY ENTRY**:** Intercurrent events such as premature treatment discontinuation can occur in RCTs and in external control studies alike. Depending on the estimated intercurrent events can lead to substantial bias. The ICH E9 addendum makes a strong effort to control such bias in a transparent manner, and the ICH E9 addendum should be similarly applied for external control studies. [77]

4.3 FDA´s expectation for successful submission of RWE

The FDA's viewpoint on the use of RWE has been progressively evolving, as seen by the successive publication of RWE guidance documents. Like any other data source, RWD has its own advantages and disadvantages which depend on the process of data curation from the original source. [11]

Depending on the case scenario´s as seen in the Table 4, the regulatory success of submissions with RWE varies and depends on a specific situation. But an estimate on the probable requirements of the FDA from the learnings can be made and is included in this section. Some important considerations to keep in mind while planning inclusion of RWE for regulatory application.

1) Determine the available data for an indication and then identify gaps in evidence to supplement the clinical study and identify the RWD which may be used for RWE generation. As per
2) Upfront planning and communication with Health authority: Sponsor need to plan ahead of time and align on the development plan for the generation of the clinical evidence using the RWD either during Pre-IND phase (using the pre-IND meeting or Type C meeting after initiation of IND with the appropriate review division).
3) Careful selection of the RWD source: here it is important to understand that the data should be complete, reliable and comparable to the target patient population.

4) Use of fit for purpose data with clear scientific rationale is also an important consideration. For example, in case of anti-cancer drugs for very specific target population harboring rare mutations the Sponsors tend to often use RWE. But in most cases the clinical evidence from the clinical study shows large treatment effect and durable response in terms of standardized clinical endpoints (often ORR as per RECIST v). In such cases the Agency relies more on clinical evidence than natural history data or literature evidence which only provides supporting evidence if any. In most cases the real-world data contains bias or post-hoc analysis performed by the Sponsors, which reduces the Agency's confidence in the data.
5) RWD provider & Sponsor need to plan the study's design and statistical analysis plan together and discuss it with the Agency prior to finalizing it or before conducting the study analysis. For this point, prior communication and discussion with the FDA is necessary. It is advisable to ask for a Type -C meeting and send a briefing package with all the information on the study protocol and SAP. It implies prior submission of the study protocol for future real-world studies, otherwise the analyses will be considered post-hoc by the FDA. The points to be discussed should include the baseline characteristics, appropriateness of the sample size considerations, measures undertaken to minimize bias: So as to ensure that the results of the real-world data study would yield interpretable and statistically significant results.
6) Another factor is to clearly understand and discuss the limitations of real-world data and the appropriate mitigation measures undertaken to address them.
7) Provide the reviewer with the raw data (patient level data) of the studies conducted in order to allow the reviewer to perform their own independent analysis and verification of the results. FDA also expects the sponsor to provide a log of any researcher or researchers who have significant involvement in the design or conduct of the study upon request. [9]
8) Lastly, the US FDA expects data integrity to ensure reliability of the RWE.

4.4 Best strategy for submission of drug approval package with RWE

Based on the use cases from the Section 3 Results, it can be inferred that there are certain cases where FDA considers RWD to support the traditional evidence for efficacy and safety:

- Rare disease with significant unmet medical need where recruitment for randomized clinical studies is not feasible. In such cases, even for the single arm studies owing to the rarity of the disease the recruitment across the globe is challenging.

- Where placebo-controlled trials are unethical and non-feasible. Since there is no approved standard of care for the patients and the medicinal product for which the submission uses RWE claims to bring significant benefit.
- When preliminary data suggests a large treatment effect in case of rare disease where recruitment of a parallel control arm is non-feasible.
- When there is existing safety or efficacy data on the use of the drug in related population.
- Where the medicinal product in the clinical studies does not show large and durable treatment effect but fulfills an unmet medical need.

Once a drug or biological candidate fulfills the above-mentioned criteria then for increasing the chances for acceptance of the RWE by the Agency the Sponsor needs to act intelligently. When the sponsor intends to submit RWE as a part of the submission for supporting or providing primary evidence for the claims of effectiveness, the following strategy must be followed.

Step I: Engage the key stakeholders in the development plan and discuss the possibility of utilization of RWD to supplement the clinical data and define purpose of the real-world data collection and sources. From this step onwards the statisticians will play a key role in finding the right study designs using external controls without substantially changing the high standard of evidence required for approval. Also, when the plan is to use RWD in the form of external control data, cross collaboration with epidemiologists and real-world data experts will be key and they should also be engaged early on. [77]

Step II: Interact early if possible, during the IND phase with the Agency about the future plans on using the RWE. Latest EOP2 meeting.

Note: Also, once the sponsor has an investigational new drug (IND) or a pre-IND number they can raise in the Advancing RWE Program a meeting request to discuss their approach for generating RWE even before protocol development or study initiation which would meet the regulatory requirements. [4]

Sept III: Discuss with the Agency about the SAP and the real-world data transformation strategies to avoid selection bias and always have Agency's feedback on the RWE generation plan.

Step IV: In the pre-submission meeting discuss the RWE data and its placement in the final submission documents. Also obtain US-FDA´s feedback, if possible, on whether the intended real-world data package would be accepted by the Agency. Also provide the Agency with the raw data (patient level data) to enable them to perform their own statistical analysis and verification of results during the review. This also ensures transparency. To be able to provide the patient level data the sponsor needs to ensure that agreements were made initially with the respective RWD owners. This ensures that patient level data can be provided to the reviewer when requested and also could be made available for inspection to show data integrity.

Step V: After submission, be prepared to receive FDA´s queries in the form of Information requests and provide valid scientific justifications or additional comparisons or metanalysis of the data as required by the reviewer.

Figure 9 shows an example of a submission strategy using RWE in the data package with the depiction of the above-mentioned steps and involving regular discussion with the FDA before employing a strategy and obtaining feedback before submitting the final data package to ensure smooth and fast approval of marketing authorization.

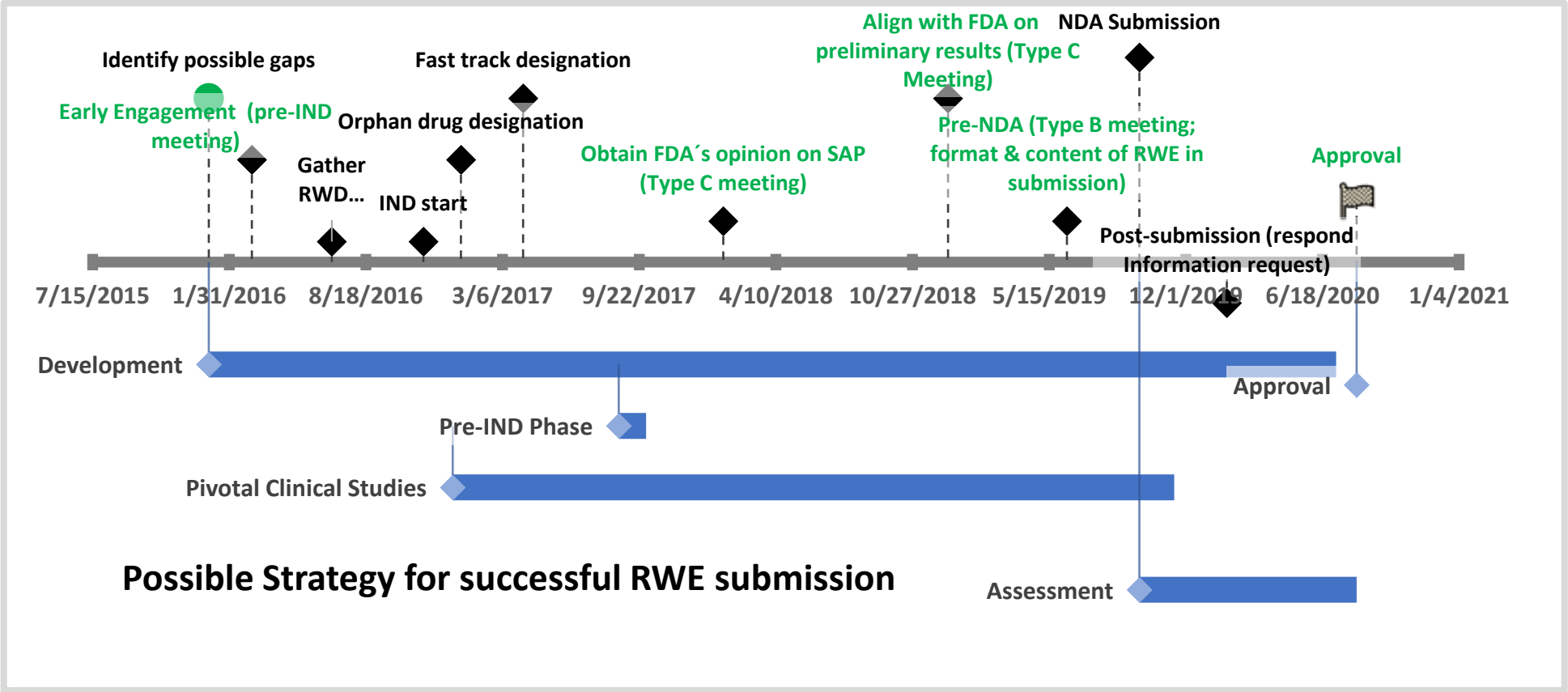

Figure 9: Depiction of a possible strategy for successful utilization of RWE in the submission (based on the example of EVRYSDI)

5. CONCLUSION

From the analysis of the submission package for all the 34 cases which fulfilled the inclusion criteria of this master thesis (plus two cases of sNDA included as examples; in total 36 cases), it is clear that the real-world data alone cannot provide sufficient scientific evidence of safety and efficacy for a new molecular entity (chemical or biological). It cannot be the sole basis of benefit-risk assessment, and thus, approval of marketing authorization. However, it can provide data to supplement the evidence for effectiveness and fill the gaps in the evidence. It can be said that real-world evidence contributes to the totality of evidence. It could be in the form of external control for a rare disease or provide therapeutic context with information on the available non-targeted therapy options which helps the US FDA reviewers to perform the benefit-risk assessment. It definitely adds value to the evidence package especially in areas of expedite approval where reviewers rely on data from abbreviated clinical studies.

Real-world evidence has its huge utility especially in case of rare diseases (as seen in Figure 8) where the clinical trial enrollment is challenging due to lower incidence rate. It also holds true for highly targeted novel oncologic therapeutics (Figure 8) which are being developed. In some cases, the special nature of disease also rendered use of RWE appropriate to provide evidence for effectiveness like in case of Viltepso, Zokinvy, Zolgensma, Besremi & Evrysdi. Real-world evidence is more often utilized in case of unmet medical need for rapid or accelerated approvals (as seen from Figure 6) and is also more readily accepted by the health authorities in such cases to provide fast access to patients. From the analysis of the submissions between Jan 2019 to Jun-2022 it is also found that all cases which utilized RWE were also considered to be the novel approvals by the US FDA (as seen in the published novel approvals by CDER & CBER between 2019-2022; except VIJOICE, Type 10 submission, IBRANCE and PROGRAF, sNDA).

