White Paper

Best Practices for RWD/RWE Used in Regulatory Filings

Key takeaways for successful regulatory engagements

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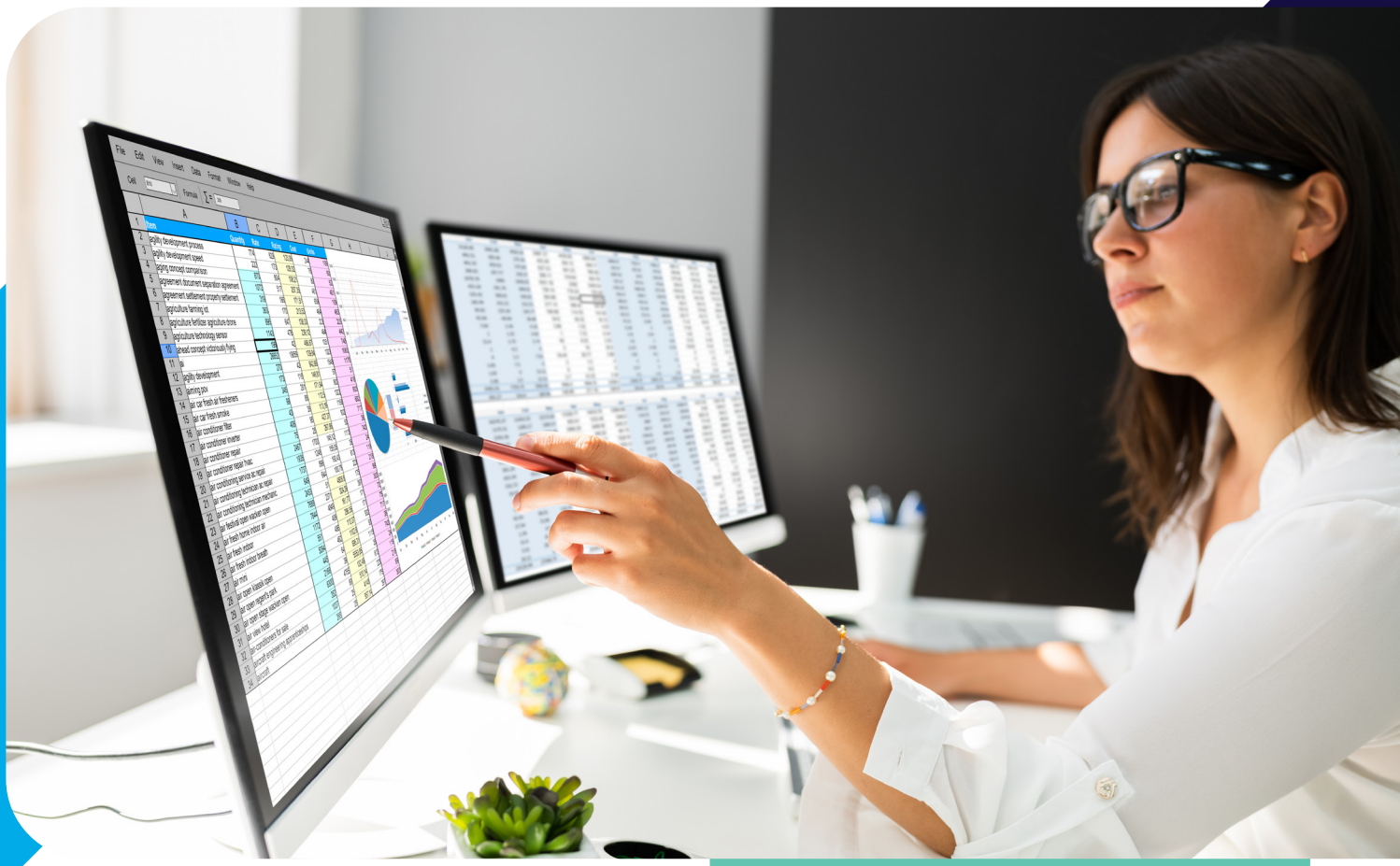