Another facet to rare-diseases is that the benefit-risk assessment is not the only aspect supported by the real-world data but also translation of the treatment in to improved quality of life for the patients (example: in case of central nervous systems disorders, autism, schizophrenia, depression). Real-world data can provide important insights into patient's requirements for specific rare disease conditions and can support incorporation of clinical endpoints which not only are relevant for the physicians but also bring an improvement in the quality of life for the patient population.

The probability of acceptance of the real-world evidence by the US FDA increases when applicant engages the agency from the beginning. Successful integration of RWE in the submission was seen in cases where the Applicant discussed the plan of RWE generation early with the Agency and had a clear scientific rationale for the use of real-world evidence from the start of development phase like in case of Ayvakit, Evrysdi, Lampit and Zokinvy to name a few. It ensures collection of good, quality real world data using a reliable data source and use of fit for purpose data. In order to win confidence of the Agency, the raw data (patient level real world data) should also be provided to the reviewers wherever possible to allow data verification and a chance to perform their own statistical assessments. However, an important point to mention is that in most cases the sponsors are not owners of real-world data and therefore cannot always comply to these requirements.

Another important point is to submit the SAP before the clinical outcomes are known which reduces the chance of bias in the data. Otherwise, the agency considers the analysis to be post-hoc by the Agency as in the case of Xpovio. Though there are examples where the Applicant could scientifically justify and invalidate the post-hoc consideration by the FDA as in case of Nulibry.

An important consideration is also to know when to use real world evidence for supporting a positive assessment. In cases where the magnitude of clinical response is huge and durable then the utility of RWE to supplement the data further is little as it will just increase the efforts of the Applicant as well as the FDA who will review the data additionally. Moreover, the reviewers rely more on evidence generated during a clinical study. In cases where the magnitude of response from the single arm clinical study is huge often the Agency acknowledges the efforts of the Applicant and considers the RWE as exploratory due to its inherent limitations which are often associated with the design of the real-world studies, missing data and bias.

Even though it is assumed that real-world evidence generation is cost effective compared to a clinical study, but it also requires an investment of resources and time to perform data extraction, curation and statistical analysis which is time consuming and requires special expertise. If not done properly it would also be of little utility. Also based on different real-world data sources different processes have to be employed to generate fit-for purpose data. For example, for use of data from registry studies there is a requirement of going through the patient consent for use of the data. Also, reliability of data source is also to be considered.

In non-rare diseases, where the enrollment in clinical studies is not challenging the Agency expects the Sponsors to perform randomized, placebo / active controlled trial to provide evidence of effectiveness. In these cases, the utility of real-world data is minimal for supporting the efficacy and safety claims. Since the data generated by RCT will always remain the gold-standard for approval as they follow a scientific investigation procedure with well-defined inclusion, exclusion criteria and clinical endpoints and are performed under a controlled environment. However, the Sponsors can use RWE for already approved products for extension of the target populations based on the real-world use data for non-target populations (also off-label use) like in case of Ibrance and Prograf or use of observational studies like in case of Vijoice. In such cases the initial approval is based on the data from one-well controlled clinical studies which provide evidence of efficacy and safety based on this prior knowledge and real-world data an indication extension or a new marketing authorization with new indication is possible.

Finally, it can be concluded that real world evidence alone cannot support the entire benefit-risk assessment, but it contributes to the totality of the evidence. It can complement and support the design of clinical study, help in selection of appropriate patient population through real world demographic distribution, selection of surrogate endpoints for accelerated approval or justify the clinical end points for regular approval. Most clinical reviewers also search the published literature related to the disease as well as patient experience related to all treatment modalities used in those settings. This aspect covers real-world data use which provides an insight into the benefit requirement of the patients. Real-world data can be definitely used to design more appropriate clinical studies which meet not only clinically significant endpoint but also patient relevant endpoints which can ultimately bring quality to their life and not only help them overcome disease condition.

In future the health care practice may be able to tap the entire potential of real-world data, by analyzing health care data, identifying biomarkers which may help in early prediction of disease conditions, and in undertaking precautionary measure or developing targeted therapy options which may stop progression to a disease condition. It could be very beneficial as often disease diagnosis is too late and for many disease conditions the treatment options are symptomatic (to subside the symptoms). This could be the future scope of application of real-world evidence to be able to predict disease conditions in a pre-disposed population. Though the current landscape analysis from 2019-2022 shows that the pharma-industry is exploring to use the real-world data in all possible ways. All health authorities

across the globe have also started to accept real-world evidence where reasonable. Now the approach is to utilize the real-world evidence to supplement the benefit-risk associated with medicinal products. Very often it is seen in the case of rare diseases where there is a high unmet medical need. The most important point here is that the goal of real-world evidence use is to establish reliable evidence for safety or efficacy which is fit-for-purpose and supported by a solid scientific foundation. It shouldn't be applied merely to include it in the submission to just try to fit into the puzzle. Rather should be backed by scientific evidence and should bring value to the entire evidence package. Hopefully the use of real-world evidence will meet its desired potential in future.

6. EXECUTIVE SUMMARY

The perspective of health authorities on the use of real-world evidence for regulatory purposes has been evolving. This is evidenced by the issuance of RWE guidance documents by the US FDA in recent years. This master's thesis makes an effort to comprehend what the regulatory agencies anticipate from the sponsors when they submit real-world evidence. This is accomplished by conducting a retrospective analysis of the submissions (to the US FDA between Jan -2019 and Jun-2022) where RWE has been utilized by the Sponsor to contribute to the totality of the evidence (either for trial design considerations, as supportive evidence or as primary/substantial evidence for efficacy or safety) and to assess the benefit-risk relationship based on the inclusion criteria mentioned in the Methods section.

Despite numerous guidance documents, a gap still exists between the understanding of the Pharma-Company and the view of the FDA. This is due to the fact that the probability of acceptance of RWE for a marketing authorization is based on the use case as seen in the analysis of the 34 cases. The analysis of the assessment reports of the marketing authorization applications for the identified 34 cases, revealed successful strategies used by the Sponsors which enabled acceptance of RWE to support the benefit-risk assessment and thus expedite the approval for the drug products. It also highlighted common mistakes in the approach of Sponsors whose RWE was not accepted by the Agency. A clear determinant for the success has been early and regular communication with the Agency about the intent to use RWD for evidence generation. This has helped many pharma companies to get an early signal from the FDA whether the use of RWE would be beneficial to support their application or not. Also, an early engagement with the FDA helped the Sponsor to select the right inclusion and exclusion criteria, accurate data curation methods and to carry out relevant comparisons which otherwise could later result in a review issue. The FDA has highlighted time and again that RWD can support the totality of evidence in cases of an unmet medical need or rare diseases, in cases where the preliminary data shows large treatment effect but there are no active comparators and use of placebo is out of question, or in case of off-label use of approved medicinal products to support extension of indication. But RWE is not always accepted by the US FDA in all these use cases.

An analysis of the indications utilizing RWE in the submissions also showed that the US FDA often accepts RWE in case of rare diseases where the sponsor faces difficulty recruiting patients for a randomized clinical study. This is in line with the FDA’s intention to support innovation in areas of unmet medical need to bring treatment options to patients as early as possible. In these cases, the RWD helps fill the gap in the evidence and supplement the totality of evidence which helps reduce the development time and thus ensures early access to the patient population.

In most cases seen in this master thesis, the natural history data has been used by the Sponsor as external control to benchmark the treatment effect of the medicinal product or to show that the improvement in symptoms is not possible without intervention. From the examples

it is evident that the natural history data for benchmarking treatment effect is only accepted and useful when the treatment effect is otherwise difficult to establish and when use of placebo control would be deemed unethical. But not when the available data shows a clear, durable treatment effect with the use of the medication. In such cases use of natural history data as external control is unnecessary.

Another key fact highlighted in this thesis is that the US FDA sets a great value on the use of fit-for purpose RWD from reliable sources with clear scientific rationale. The Sponsors must keep in mind that RWE is not mandatory to be used in case of rare indications and cannot always replace evidence generated from the randomized controlled clinical studies. The purpose of RWE should be to supplement the evidence by filling the gaps and needs to be planned well in advance.

Comparing the timelines with use of RWE against the traditional approach of the randomized clinicals studies, it seems that the use of RWE is less time consuming and requires less efforts which is misleading. As use of RWE to supplement the evidence for efficacy or safety also requires a lot of resource planning with specialized expertise. RWE should be used only when it can support the totality of evidence. Finally, this work highlights the need to develop a more streamlined interactive approval strategy when using RWE by involving the right stakeholders with clear scientific objective from the beginning to provide a customized solution which fulfils the purpose of faster approval.

7. Annex 1: Details of the assessment and communication history between the applicant and US-FDA from assessment reports for all case studies

7.1 Egaten (triclabendazole) [12]

Triclabendazole was originally formulated as a veterinary medicinal product, Fasinex. The initial/intermediate human formulation was CGP23030. Egaten was first registered in Egypt in 1997, and then in France in 2002. It was put on the WHO list of essential drugs in 1997. It was also registered in 2001 in both Ecuador and Venezuela but has subsequently been de-registered in both countries. Between 2006 and 2018, an estimated 2.6 million treatment courses (single dose of 10 mg/kg) had been distributed worldwide. [12]

Egaten was not approved for marketing in the U.S. It was available under expanded access and dispensed by the CDC. [12]

Discussion

The evidence provided to support the safety of TCBZ for treatment of fascioliasis is based on patient-level data and information summarized in published studies. [12]

The studies providing supportive evidence were primarily either clinical studies or study reports. None of the study data were collected as part of registrational trial, because of which they do not fit the standards of adequate and well-controlled trials that FDA normally requires in an NDA. Virtually all, except the PSUR, were old studies, not conducted under GCP and non-uniform in their methods of obtaining and recording safety data. However, a descriptive analysis of the Egyptian government-sponsored studies and the paragonimiasis studies was attempted by the reviewer. The latter provided a useful opportunity to analyze the safety of TCBZ in patients with a condition of pathophysiology different from fascioliasis. Finally, in addition to the literature references provided by the Applicant, an independent literature search was conducted for studies assessing TCBZ safety. In the supportive studies, various formulations of TCBZ (Fasinex, CGP23030, and Egaten) were used; where possible, the specific formulation used in each study is noted.

The basis of acceptance of the real-world data in support of safety is the fact that TCBZ has been used widely for decades, a robust literature exists– of which some of the main studies were reviewed previously. These disparate studies with patient-level data, post-market data, and literature reports together consistently support the safety of TCBZ for treatment of fascioliasis. [12]

7.2 Ibrance (palbociclib)

Ibrance's sNDA was approved for extension of indication in men with HR-positive, HER2-negative advanced or metastatic breast cancer based on the real-world evidence. The initial marketing authorization was based results of the clinical studies (PALOMA-2 and 3) which included only women patients (male patients were ineligible for the studies).