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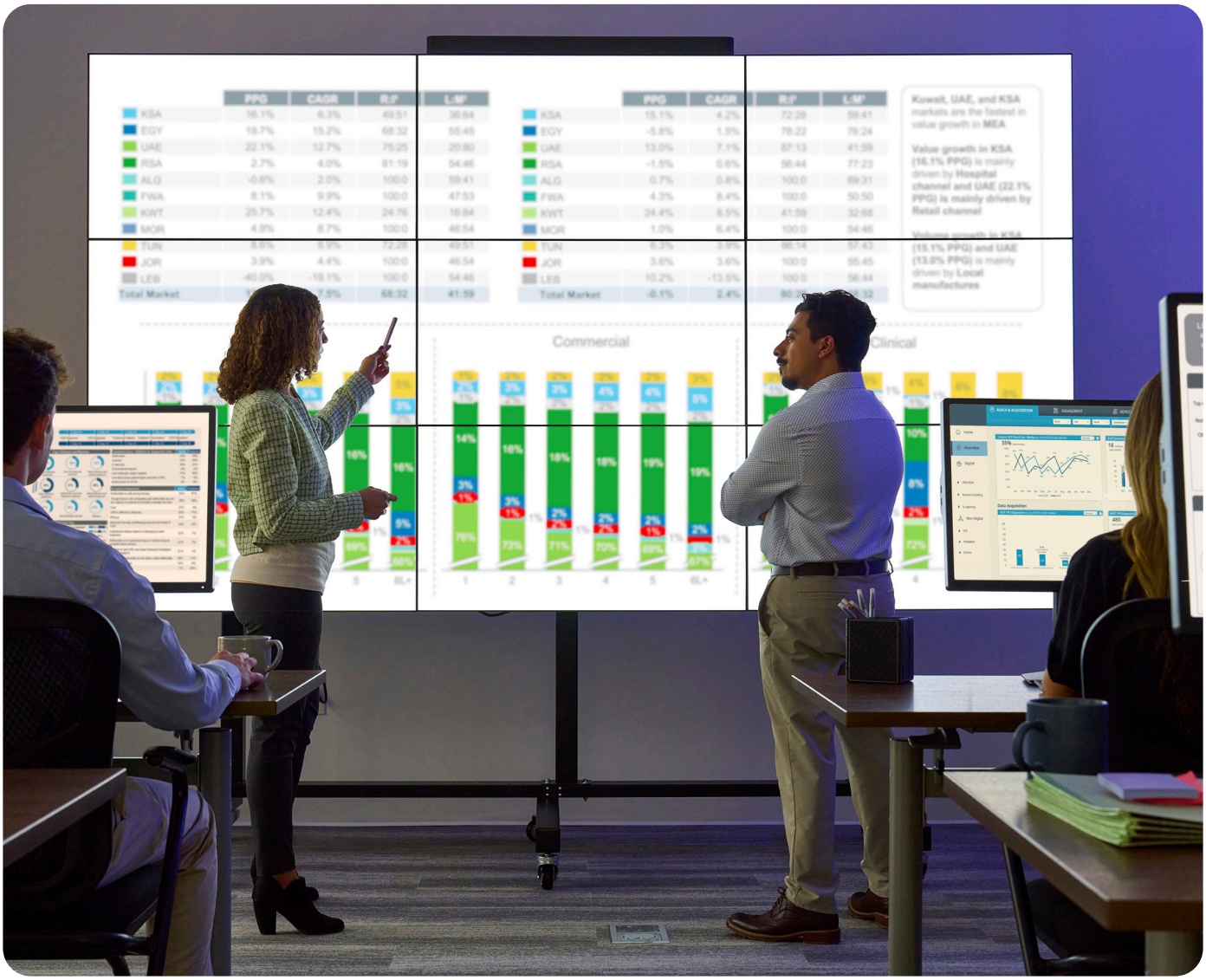
Executive summary

The contribution of real-world evidence (RWE) to regulatory submissions as supportive or substantial evidence has increased in the pre-marketing authorisation space over the last decade. An extensive series of guidance documents have been put forth by the United States (US) Food and Administration (FDA) on the use of real-world data (RWD) and RWE in regulatory submissions, with several guidance themes emerging. Sponsors are required to navigate this diverse body of information when planning and generating their evidence.