Communication with the FDA

- On Oct 4, 2016, in a Type C meeting, the Applicant proposed the use of real-world data as evidence of efficacy and safety for male patients with the FDA and discussed about the protocols for the proposal. [13]
- On Jan 23, 2018 in a Type B Pre-sNDA meeting the Applicant discussed the real-world data with the Agency, before submission. [13]

Discussion

This case is additionally included in this master thesis as an example of real-world evidence from off-label use of the medicinal product which became the basis for indication extension.

Real-world data studies: The Flatiron study provided some evidence in the form of real-world tumor response in men with metastatic breast cancer with Palbociclib and endocrine therapy compared to endocrine therapy alone. But the study had limitations like it was not randomized, included small patient population, did not employ statistical tools to balance the two cohorts (Palbociclib+ endocrine therapy and endocrine therapy alone).

The IQVIA study also had limitations like limited information on whether the data was confounded or balanced regarding baseline covariates, it was also not randomized. Also, it seemed that prolonged prescription duration was considered to translate into prolonged survival which was not always the case.

In this case the sponsor started discussion with the FDA about their proposal to use RWD as early as 4 Oct 2017 and the discussed the preliminary data in a pre-sNDA meeting and obtained Agency´s opinion on the format of the data and submission plan. Finally, the s-NDA was submitted on 15 Jun 2018 and FDA granted approval based the real world-evidence and the extensively established efficacy and safety of the drug in women and absence of any new safety signals in the post-marketing reports neither in women nor in men.

7.3 Balversa (erdafitinib)

The efficacy and safety of Balversa was shown in phase 2 clinical study BLC2001 (a multicenter, open-label, single-arm study with 87 patients).

Communication with the FDA

Several communications took place between the FDA and the Applicant to discuss the statistical analysis plan for the retrospective study using data from Flatiron. In a pre-NDA meeting held in July 2018 the Applicant discussed the final plan to conduct a retrospective real world evidence study with the FDA.

Discussion

The submission of Balversa employing RWE highlighted the challenges with the data from EHR. EHRs often contain incomplete data. Determining the timing of a diagnosis from clinical data alone is challenging. First diagnosis in a database is not necessarily an incident case of disease. Flatiron's database did not capture all therapies received by individual patients, as patients could seek care from providers that do not contribute to the Flatiron database. Thus, defining the number of lines of therapy that patients have previously received was problematic.

The Applicant performed the real-world tumor response assessment which was limited by the lack of utilization of a standardized approach (such as RECIST v.1.1). In RECIST response assignment is quantifiable and time-dependent assessments which is not typically captured in EHR data whereas the real-world tumor response (rwTR) is defined as a qualitative change in burden of disease over the course of treatment of a given therapy and is assessed and described in a variety of ways in the real-world, and therefore the data usually carries large variability.

The Applicant communicated with the Agency the SAP as early as March 2018 (final submission 18-Sep 2018). The Flatiron data analysis was also shared with the FDA in pre-NDA briefing book and was discussed in 24.07.2018. But during review deviations from the original SAP were found which initiated need for Information Request. According to the Applicant, the decision to use this model was made before any analysis was done or results revealed. Finally, no definitive conclusion could be made about the prognostic or predictive impact of FGFR alterations in patients with metastatic urothelial cancer due to the mentioned limitations.

7.4 ZOLGENSMA (onasemnogene abeparvovec)

Zolgensma was approved for a rare disease, spinal muscular atrophy (SMA), with an unmet medical need for the treatment. The primary evidence of efficacy and safety was provided by an open-label, single-arm, single dose gene replacement therapy clinical trial with n=21 patients (Study CL-303).

Communication with the FDA [50]

Post-Breakthrough Therapy Designation Comprehensive Type B meeting was held to discuss design of Phase 3 trial (on 30/09/2016) and following points were discussed:

- FDA acknowledged applicant's rationale for conducting an open-label, single-arm Phase 3 trial in subjects with infantile-onset SMA. The proposed comparison group was natural history data from the Finkel et al. [51] and NeuroNEXT studies. [51] [53] [52]
- FDA recommended the following co-primary endpoint for the proposed Phase 3 clinical trial:
    a. the proportion of subjects who survive (i.e., alive without permanent ventilation),
    b. the proportion of subjects who meet the motor milestone of sitting independently.

Discussion

In this submission the natural history data was used as external control to benchmark the treatment effect and the effectiveness of the biological. Use of placebo control was not feasible (unethical) after the results of the phase 1 clinical studies were known. For safety evaluation the data from the patients from the expanded access program in US was also considered.

The applicant discussed the design of phase 3 clinical studies using natural history control group (from the Fink et al 2014 [51] and NeuroNEXT studies) during the post-breakthrough therapy designation type B meeting (as early as 30-Sep 2016). During this meeting the FDA also recommended the co-primary endpoints for the phase 3 trials (proportion of subjects who survive without permanent ventilation and the proportion of subjects who meet the motor milestone of sitting independently).

The only approved therapy option for SMA since Dec 2016 was nusinersen. But the enrolled population was also not comparable to the one utilized for Zolgensma and therefore no comparisons could be made between the two. Use of active comparator in the clinical study was not done due to extra cost associated with the invasive use of nusinersen. The use of

historical external control, though not ideal, appeared to be reasonable in this case because of an unmet medical need for this fatal condition. Moreover, the natural history of this condition is well documented and follows a relatively predictable course that can be objectively measured and verified, and all these facts were already discussed with the FDA.

7.5 Xpovio (Selinexor)

Xpovio received accelerated approval from the FDA based on the results of phase 2 clinical trial (an open label, single-arm study; KCP-330-012 (STORM) Part 2) which included patients who received atleast 3 prior anti-multiple- Myeloma regimen.

Communication with the FDA

Before submission of the NDA there was no discussion between the Applicant and the FDA about the use of RWE. After the NDA submission, the FDA made a number of informed requests (IR) to the applicant to address the RWD and STORM-2 comparability issues. Finally the applicant acknowledged the need for prior consultation and approval of the protocol and SAP with the FDA and submitted sensitivity analysis for adjustment of the confounding factors one by one. [15]

Discussion

In support of NDA 212306 for selinexor, the Applicant submitted analyses using retrospectively collected electronic health record (EHR) data. However, neither the protocol nor the SAP for RWD analysis was submitted to FDA prior to the conduct of the study. FDA was made aware of the retrospective observational study KS-50039 upon NDA submission. In this case, the Applicant did not fulfill the FDA´s expectation for prior consultation and approval of the protocol and SAP with the FDA. Therefore, the FDA could not be certain that the protocol and SAP were pre-specified and unchanged during the data selection and analyses. This was not the only issue with the use of RWE in the submission, but it ultimately led to the FDA´s conclusion of a selection bias, misclassification and confounding.

The Applicant also submitted sensitivity analysis for adjustment of the confounding factors in response to FDA´s information requests. But FDA's analysis found that post-hoc strategies to create greater comparability across cohorts were inadequate and resulted in very limited sample size and unstable estimates." [15]

Thus, due to the methodological limitations which could have been avoided by prior consultation, it was concluded that the evidence generated from the RWD analysis was not

adequate to provide context or comparison for the overall survival observed in the STORM patients.

7.6 Pretomanid (pretomanid)

Pretomanid was approved as a part of combination regimen with bedaquiline and linezolid for treatment of nonresponsive multidrug-resistant (MDR) tuberculosis (TB). The applicant provided substantial evidence of effectiveness in a single phase 3 clinical trial in patients with XDR-TB or TI/NR MDR-TB, superiority of the pretomanid, bedaquiline, and linezolid (BPaL) combination regimen on clinical outcomes was demonstrated compared to XDR-TB historical controls. [16]

Communication with the FDA

At the pre-NDA meeting held on June 1, 2018, the applicant agreed to provide a literature summary and case-matched analysis of historical control data for XDR-TB patients to support the efficacy outcomes in Nix-TB trials. [16]

Discussion

Around six months prior the final submission (14/12/2018) in the pre-NDA meeting held on June 1, 2018, the applicant agreed to provide a literature summary and case-matched analysis of historical control data for XDR-TB patients to support the efficacy outcomes in Nix-TB trials. [16] The Applicant had submitted literature review and the constraints of literature review were the ones relating to heterogeneity and lack of comparability in terms of geography, patient characteristics, and study assessments. The applicant also provided a comparison of BPaL and a matched historical control group in their analysis in which the constraints of the literature review were somewhat addressed by this comparison. The FDA accepted the data even though there could be a possibility of confounded results because the treatment effect was too large to be easily explained by confounding factors. Thus, historical controls could offer strong evidence of efficacy in the case of Pretomanid.

7.7 Wakix(pitolisant) [18]

Pitolisant was authorized by the EMA for the treatment of narcolepsy with or without cataplexy on March 31, 2016. It was an NME which was not previously approved in the United States. [18]

Communication with the FDA

In May 2015, the Agency provided written responses on the use of foreign data for safety and efficacy. [18] The Applicant had also inquired about the number of patients needed to

assess clinical safety (given the orphan indication and recruitment difficulties). The number of participants who received pitolisant in the clinical trials approached the ICH E1 requirements when clinical trial data from all indications were considered. DNP indicated that the extent of exposure including the patients in the non-narcolepsy indications would be adequate to support filing of the NDA. [18]

Discussion

In the case of Wakix, Pitolisant was already authorized by the EMA since March 31, 2016. It was an NME which was not previously approved in the United States. It was for chronic use which necessitated long term safety data. Thus, the Applicant made use of RWE from the post-marketing experience from EU and safety data from use of the drug in non-narcolepsy indications obtained from literature reports.

The Applicant started communication with the FDA regarding use of RWD as early as May 2015 (final submission 14.12.2018). [Section 2 Background, Summary Review, Page 9-10]. An inquiry about the number of patients needed to assess clinical safety (given the orphan indication and difficulties meeting the numbers recommended by the ICH E1 guidance for chronically administered drugs) was also made on using data from Expanded access and the off-label use of the drug. An agreement that the extent of exposure including the patients in the non-narcolepsy indications would be adequate to support filing of the NDA. [18]

During the review, the Reviewer commented that overall, the SAEs reported in the narcolepsy clinical trials and the off-label use of the drug did not appear to indicate an unexpected safety signal or suggest that additional monitoring of any safety signal. [18]

7.8 Rozlytrek (entrectinib) [19]

Rozyltrek received accelerated approval based on the results of ALKA, STARTRK-1, STARTRK-2 multi-centre single arm open-label studies.

Communication with the FDA

From the regulatory history, no prior discussion about the submission of RWD was found between the applicant and the FDA.

Discussion [19]

The Applicant presented Crizotinib RWE arm to establish the natural history of disease for ROS1-positive NSCLC and to compare treatment outcomes between the entrectinib arm and crizotinib arm in this study. In the case of Rozyltrek prior submission of study protocol

was not performed. On 11.07.2019 review by Office of Surveillance and Epidemiology Review (OSE)Office of Pharmacovigilance and Epidemiology (OPE). of sponsors study report comparing the clinical trial data with the RWD was obtained. [19]

In review, DEPI concluded that the crizotinib arm was unlikely to be generalizable to the entire population of patients with ROS1-positive NSCLC and substantial differences in TTD, PFS, and OS between study arms, all favoring the entrectinib arm were identified. [19] Moreover, differentially implemented study eligibility criteria, resultant differences in baseline criteria, and limitations in statistical modeling due to low sample size made it difficult to determine what proportion of the observed differences in rates of clinical outcomes were due to imbalances in study populations at baseline (i.e. selection bias). Despite a well-done attempt at defining treatment outcomes, there were limitations. The study report was not adequate to allow a robust comparison of treatment outcomes between crizotinib and entrectinib study arms and the Applicant was advised to submit an a priori study protocol for future studies, as the analyses were considered post-hoc.

7.9 Enhertu (fam-trastuzumab deruxtecan-nxki) [54]

Enhertu was approved to fulfill an unmet medical need to improve the outcomes of female and male patients with HER2-positive advanced or metastatic breast cancer after 2 lines of therapy in metastatic setting. The primary evidence for safety and efficacy came from the Phase 2 study DS8201-A-U201 (DESTINY Breast-01, n=184) which is a multicenter, single-arm, trial. [54]

RWE Studies were not mentioned in the list of clinical trials relevant to the BLA. Also not mentioned in the Label.

Communication with the FDA

No information could be found on the discussions between the Agency and the Applicant about the use of RWE studies. The reviewers' comments also do not explicitly mention the comparisons between the RWE and the results from the clinical study.

Discussion [54]

The RWD from the matched historical cohort and the analysis from the literature review was used to supplement the clinical data package to estimate the expected clinical benefit (PFS, ORR) of fam-trastuzumab deruxtecan with a comparable patient population. [54]

The results from the Study DS8201-A-U201 showed durable ORR that represents improvement compared to the available therapy which is reasonably likely to predict clinical benefit and thus accepted as surrogate endpoint for accelerated approval. RWE submitted was not considered for comparison of the results due to the following probable reasons:

- The matched cohort and clinical trial; may have different ORR and PFS measurement and timing schedules.
- Data on ORR and PFS for the patients from the matched external cohort were not provided to the Agency.
- Issues with the comparability of patient groups for variables other than those taken into account during matching.

7.10 Ayvakit (avapritinib) [20]

Ayvakit received regular approval for metastatic GIST with a specific platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations. The enrollment of patients with this specific mutation type was slower than anticipated and with smaller dataset it was difficult to provide sufficient information regarding the safety and efficacy of Ayvakit.

The primary evidence came from the clinical trial, NAVIGATOR (BLU-285-1101, NCT02508532), a multi-center, single-arm, open-label clinical trial based on durable response. [20]

Communication with the FDA

The applicant discussed early during a Type B End-of-Phase 1 (EOP1) meeting the relevance and clinical significance of the clinical endpoints (Overall response rate (ORR) and DOR data from 50 patients) with the Agency for supporting an accelerated approval. [20]

One of the Agency's recommendations for an accelerated approval was the need to demonstrate, that the findings of the retrospective natural history study using BLU-2851002 were in line with those of published studies demonstrating that patients with PDGFR-D842V-positive GIST have extremely low response rates to FDA-approved treatments for GIST. [20] The totality of the submitted data would determine the final approval.

Discussion

In case of Ayvakit during a Type B End-of-Phase 1 (EOP1) meeting held on 19 April 2017 FDA recommended the Applicant to demonstrate, through the findings of the retrospective natural history study (BLU-2851002) that the patients with PDGFR-D842V-positive GIST have extremely low response rates to FDA-approved treatments for GIST for an accelerated approval. Later in a Type B EOP2 on 5 Dec 2017 the plan for submission of initial NDA with natural history data was discussed. The final NDA was submitted on June 14, 2019. The data was obtained from clinical charts and was used to characterize the natural history of disease in patients with PDGFRα D842 mutant GIST.

The strength of the submitted RWE was that Blueprint provided retrospective data from 22 patients which was collected over a relevant time period and to minimize the potential for confounding, data were only collected at 3 centers in the US where high-quality mutational analysis was done routinely. [20] The results of natural history were in agreement with the two-retrospective analysis of the published literature.

7.11 TAZVERIK (tazemetostat) [21]

Communication with the FDA

On January 14, 2019, in Type C pre-NDA meeting: FDA recommend Epizyme to include information of natural history of epithelioid sarcoma patients, and an analysis of the effectiveness of available therapies in a comparable patient population. Since the ORR observed till date was insufficient to serve as evidence of treatment effect. [21]

•On April 29, 2019, in Type B pre-NDA meeting: FDA did not agree with Epizymes proposal to use their natural history study in patients with epithelioid sarcoma as a comparator arm to support regular approval. In addition, FDA stated that doxorubicin and pazopanib were considered available therapy for patients with epithelioid sarcoma. This indicated a need for randomized control trial with available standard of care anti-cancer agent. [21]

Advisory Committee Meeting and Other External Consultations: An Advisory Committee (AC) meeting was held on December 18, 2019. While the committee acknowledged that the response rate was low, the vote seemed to be influenced by the occurrence of prolonged response to tazemetostat in a few patients, by the number of patients who experienced some period of stable disease on tazemetostat, and by the rarity of the disease and lack of satisfactory therapies. [21]

Discussion

In case of Tazverik, the Applicant intended to use natural history data for obtaining accelerated approval. During initial discussions with the FDA, the Agency recommended (in a Type C pre-NDA meeting) the Applicant to use natural history data to provide therapeutic context and compare the effectiveness of Tazemetostat with the available therapy options. However, FDA cautioned that comparisons of time-to-event endpoints against an historical population are challenging because of difficulties in ensuring matching for known and unknown prognostic factors, which may confound the assessment of observed differences.

Later a key uncertainty of the reviewers regarding this application was whether the low response rate observed with Tazverik (in study EZH-202) would translate into a positive impact on survival or other clinical benefit. Moreover, the reviewer could neither find evidence in the literature nor in the applicant's natural history study to substantiate the claim that patients with ES were less likely to respond to other therapeutic agents (like doxorubicin or pazopanib) than patients with other forms of sarcoma. There were available therapy options which were considered standard of care due to which using natural history control for regular approval was not considered as intended by the Applicant.

Finally, the Agency did not agree with the Applicants proposal for the use of natural history study in patients with epithelioid sarcoma as a comparator arm to support regular approval. FDA mentioned that for regular approval available therapeutics could be used for comparison of therapeutic outcome. Moreover, in the case of Tazverik the ORR was not considerably higher than the ORR from the published literature with use of other agents which also did not help the review process for accelerated approval where data should indicate significant benefit over available therapy options. But the application still got accelerated approval based on the outcome of AdComm meeting (11- 0 vote).

For Tazverik later the Applicant also submitted a s-NDA for another indication and used natural history data to evaluate the impact of a specific (EZH2) mutation status on response to standard of care and thus analyze its beneficial prognostic value. For this indication as well, the applicant gained alignment with the FDA early during a Type B meeting (End-of-Phase 2 meeting). In this case the FDA did ask for additional details which were provided by the applicant and thus, this supported the efficacy evidence. Though this is not mentioned

in the benefit-risk evaluation but only in the administrative correspondence between the Agency and the Applicant.

7.12 KOSELUGO (selumetinib sulfate) [22]

Neurofibromatosis type I (NF1) is a syndrome caused by germline mutations in the NF1 gene resulting in widespread phenotypic outcomes, including plexiform neurofibromas (PN). Although PNs are benign tumors there is potential for them to undergo malignant transformation. The efficacy of KOSELUGO was evaluated in SPRINT Phase II Stratum 1, an open-label, multicentre, single arm trial (NCT01362803).

Communication with the FDA

Type B Pre-IND meeting held on September 8, 2014: Supportive preliminary data from the ongoing NCI POB NF1 Natural History study was discussed. The FDA stated that if the prospectively collected data from the ongoing NCI natural history study demonstrate a consistent PN growth rate, evidence that spontaneous tumor regression does not occur, and that improvement or worsening in measurable functional impairments correlate with decrease or increase in tumor volumetric $\geq$20% then this information should be sufficient to establish the natural history of the disease such that observed effects during the proposed study could be attributed to the selumetinib treatment effect and not the natural history of disease.

Type C face-to-face meeting held on 2-Nov-2017: In this meeting FDA agreed that the NCI POB NF1 Natural History study will provide supportive data for the regular approval along with the data from SPRINT Phase II Stratum 1. [22]

Type C Meeting held on November 13, 2018 (Written Response):

The FDA stated that the Applicant's plan to reference tumor volume data from the NCI NF1 Natural History study and the placebo arm from Part A of the NCI Study 01-C-0222 as external controls for tumor growth and for the efficacy endpoints progression free survival (PFS) and time to progression (TTP) was acceptable b [22]ut noted that these analyses would be considered exploratory.

Breakthrough Therapy Designation held on March 29, 2019: For the Breakthrough Therapy designation the published results from the NCI Natural History study were considered.

In the Type B Pre-NDA meeting held on June 28, 2019, the Applicant's plan to submit external control data to support the efficacy analysis using the NCI POB NF1 Natural History Study was accepted by the FDA.

Discussion

In case of Koselugo the applicant communicated with the FDA early and regularly regarding the use of RWE (starting from Type B Pre-IND Meeting September 8, 2014, Type C face-to-face meeting held on 2-Nov-2017, Type C Meeting held on November 13, 2018 (Written Response), Breakthrough Therapy Designation held on March 29, 2019 & In the Type B Pre-NDA meeting held on June 28, 2019). Still during review issues were found with Study differences including patient eligibility criteria, assessment frequencies of endpoint, and endpoint definition. Furthermore, the lack of covariate information available for these external data limited the ability to compare data sources or to adjust for potential confounding or bias, and so the results of any natural history comparisons were not interpretable.

The natural history study provided evidence that spontaneous regressions are uncommon in case of NF1 PN.

During review, FDA considered any comparison of results between the clinical study and the Natural History study as exploratory due to the lack of information available to adjust any comparison for potential confounding or bias. FDA considered the comparisons of efficacy endpoints to be exploratory.

7.13 TABRECTA (capmatinib) [23]:

The efficacy data of capmatinib was generated primarily from Study A2201, the Phase II pivotal trial. [23] Due to the relatively low incidence of MET mutations leading to exon 14 skipping in NSCLC, a randomized trial in this patient population was not feasible.