Significant insights and learnings have emerged from current guidelines and case studies that sponsors may consider to prepare for successful regulatory engagements. While each sponsor application is specific and necessitates its own tailored regulatory approach, applying these key learnings to evidence planning can help with managing expectations and enhancing regulatory interaction. In this white paper, we discuss key takeaways from a series of FDA guidance and review selected case studies of RWD/RWE to highlight best practices and learnings that sponsors can implement when planning and managing their regulatory submissions.



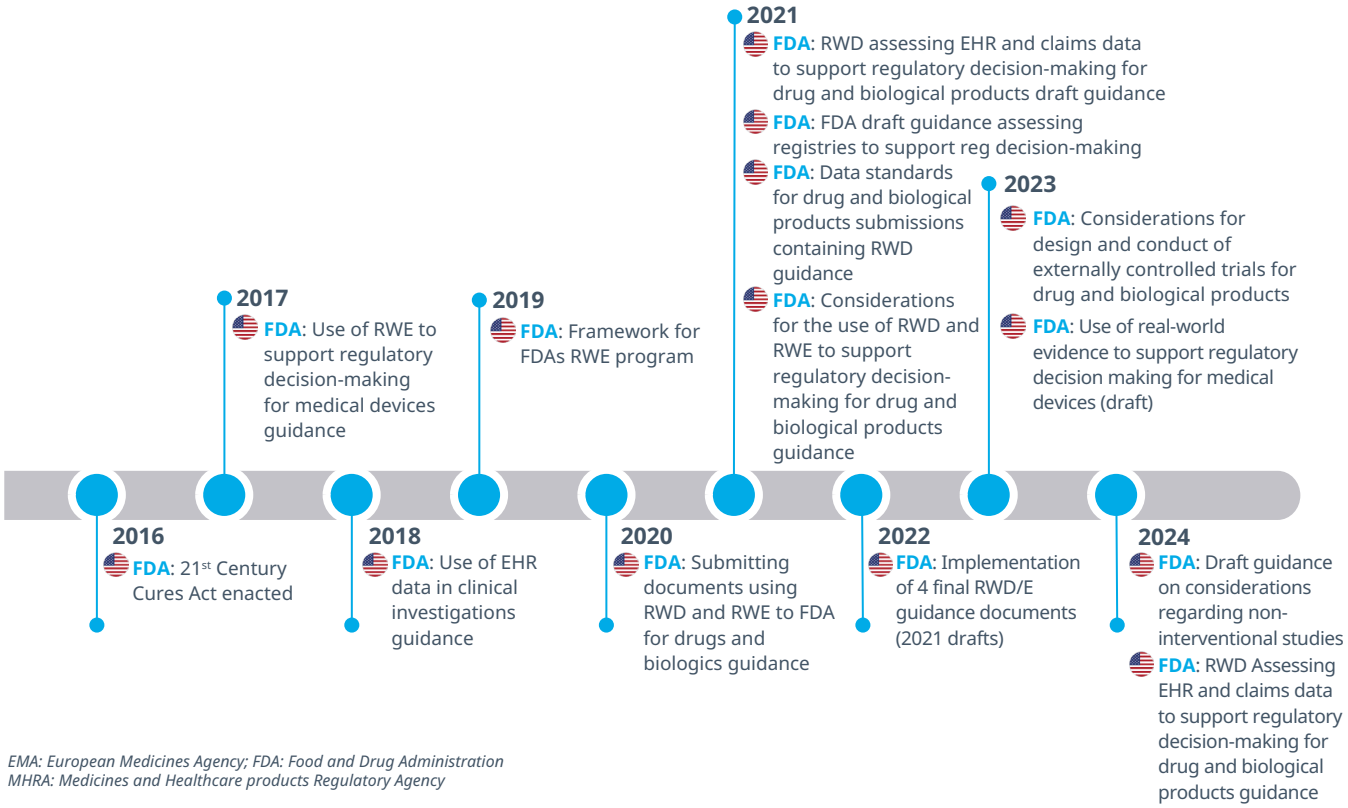
Section 1. Introduction: Present Day RWD/RWE Implications from the 21st Century Cures Act