Communication with the FDA [23]

At an End-of-Phase II (EOP2) meeting held on 01-Mar-2017, FDA agreed that the proposed study endpoints and statistical assumptions would be acceptable for submission if the ORR was large in magnitude and durable, and a description of the natural history of subjects with NSCLC harboring MET-mutations or MET amplification (RWE chart collection) was provided. [23]

During a discussion with the Agency on July 22, 2019: The Agency accepted the proposed approach to' provide the requested "real world" data characterizing the natural history of NSCLC with MET exon 14 skipping mutations and stated whether the data will be fit for purpose, will be determined during the NDA review. Novartis was asked to submit the study protocol for the retrospective chart review to the IND within 30 days of this meeting. [23]

Discussion

During the End of phase 2 meeting held on 01 Mar 2017 FDA asked for a description of the natural history of the subjects with NSCLC harboring MET mutations (from retrospective chart collection) to validate the proposed endpoints and the statistical assumptions. There were several communications on the use of natural history data but during the review it was not considered for efficacy evaluation as it is mentioned in the Section 8.1.5 Additional efficacy consideration that Novartis did not submit this data due to which FDA could not independently verify the results of study X2401 (natural history study providing an estimate of the MET dysregulated NSCLC via global retrospective chart collection). Since the FDA could not independently verify the results presented in the clinical package by the Applicant it was not considered for the primary efficacy evaluation.

7.14 MONJUVI (tafasitamab-cxix)

The Applicant used data from the Study MOR208C206 (RE-MIND), a retrospective observational cohort study evaluating lenalidomide monotherapy using real world data, and literature reports regarding the activity of single agent lenalidomide.

Its purpose was to generate a matched control cohort for MOR208C203 (L-MIND) to isolate the contribution of tafasitamab to the combination. However, there were several limitations to the observational study which render formal statistical comparisons unfeasible.

The limitations of the real-world data include:

1) the uncertainty of the magnitude of effect due to the small sample size and lack of a comparator arm

2) the limitations of the retrospective observational data referenced, 3) and the data collected on time-to-event endpoints are not interpretable, therefore, it cannot be determined if PFS or OS are prolonged.

7.15 BLENREP (belantamab mafodotin-blmf)

At the time clinical study (DREAMM-2) was designed, there was no standard of care approved for the study population and therefore a randomized study with a globally acceptable comparator in this patient population was not feasible. The single-arm trial design comparing belantamab mafodotin to historical data was discussed previously with FDA and CHMP.

Comparison with historical control of 15% was planned for each dose level separately, with one sided type I error controlled at 0.0125 for each comparison and the overall one-sided type I error controlled at 0.025.

FDA noted that for a single-arm study without a control arm, efficacy based on the ORR rate needs to be supported by an adequate ORR magnitude and a clinically meaningful DoR. The FDA also noted that the patient population for the single-arm trial of selinexor in combination with dexamethasone, penta-refractory, was different than the patient population used in the DREAMM-2 study, triple-class refractory. Therefore, comparisons of the efficacy in the two studies should be interpreted with caution.

The reviewer's OS analysis results agree with the results presented by the Applicant. The FDA reiterates the challenges with interpretation of time-to-event endpoints in single arm trials including inconsistent definitions of time intervals across studies leading to biased estimates, and bias associated with comparison to historical controls due to differences in the study population, differences in the frequency and timing of assessments, and advances in medical care over time.

7.16 LAMPIT (nifurtimox) [24]

Additional supportive evidence of efficacy was obtained from the F29 ELISA test (thought to detect antibody response to live parasites) which was positive at baseline in 214/330 (65%) of the study population. These data showed a significant increase in the seroconversion rate on the F29 ELISA test compared to a historical placebo control in Chagas disease patients 6 to 12 years of age [26]. These rates were higher than the 2.8% conversion rate from the historical data for untreated patients between 6 and 12 years old at 12 months using the F29 ELISA

Communication with the FDA

In the pre-IND meeting the nonclinical and clinical data, as well as data from other clinical trials and literature in support of both the efficacy and safety of nifurtimox in the treatment of Chagas disease for nifurtimox tablets were discussed. The clinical development program was discussed beforehand with the FDA.

Discussion

In the NDA submission, trial results were only available for Month 12 follow-up after treatment, which was a relatively early time point for assessing T. cruzi serological assay endpoints. In previous studies that evaluated potential Chagas disease treatments (including studies used for the historical control cohorts of the current trial), seroconversion endpoints were assessed at 36 – 48-month follow-ups. Seroconversion of F29 ELISA results from positive to negative has been used in a previous NDA as a surrogate endpoint. In this submission the applicant use the data on seroconversion using the F29 ELISA test from placebo treated patients from the published literature de Andrade et al. 1996 [25]; Sosa Estani et al. 1998 [26] and used as historical control data for comparison. [24] Selection of the surrogate endpoint was based on the historical data which was accepted by the FDA. The applicant could show superiority of the nifurtimox over the historical placebo control.

The Applicant had submitted patient level data from the historical placebo study conducted in Argentina in 1982 which is an important point to consider as FDA requires the data to carry out their own analysis using the data and give importance to submission of such patient level data for transparency. In this case the reviewers compared the age of the patients in the clinical study to that from the placebo group as age can greatly affect the rate of sero conversion and thus the interpretation of the results. The application was further supported by literature study data. In the pre-NDA meeting the applicant also discussed the sufficiency of the clinical data package and obtained FDAs recommendations on possible review issues and clarifications to be included.

7.17 EVRYSDI (risdiplam)

The applicant has provided data from two clinical studies in SMA:

•BP39056 (FIREFISH) – an open-label study in infants with Type 1 SMA which was externally controlled using natural history data and provided additional evidence of efficacy and safety in in infants with type 1 SMA. [27]

•BP39055 (SUNFISH) – a randomized, double-blind, placebo-controlled study in patients with Type 2 and 3 SMA which is an adequate well controlled efficacy and safety study. [27]

The Applicant discussed their intent to use natural history data as external control for FIREFISH study with the FDA and also discussed the duration of study and the endpoints for comparison and in this way safeguarded acceptance of the RWE for fulfilling the gap.

The reasons for success with use of RWE in this case were: Early engagement, well-defined natural history of SMA, objective endpoint, patient comparability was ensured, large treatment effect (ability to sit) and good covariate measurement.

7.18 VILTEPSO (viltolarsen) [30] [24]

The dystrophin biomarker data was proposed by the applicant as a surrogate endpoint that is reasonably likely to predict a clinical benefit, in support of the approval of viltolarsen under the accelerated approval pathway. This was based on a previous conclusion by CDER that the increase in dystrophin level was reasonably likely to predict clinical benefit. [30]

The increase in dystrophin levels demonstrated for viltolarsen was similar in size or slightly greater to that established for eteplirsen and golodirsen, drugs that received accelerated approval.

Communication with the FDA

At the Type C meeting in May 2018, the Agency noted that the applicant must provide in the NDA evidence that truncated dystrophin produced by viltolarsen were at levels reasonably likely to predict clinical benefit. The applicant addressed this by providing epidemiological and pathophysiological evidence from scientific literature.

In conclusion, the published article cited by the applicant did not provide conclusive evidence that the levels of dystrophin produced by viltolarsen are likely to predict clinical benefit in patients and whether dystrophin alone can explain clinical severity in a patient and the likelihood of clinical benefit.

20 Oct, 2015: Agency advised that historically controlled studies will be unlikely to provide substantial evidence of efficacy. [30]

Discussion

The Applicant ensured high quality, comparable data by conducting the Study 201 at clinical sites participating in the CINRG network, so the SOPs (clinical manuals) and clinical

evaluator (CE) training protocols were harmonized between Study 201 and the CINRG natural history database. From the clinical review, the variability in the natural history of the disease comparisons to a natural history cohort, even when matched controls were utilized, did not appear reliable. This led to issues with the population matching due to lack of control of all known and unknown biases. Moreover, the Applicant was not able to show any clinically meaningful difference in clinical function at the end of treatment with viltolarsen 40 and 80 mg/kg/wk compared to natural history. [30]

7.19 VEKLURY (remdesivir)

Remdesivir was not approved by the FDA for any indication until 2020. It was previously assessed for Ebola Virus Disease. Given the rapidly emergent nature of the 2019-2020 pandemic and the urgent need for medical countermeasures, on May 1, 2020, the FDA issued an emergency use authorization (EUA) for remdesivir for the treatment of suspected or confirmed severe COVID-19. [31]

Communication with the FDA

During the pandemic situation there was regular communication between the Agency and the Applicant for discussion on the efficacy and safety data.

Discussion

This was a special case, given the rapidly emergent nature of the Covid pandemic and urgent need for medication the development of Remedesivir occurred rapidly. Based on the non-clinical virology data the applicant obtained emergency use authorization. Rolling review was granted to the application and each step of development was guided by robust scientific data. The main efficacy and safety evidence were provided by the clinical studies, but the EUA also supported the safety issues seen in the clinical studies (The EUA safety data analysis identified greater number of cases of hypersensitivity reactions including infusion related and anaphylactic reactions compared to the phase 3 clinical trials.) and thus provided supportive evidence.

The Applicant had also submitted data on 163 patients who received Remdesivir under expanded access program between 26 Jan 2020 and 14 Mar 2020. But the available clinical data from these patients was limited and therefore it was not considered for assessment of safety and efficacy. [31]

7.20 Zokinvy (lonafarnib)

The Applicant identified the full natural history cohort from the Progeria Research Foundation International Progeria Registry which maintained the natural history study records and directly submitted the updated vital status data and records to FDA. For the main efficacy assessment, patients born in 1991 or later (the contemporaneous control) served as the pool for potential matches for the treated patients in ProLon1 and ProLon2. [32]

Communication with the FDA [32]

In April 2018, the trial investigators published their findings on the survival benefit of lonafarnib treatment in HGPS patients based on their matched analysis of the mortality data of these trials and those of the untreated patients from a natural history cohort [78]. The endpoint and analyses for the NDA were discussed at pre-IND and IND meetings. The Agency also agreed to the main endpoint of mortality for the NDA and additionally, recommended the SAP to include a longer follow-up time for all treated and untreated patients.

During the NDA review, the Agency requested the Applicant to submit, the survival analysis based on the new matching criteria (by variant status, sex, and continent of residency) and the fixed 50^{th} percentile matching algorithm was considered as the main analysis, and all other analyses were considered as supportive analyses.

The Agency also requested the Applicant provide evidence to demonstrate comparability of the treated patients and their matched untreated controls.

Discussion

In case of Zokinvy, the use of external control from a natural history cohort for efficacy evaluation is mentioned in the product label. [32]

The Applicant ensured that all possible reasons for non-comparability, selection bias & confounding errors were addressed. The Strengths of the data included the fact that the trial investigators undertook rigorous efforts to identify patients with HGPS globally and offered all patients the same opportunity to participate in the natural history study, reducing potential selection bias. [32] Known potential confounders (age at treatment initiation, variant status, sex, and continent of residence) were adequately addressed in the analyses. Though the analysis plan was not submitted prior to analyzing the data, which raises the likelihood of a type I error. But these concerns were minimized by the objective mortality

endpoint and steps taken by the trial investigators and applicant to mitigate potential sources of bias. The Applicant resolved all sources of biases found during the review with a revised algorithm that matched on variant status and by censoring follow-up time of the untreated patients at the follow-up time of the treated patients.

With the final submission on March 20, 2020 the Applicant had discussed as early as in April 2018, their findings on the survival benefit of lonafarnib treatment in HGPS patients in comparison to the matched untreated patients from a natural history cohort. [78] The endpoint and analyses for the NDA were discussed at pre-IND and IND meetings. The Agency also agreed to the main endpoint of mortality for the NDA. The Agency also requested the Applicant provide evidence to demonstrate comparability of the treated patients and their matched untreated controls.

7.21 Oxlumo (lumasiran)

Approval is based on two phase 3 trials (ILLUMINATE-A in patients $\geq$ 6 years (n=39) and ILLUMINATE-B in patients <6 years of age) which are also listed in the list of CT submitted to support the efficacy and safety. [33]

Communication with the FDA

None in support of real-world study or literature evidence.

Discussion [33]

The Article published by Lawrence J, Wattenberg DJ summarized the concerns of the primary hyperoxaluria community through multiple in-person meetings convened and a web-based survey developed by families, the Oxalosis and Hyperoxaluria Foundation (OHF), the Kidney Health Initiative (KHI), and the American Institutes for Research. The patient and caregiver perspectives were listed in this paper along with the survey findings to highlight the daily challenges and the great need for new therapies. [33]

The companion paper by Milliner *et al.* presented a systematic analysis of available data to identify appropriate end points to assess the efficacy of potential therapies in clinical trials. These publications supported the selection of clinical endpoints based on the analysis of real-world data. This data was considered in the assessment but was not submitted by the applicant. [33]

7.22 DANYELZA (naxitamab-gqgk)

This application is supported by evidence of a substantial, clinically meaningful ORR and durability of responses in the disease population, which has no approved therapies, in two single-arm trials, Trial 201 (n=22) and Trial 12-230 (n=39). [64]

Communication with the FDA [64]

IND submission: on 05 September 2017 by Y- mAbs after acquiring the rights to naxitamab from Memorial Sloan Kettering Cancer Center (MSK). As part of the pre-BLA meeting, FDA agreed with the use of MSK Trial 12-230 as the pivotal efficacy trial, with supportive efficacy data coming from Y-mAbs Trial 201 and retrospective Study 2PR01.

After interactions with FDA, one of the key changes to the naxitamab program included conduct of a retrospective review of the naxitamab compassionate-use program in Spain for additional efficacy and safety data.

FDA requested that any early efficacy data from the expanded access trial or Y-mAbs Study 201 also be submitted in the BLA, given that Study 12-230 is limited to a single institution's experience, and given that the product administered to patients in the trials was different.

Agreements at the June 26, 2019 pre-BLA meeting are summarized below: •FDA generally agreed that the results from Studies 12-230 and 201 will provide the primary support for the BLA and that results from Studies 11-009, 12-116 and 2PR01 will provide supportive safety information. FDA provided guidance regarding the content of the safety narratives.

IND 132793 pre-BLA Meeting Minutes: June 26, 2019: Patients in the compassionate use program received naxitamab in combination with GM-CSF or in combination with GM-CSF and chemotherapy depending on the disease status of the patient to provide additional supportive safety and efficacy information in the planned BLA. The US FDA also agreed that the 2PR01 will provide supporting evidence.

Discussion

In case of Danyelza, with regard to use of Study 201 as a confirmatory trial, FDA acknowledged the challenges inherent in designing a randomized trial of naxitamab to serve as the confirmation of clinical benefit in the population of interest. Still US FDA asked for a justification for not conducting an internally controlled trial. Additionally, the US FDA made the recommendation that OS should be incorporated as a key secondary endpoint for

Study 201 to assess for possible impairment in OS as compared to historical data and to further characterize safety.

Strengths of the RWD submission included:

Data entry for this retrospective observational study was done in accordance with the protocol, the principles of the Declaration of Helsinki, International Council for Harmonisation (ICH) guidelines for data entry and monitoring, and with the laws and regulations in Spain. [64]

Overall, the enrollment demographics and baseline disease characteristics for Trials 12-230 and 201 and retrospective Study 2PR01 (Categories 1 and 2) were similar. The trial populations analyzed for efficacy were considered to be sufficiently similar to allow comparison of the efficacy results across the trials. In addition, these demographics are sufficiently representative of the anticipated patient population that will receive the commercial product in the United States. [64]

Statistical Analysis Plan and Amendments A: standalone SAP was made for the analyses performed to support the BLA. The SAP was signed before the statistical analyses of efficacy started.

But in the FDA's Assessment, the FDA did not perform dedicated analyses for the retrospective study. As it does not consider the retrospective study to provide substantive information to support the safety and effectiveness of naxitamab because the efficacy results were determined by investigator assessment rather than independent central review, which FDA generally recommends for assessment of ORR in single arm trials to minimize the potential for bias. FDA considered that the nature of the study may lead to incomplete data collection that renders interpretation of the results of the study difficult. Well established and reliable endpoint of blinded, independent, central review (ORR and DOR) in single arm trials were sufficient to support marketing applications. [64]

7.23 TEPMETKO (tepotinib)

Communication with the FDA

As per the Administrative correspondence for safety: The FDA agreed that the results of the observational study to monitor adverse events, on all included tepotinib-treated patients will be indirectly compared to the results from the historical control study performed to support

the expedited approval and assess effectiveness of previous therapies considered as standard of care.

Discussion [36]

The efficacy assessment in this submission was based solely on the VISION study. But it was also possible to place the VISION efficacy results in the context of data from available therapies to help further substantiate the clinical activity of tepotinib.

In a teleconference for the application of breakthrough therapy designation held on March 5, 2018, FDA recommended that EMD Serono to include any available information from clinical studies and the literature, regarding expected response to available standard therapy and the natural history of disease for these patients.

Since VISION was a single-arm study, EMD Serono proposed two methods to the FDA to estimate effectiveness:

•Method 1: to use external historical data from US databases to identify 30-40 patients with METex14 skipping alteration-positive NSCLC, regardless of treatment. [36]

FDA did not object to the use of external controls for this strategy, provided that the analysis plan would be adjusted for imbalances in demographic and tumor prognostic characteristics to minimize bias. Also, the Applicant was recommended to use appropriately sized external control data otherwise it would result in under-representation of the relevant patient population. The inclusion criteria for the external control population should also be similar to patients enrolled in the VISION trial with regard to demographic and important disease-related prognostic factors.

•Method 2: to use the previous efficacy outcomes (i.e., prior-line best-overall response (BOR) and PFS) in patients enrolled in VISION receiving tepotinib as 2nd (N=20-30) or 3rd line (N=20-30) treatment as the comparator for efficacy outcomes for patients receiving tepotinib as 1st line treatment in VISION. But the FDA did not agree with this approach. [36]

From further discussions it was clear that FDA was open to explore the use of real-world experience and also pointed out the methodologic challenges with use of such approach while assessing the clinical endpoint.

During assessment the FDA did not consider the comparisons presented by the Applicant for efficacy assessment due to the limited nature of the data regarding response to other

anticancer therapies for patients with NSCLC harboring METex14 skipping alterations and the limitations of the approaches used to collect this data as described by the Applicant.

7.24 NULIBRY (fosdenopterin)

Before approval of fosdenopterin, recombinant PMP (rcPMP) was used for treatment of patients with Molybdenum cofactor deficiency (MoCD) type A. [37]

Communication with the FDA

The clinical evidence for obtaining BTD was from the individual literature study reports and the information on the 17 patients whose comprehensive data was collected through the conduct of a retrospective data collection study (ALX-MCD-501) to confirm the reported improvement.

Due to issues with the recruitment for Study MCD-202, the Applicant initiated discussions with the Agency regarding the use of data across multiple studies to compare treated patients to untreated patients in the natural history study. [37] In the pre-submission meeting held in Dec 2019 the content of the application was discussed with the FDA.

Discussion

The Agency accepted the real-world evidence for approval of Nulibry for the treatment of a very rare autosomal recessive neurodegenerative disease.

In case of Nulibry, the review team concluded that the potential for selection bias was adequately overcome by the genotype matching used for the analysis and the similarity between the treated and untreated control groups in terms of the other characteristics that could have impacted survival (i.e., of age of onset of symptoms and geographic location) was also maintained. Furthermore, additional survival analysis using the entire untreated natural history group (without genotype matching) yielded a similar survival effect as the genotype-matched analysis (with the smaller control group). The consistency of the results from these two different analyses further supports the survival benefit." [37]

In this case, the SAP for the adequate and well-controlled clinical study was developed after the mortality outcomes were known. But the Agency reviewed and agreed with the SAP before the NDA submission since the effect of Nulibry on the mortality was not likely a chance observation. Here the Agency relied on the evident treatment effect which assured efficacy even when SAP was post-hoc. [37] The positive learning from Nulibry were the facts that the natural history data had well defined inclusion and exclusion criteria and

consisted of a genotype matched analysis set (GMAS). The use of a reliable and objective endpoint of mortality and the demonstration of a large treatment effect size outweighed the limitations in the context of a very rare disease which is rapidly fatal with no other therapy option. Additionally, the potential sources of bias were adequately addressed in the study designs and in the analyses of the efficacy data. [37]

7.25 ABCEMA (idecabtagene vicleucel) [65]

The primary evidence of safety and efficacy came from a single clinical trial, Study BB2121-MM001 (MM-001).

Communication with the FDA

30 May 2017: EOP2 meeting the Agency had recommended that applicant to perform randomized controlled trial comparing the bb2121 to another therapy. In march 2018 the sponsor notified the Agency about the plan to conduct phase 3 studies comparing triplet therapy (daratumumab, pomalidomide and dexamethasone) to support future label expansion.

Final approval was based on the results of phase 2 single arm clinical study MM-001 sponsor committed to provide final report with data from clinical trials MM-002 and MM-003. [65]

Study MM-001 was an adequate and well controlled study that met the study objective that ORR was statistically significantly greater than the pre-specified null hypothesis rate of 50%.

July 24, 2019: Type B meeting request: Written response only: Agency communicated concerns about the real-world evidence (RWE) study (NDS-MM-003) which was being conducted to provide an indirect comparison of effectiveness of bb2121. [65]

Discussion

There were several methodological limitations of this comparative analysis outlined below that impact the interpretability of the study results.

- There was a significant amount of missing data for baseline prognostic features such as ECOG performance status, revised ISS, cytogenetics and LDH in the eligible RRMM cohort which required imputation.
- The results of NDS-MM-003 are based on data that is collected and merged from multiple sources such as registries, clinical trial sites and external research databases.

Differences in follow up and response assessment of subjects from these different sources may impact the interpretability of the study results.

- Subjects in the eligible RRMM cohort were treated with 90 different treatment regimens with differing toxicities and efficacy. This creates significant heterogeneity in the RWE population limiting its utility as a control arm.
- The follow up schedule for response assessment in myeloma patients treated in the real-world setting and subjects treated in a clinical trial may be different. Subjects treated in MM-001 had a fixed schedule for response assessment. This can result in potential bias in the estimate of duration of response. The efficacy results from the RWE study population are uninterpretable as compared to efficacy evaluable population determined by the Agency (N=100) and based on FDA adjudicated efficacy results.

Given the methodological limitations discussed above, we conclude that the evidence generated from the RW analysis is not adequate to provide context or comparison for the outcome of MM-001 study. As per the reviewers' comments, a detailed review of these studies was not conducted. [65]

7.26 RYBREVANT (amivantamab-vmjw)

Rybrevant received accelerated approval based on the results of clinical trial (CHRYSALIS, NCT 02609776, n=81). [66]

Communication with the FDA

Based on the administrative correspondence, [66] the Applicant had communicated his intention to the FDA that an additional retrospective cohort study data from 181 patients with NSCLC harboring EGFR exon 20 mutation and 2833 patients with NSCLC with common EGFR mutations from Flatiron Health Advanced NSCLC database will be submitted in the BLA in Nov 2020.

The Agency had also asked the Applicant to submit the real world PFS and real-world OS for 111 patients who received platinum-based chemotherapy as their first line treatment. Also, the Agency recommended that the RWD should demonstrate that the patients in the target population do not benefit from the first-line immunotherapy.

Discussion:

The RWD in case of Rybrevant gave information on the treatment patterns and provided context for interpreting the efficacy data for Rybrevant in the intended target indication.

Real world data from a retrospective cohort study (Study NSC1002) was also submitted by the applicant.

The Applicant had communicated with the Agency their intent to submit an additional retrospective cohort study data from 181 patients from Flatiron Health Advanced NSCLC database as early as Nov 2020. On which the Agency had recommended that the RWD should demonstrate that the patients in the target population do not benefit from the first-line immunotherapy and to submit the real world PFS and real-world OS for 111 patients who received platinum-based chemotherapy as their first line treatment.

The real-world evidence provided by the sponsor to support the unmet medical need and the lack of effectiveness of the therapy options used in the real-world for this subset of patients was considered by the FDA. Also, the comparability of the demography of the patient populations included in the clinical studies was considered by the FDA with the exception of the lower percentage of African Americans in the clinical study, for which a post marketing commitment was issued to the Applicant. But the basis of approval for efficacy was based on large treatment effect and durable overall response rates according to RECIST v1.1. RWD was not used for comparison of results from the clinical study as mentioned in Section 9.1 Statistical issues of multi-discipline review.

7.27 LUMAKRAS™ (sotorasib) [38]

The basis of approval of Lumakras is efficacy demonstrated by the overall response rate in a single-arm, open label multicentre clinical study with n=124 patients (CodeBreaK 100; Study 20170543 [NCT03600883]) [38]

Communication with the FDA

From the administrative correspondence and regulatory history no specific information was found.

Discussions

From the real-world data it was shown that there were no approved therapies which target KRAS mutations in lung cancer. Lumakras received accelerated approval based on the results of single arm multi-centre phase 2 pivotal study. The real-world data from the retrospective studies was used by the applicant to show lack of therapy options and also provided supportive evidence for demography of patient's population included in the safety analysis with the exception that African Americans were underrepresented. This formed the basis of the post- marketing commitment requirement from the Agency to submit clinical

data on African American NSCLC patients harboring this specific mutation. From the entire strategy of submission, it is evident that the applicant did not intend to use real-world data as the basis for the approval but only to supplement the efficacy and safety data for the assessment from the FDA.

7.28 TRUSELTIQ (infigratinib) [39]

Study CBGJ398X2204 (NCT02150967), a multicenter open-label single-arm trial, evaluated the efficacy of TRUSELTIQ in 108 patients. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DoR), as determined by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. [39]

A preliminary assessment of the real-world data and the retrospective studies yielded results with a non-statistically significant trend towards longer survival in patients with cholangiocarcinoma and FGFR2 fusion or rearrangement compared with patients with wild-type tumors. [39]

Discussion

Infigratinib was submitted for marketing authorization approval for the indication Cholangiocarcinoma which is a rare cancer with no effective (median survival <1 y) therapy options. Efficacy and safety data was submitted from an open label single arm international clinical trial. To confirm the clinical benefit FDA requested post marketing clinical study.

FDA conducted a preliminary assessment of the real-world data which showed longer survival in patients from the real-world cohort (cholangiocarcinoma with FGFR-2 fusion or rearrangement) when compared to the wild-type tumor. Whether the FGFR-2 fusion or rearrangement are prognostically relevant was not clear. The FDA did not consider the real-world retrospective study data further. Also, no information on prior discussion between the FDA and the Applicant over the use of RWE for providing evidence for efficacy or safety could be seen. Thus, FDA acknowledged QED's interpretation of the literature and RWE data but noted that the prognostic value of FGFR rearrangements was somewhat controversial.

7.29 BREXAFEMME (ibrexafungerp) [40]

BREXAFEMME received regular approval based on the results of two identically designed double blind, multicenter, randomized, placebo-controlled Phase 3 Studies Study 303

(VANISH 303) & Study 306 (VANISH-306). Initially the Applicant planned to include at least 10 adolescent girls (<12 y) to be randomized in each trial in the Phase 3 studies. But only one adolescent girl was enrolled in VANISH-303 in the placebo arm. [40]

The natural history data from literature sources was used to show similarities in the disease characteristics for adolescent girls and adult women. The approved label contained no information about the use of natural history data. This supported the waiver of assessing the drug in pediatric patients (<12 y) based on its rare occurrence.

Communication with the FDA: [40]

On 25 February 2019, the Applicant submitted the Agreed Initial Pediatric Study Plan (Agreed iPSP) to enroll adolescents >12 y in the Phase 3 trials and a partial waiver for girls <12 y.

On 6 April 2020, the Applicant requested a deferral for completion of an adolescent PK study because only 1 adolescent was enrolled in the Phase 3 VVC trials.

On 19 June 2020, the Division informed the Applicant that a dedicated PK study for >12 y post-pubertal girls was not necessary and that extrapolation of efficacy from the adult population was acceptable.

On 26 June 2020, a pre-NDA meeting was held to discuss the content of an oral ibrexafungerp NDA for VVC treatment. The discussion included a confirmation regarding no requirement of PK study for NDA submission.

Discussion

BREXAFEMME is an example of using real world evidence for the extrapolation of real-world data from adults to adolescents without need of additional recruitment of adolescents in the clinical study. In this case, the natural history of vulvovaginal candidiasis (VVC) showed similarities in the disease characteristics for adult women and adolescent girls based on which it could be expected that the pharmacokinetic profiles for the drug would be similar in both the patient population. Thus, providing the scientific justification for extrapolation of the results of efficacy and safety from adult women to post-pubertal girls (>12 y). [40]

7.30 PROGRAF (tacrolimus) [45]

Communication with the FDA [45]

A Written Response Only (WRO) meeting request (August 2019): to discuss the addition of a new indication for the prophylaxis of rejection in lung transplantation based on RWE.

RWE subcommittee meeting (September 26, 2019): To discuss the submission and the suitability of RWE in support of an efficacy supplement for lung transplantation indication.

On October 3, 2019 (WRO Meeting Minutes): FDA´s response included comments on the selected data source, proposed statistical analysis plan (SAP) for primary and secondary efficacy outcomes, safety analysis, and the methodology and format of the output to support an sNDA.

A pre supplemental NDA meeting (August 21, 2020): To discuss the adequacy and content of the submission which utilized RWE.

Discussion:

Prograf® (tacrolimus) was approved in the US market since 1994. Its product category and widespread off-label use in lung transplantation made it an ideal candidate for extension of the indication using RWE. The submission of RWD to support the extension of indication in this case is consistent with the framework for FDA's RWE program since placebo-controlled trials would be highly unethical.

The Applicant made use of the available safety data from all approved indications and the post-market experience along with efficacy data from off-label use. This is one of the best examples of the application of available RWD as placebo-controlled trials would be unethical to support the efficacy of CNIs in lung transplantation. [45]

The review team, with the support of the RWE subcommittee, determined that Study F506-CL-3001, with comparison to historical controls, constitutes an adequate and well-controlled study and supports approval of an indication for tacrolimus in lung transplantation in combination with other immunosuppressants. It is worth mentioning that confirmatory evidence from randomized controlled clinical trials in the setting of other solid organ transplants, and the published reports indicating the independent contribution of tacrolimus in a multi-drug immunosuppressive regimen were also considered for the overall assessment of efficacy and safety. [45] The Applicant discussed the use of RWE with the FDA for the extension of indication in lung transplantation early on during the planning for submission and obtained FDA´s feedback on the selected data source, proposed statistical analysis plan (SAP) for primary and secondary efficacy outcomes, safety analysis, and the methodology and format of the output to support an sNDA. Further, a RWE subcommittee meeting (September 26, 2019) was held to discuss the submission and the suitability of RWE in support of an efficacy supplement for lung transplantation indication.

In the pre supplemental NDA meeting, the Applicant also discussed the adequacy of the plan and content of the submission which utilized RWE. FDA´s opinion on the proposed primary endpoint, pediatric data and labeling for the pediatric indication and statistical issues was obtained which seems to be an ideal step and safeguarded the submission.

For the non-interventional, observational study due to the lack of contemporaneous data collection, differences might exist between the treatment and the historical control groups. Nonetheless, the clinical benefit seen with the tacrolimus-containing immunosuppressive regimen was so large compared to historical controls that differences in baseline characteristics, surgical technique, or supportive care between groups were highly unlikely to explain the outcome differences, and therefore did not change the conclusion of effectiveness. The Applicant did a well-planned and well-executed study demonstrating clinically meaningful increases in one-year graft and patient survival that would otherwise not occur after lung transplantation and can be considered an adequate and well-controlled study when results for the treated patients are compared to historical controls. [45]

The strengths of the real-world data utilized for Tacrolimus was that the non-interventional study (Study F506-CL-3001) satisfied the regulatory requirements for an adequate and well-controlled study under 21 CFR 314.126. The data utilized for the study was from a reliable source (SRTR) and was found to be fit for purpose. Moreover, the study was designed and conducted according to a protocol with clear research objectives and a statistical analysis plan. [45]

7.31 Exkivity (mobocertinib) [46]

Communication with the FDA

Type B Meeting: Pre-NDA Meeting (held on November 10, 2020): Applicant discussed their plan to conduct an analysis of RWD as historical benchmark. They obtained Agency´s opinion on the preliminary data from the Study TAK-788-5002 and their approach. [46]

Discussion [46]

The applicant discussed their plan to conduct an analysis of RWD as historical benchmark in the Pre-NDA Meeting (held on November 10, 2020). The Applicant used the RWD analysis to prove the rarity of EGFR Exon 20 insertion mutations and the fact that there is no approved targeted therapy in this rare population and that there is no current standard of care for these patients. Based on findings from multiple RWD sources, the currently available therapies (EGFR TKIs, chemotherapy, and immunotherapy) have limited clinical

benefit to patients with EGFR Exon 20 insertion mutations in a second line setting or beyond, as well as concerns about adverse drug reactions and patient inconvenience. Therefore, these patients constitute a distinct, well-defined patient population with urgent unmet medical needs. To address these challenges and support single-arm clinical study data, the Applicant collected and conducted analysis of RWD on patients with NSCLC and EGFR Exon 20 insertion mutations as a historical benchmark (Study TAK-788-5002). Study name: TAK-788-5002 was a retrospective observational cohort study conducted in patients with advanced NSCLC with EGFR Exon 20 insertion mutations. This study used longitudinal data from the Flatiron Health Research Database, a nationwide electronic health record (EHR)-derived de-identified database.

The historical benchmark from the different literature-based reviews was similar to that of the historical benchmark from the Flatiron Health EMR database in Study TAK-788-5002 (as seen the Table 5).

Table 5: Compilation of the REAL-WORLD overall response, real world progression free survival and overall survival from different real world data sources [46]

RWD Source	**Real world cORR**	**Real world PFS**	**Median OS**
Real world Data from Flatiron Health Research Database* (For two cohort a) study-aligned patients (n = 63) and b) prior platinum study-aligned patients (n = 50)	11.1% and 14.0%	median 3.4 and 3.3 months, respectively. PFS were consistently poor	13.6 and 11.5 months, respectively
RWD from China	17.1%	median PFS in the second-line setting was 3.2 months	13.3 months
German Chart Review from Study 5008 (N = 57)	5%	-	-
Review of Second-line or Greater Immunotherapy**	3.5%	-	-

The applicant obtained Agency´s opinion on the preliminary data from the Study TAK-788-5002 and their approach in the pre-NDA meeting.

Mobocertinib demonstrated clinically meaningful improvement, when compared to currently available therapies, for metastatic NSCLC patients with EGFR exon20 insertion mutations who have been previously treated with platinum chemotherapy. In the FDA's Assessment, the Applicant's assessment of RWD was acknowledged but the FDA considered the RWD analyses to be exploratory and did not verify the submitted RWD analysis. Due to the limitations of external controls these data are considered supportive and were not independently verified by the FDA. [46]

7.32 TIVDAK (tisotumab vedotin-tftv) [67]:

Communication with the FDA

FDA Type C Meeting held on 15 Aug, 2019: FDA provided a written response on the systematic literature review and the proposed design of the real world evidence studies. The FDA also mentioned that while a systematic literature review can be useful to describe the treatment landscape and ORRs and DORs in the available therapy population, pooling of disparate ORRs is not appropriate. [67]

Discussion

The Applicant had obtained a written response on the literature review and proposed designs for real world evidence studies as early as Aug 2019. From the administrative correspondence it is also seen that the Applicant had obtained insights to the value of the systematic literature review and meta-analysis report where the FDA responded that "systematic literature review can be useful to describe the treatment landscape and ORRs and DORs in the available therapy population, pooling of disparate ORRs is not appropriate.)"

The final approval was based on overall response rate (ORR) as assessed by an independent review committee (IRC) according to RECIST v1.1, and DOR from the single arm clinical study (innovaTV 204 (NCT03438396). [67]

From the review it is evident that the FDA did not address the real-world evidence provided by the literature review for comparison of efficacy outcomes.

7.33 BESREMI (ropeginterferon alfa-2b-njft) [79]

Communication with the FDA

Though the content of the BLA were discussed with the Agency in the pre-BLA meeting. No information on the discussion with the Agency on the use of natural history control was found in the administrative correspondence and the Regulatory history**.**

Discussion

The natural history data provided information on the rare disease condition of polycythemia vera and helped in establishing clinical benefit with the use of the biological medicinal product.

The sponsor used the well-established natural history data to show the treatment effect and to prove that spontaneous remissions don't occur in this rare condition.

The evidence of effectiveness of the medicinal product was obtained from a single adequate, well-controlled trial (PEGNIVERA) with confirmatory evidence from another trial PROUD-PV. Based on the rarity and severity of the disease conditions and lack of approved therapies (most therapeutics are off-label use) the Agency warranted flexibility in the amount and type of evidence needed as per the 2019 Draft Guidance "Demonstrating Substantial evidence of effectiveness for huma drug and biologic products."

PEGNIVERA was considered an adequate well controlled trial when its treatment group was compared to a historical control (as per regulation 21 CFR 314.126). The historical control group was utilized under special circumstances (for a disease with high mortality and unmet medical need). [79]

7.34 VOXZOGO (vosoritide) [47]

Substantial evidence of effectiveness was established from study 111-301 (Phase-3, adequate and well-controlled) and confirmatory evidence came from Phase 2 study (111-202/205 & 111-302) with natural history study as external control.

Communication with the FDA

•Type C meeting, January 26, 2017: FDA suggested to develop and submit a new dedicated historical study protocol.

•On March 7, 2018, the Applicant submitted the updated clinical development program. It included the Applicant's plan for the new national history registries (Kaiser's Study, 111-

501 European cross-sectional and retrospective study, and prospective/retrospective study at Johns Hopkins University). [47]

•On 11 May 2018, a joint meeting of the Pediatric Advisory Committee (PAC) and the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) was held.

The AC members acknowledged that the use of placebo was not feasible, and the other option was to use historical control data as a comparator. However, the committee also concluded that the existing natural history data to date were not sufficient for use as a reliable comparator and gave recommendations. The AC recommendations and the overall development program based on AC recommendations were further discussed between the Applicant and FDA on July 30, 2018 (Advice/Information Request letter), and October 17, 2018 (Tele-conference).

Of note, FDA provided the same recommendations regarding the clinical development program, including endpoints, number of studies, and NH study design to the Applicant on multiple occasions (refer to FDA Advice Letters on July 25,2019, and on January 23, 2020).

The pre-NDA meeting was held on March 4, 2020, in which the FDA also indicated that the proposed use of retrospective natural history database for the comparison may be acceptable provided the data were properly collected, analyzed, and matched to study subjects' characteristics. [47]

On April 6, 2021, the Real-World Evidence (RWE) Subcommittee reviewed the AchNH data and concluded that the data "appears to be fit for use" and can be utilized as confirmatory evidence to establish efficacy in the clinical program.

Discussion: ***[47]***

In this case, the Applicant discussed their plan to use NH data on several occasions in Type C meetings almost 3 years before submission and obtained opinion from Pediatric Advisory Committee and FDA on the available natural history data in support of the application. Of note, FDA provided the same recommendations as Advisory committee on the NH study design to the Applicant on multiple occasions (refer to FDA Advice Letters on July 25,2019, and on January 23, 2020). In the pre-NDA meeting held on March 4, 2020 (5 months before submission), FDA had indicated that the proposed use of retrospective natural history database for the comparison may be acceptable provided the data were properly collected, analyzed, and matched to study subjects' characteristics.

The Applicant communicated timely with the FDA about their plan to use RWE in their submission, used fit for purpose real world evidence and performed the post-hoc analysis

requested by the FDA and to satisfy their doubts which lead to acceptance of the RWE as supportive evidence for efficacy.

7.35 Kimmtrak (tebentafusp) [70]

Discussion

The basis of approval was an open label randomized study which showed statistically significant improvement in the overall survival in patients with uveal melanoma compared to those who received investigators choice of therapy. The applicant did a comparison of the control arm with the historical data from literature and found it to be consistent with the data from the historical reported trials confirming that tebentafusp provided substantial improvement over the available therapies. Since data from the clinical study provided sufficient evidence of effectiveness and efficacy to support a regular approval the use of historical data from the literature had little utility and was not considered for further evaluation.

7.36 VIJOICE (Apelisib) [80]

Communication with the FDA [80]

25-Jul-2019: Pre IND meeting on use of retrospective chart review.

02 April 2020: Type B meeting: Confirmation on the strategy of submitting a type 10 NDA in 06-Oct 2020 Feedback on sample size and site selection to be appropriate.

09-Jul-2021 Pre-NDA Type B meeting: FDA confirmed that EPIK-P1 would be sufficient to support approval based on the efficacy population of n=37.

Discussion

FDA approval was based on real-world evidence from EPIK-P1, a retrospective chart review study.

The results showed patients treated with Vijoice experienced reduced target lesion volume and improvement in PROS-related symptoms and manifestations.

At week 24, the primary endpoint analysis revealed 27% of patients (10/37) had seen a verified response to treatment, which was indicated by a reduction of 20% or more in the total of the PROS target lesion volume.

Furthermore, at week 24, researchers noticed reductions in the patients' levels of pain (90%, 20/22), weariness (76%, 32/42), vascular malformation (79%, 30/38) limb asymmetry (69%, 20/39) and disseminated intravascular coagulation (55%, 16/39) as well as other

symptoms. Subgroups of research participants (n=57) who reported symptoms at baseline and at week 24 showed these improvements. [81] [48]

Apelisib was initially approved in US (since 24 May 2019) as PIQRAY for the treatment of breast cancer as a PI3K inhibitor (PI3K; phosphatidylinositol-3-kinase) on the basis of a phase 3 randomized double-blind placebo controlled clinical study.

Vijoice got its approval mainly based on the retrospective chart review study (EPIK-P1) which was a part of an expanded access program. Due to the rarity of the disease condition and lack of approved therapy options FDA considered the data from the retrospective chart review appropriate for evaluation of efficacy and based on the real-world evidence accelerated approval was granted. The Applicant engaged FDA as early as July 2019 during a pre-IND meeting to obtain their opinion on the development plan using EPIK-P1 for evidence of efficacy. The strategy of submission of the application as Type 10 NDA was also discussed with the FDA.

In Oct 2020 applicants received communication from the FDA regarding the sample size (n=37) and site selection. From the 11 sites where patients were receiving alpelisib 7 were selected for participation and the dose of the drug varied as per the physician's selection. The patient level data was abstracted from the medical record using an electronic data capture platform which is compliant with 21 CFR part 11to complete the electronic case forms. To minimize investigators, bias in the estimation of treatment effect a blinded independent central review (BICR) was implemented which was found to be satisfactory by the FDA reviewers. Appropriate measures were used by the applicant to address all possible statistical issues.

This approval was based on the primary evidence of efficacy and safety from real-world evidence along with the experience with the use of drug from previous approval (PIQRAY) for the treatment of breast cancer. It is one more example of the utility of RWE in case of rare diseases where traditional RCT may delay the entry of an approved therapy option for patients.

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EIDESSTATTLICHE ERKLÄRUNG

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

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Ort, Datum

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