Over the last decade, regulators have become receptive to the use of RWD and RWE in regulatory submissions, expanding beyond the more traditional application of RWD/RWE for safety reporting in the post-marketing authorization space. Examples include RWE used as supportive or substantial evidence[1] for new indications or label expansions in new or supplemental drug or biologic license applications (NDAs and BLAs, [s]NDAs and [s]BLAs respectively).[2]

The 21st Century Cures Act, enacted in 2016, served as a catalyst for a global surge in the development of frameworks and guidance documents related to RWD and RWE. The FDA has been particularly active in this area, issuing a comprehensive framework in 2018 that outlines the potential use of RWE for regulatory decision-making. In recent years, the FDA has issued several draft and final guidance documents on the use of data sources including electronic health records (EHRs), claims, and registries, data standards, and considerations for the use of RWD/RWE and non-interventional studies (NIS) for regulatory decision-making (Figure 1). Guidance governing the application of RWE has evolved rapidly, with intense regulatory activity creating opportunities for the inclusion of RWE in clinical development programs while also increasing the evidentiary requirements that sponsors are expected to meet.

In this white paper, we discuss key takeaways from the series of FDA guidance and review selected case studies of RWD/RWE in regulatory submissions to highlight best practices and learnings.

Figure 1. U.S. regulatory milestones for the use of RWD/RWE



EMA: European Medicines Agency; FDA: Food and Drug Administration
MHRA: Medicines and Healthcare products Regulatory Agency

[1]Definition of substantial and supportive evidence is based on 3 complimentary FDA guidance documents (Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products, 1998; Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products, 2019; Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence, 2023). Substantial evidence is defined as '[E]vidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labelling or proposed labelling thereof' (2023). Supportive evidence instead includes data that helps to bolster or add context to primary or confirmatory evidence, but on its own, it may not be sufficient to prove efficacy or safety (e.g., studies providing therapeutic context can help reviewers understand the landscape of the disease - such as disease prevalence and incidence- and any current standard of care). Cfr. The Role of Real-World Evidence in FDA-Approved New Drug and Biologics License Applications (2022)

[2]NDA = new drug application. BLA = biologics license application. sNDA = supplemental drug application. sBLA = supplemental biologics license application.

Section 2. RWE for regulatory decision making

Real world (RW) studies, which are mostly non-interventional in nature, encompass a wide range of designs. These include studies that describe the natural history and burden of disease, comparative studies that assess the safety or effectiveness of a treatment versus a comparator, and external control arms (ECAs) that use real world data to create a control group of real world patients for externally controlled trials (ECTs). Other study designs may also be employed, depending on characteristics of the disease, clinical treatment of interest, and research question.

The RWE generated by these studies may contribute to regulatory submissions as supportive evidence, such as background disease rates, or substantial evidence such as treatment effect of the standard of care (SOC) within a specific patient population. Per FDA guidance, RW studies that provide safety and effectiveness data (i.e., substantial evidence) for a marketing authorization application (MAA) must meet the legal requirements for the application. This may result in high evidentiary standards for certain types of RWE in regulatory submissions.

External control arms for externally controlled trials: the highest bar

In the realm of clinical evidence, externally controlled trials (ECTs)[3] designate a specific study design where the outcomes of a subset of study participants are compared to historical or concurrent data derived from an external arm (i.e. an external control arm or ECA), rather than to a contemporaneous control group within the trial itself. ECAs have the potential to play a pivotal role in regulatory submissions in specific cases by offering an external control for single-arm clinical trials, allowing for contextualization of investigational drug efficacy or safety compared to the SOC where there would otherwise be none. When data from the real world are used to derive externally controlled arms, the FDA requires that the RWD and RWE contributing to ECTs in regulatory submissions is held to and conducted with the same evidentiary standard as randomized trials.

Externally controlled designs should be strategically employed in specific contexts, such as trials of diseases with high and predictable mortality or progressive morbidity (e.g., certain malignancies or rare diseases) or when conducting a randomized controlled trial (RCT) may be ethically challenging (for example, due to the absence of a SOC coupled with the urgency of treatment needed in the patient population). Additionally, external comparator designs may be suitable when the drug has a large treatment effect. In such situations, external controls may provide a feasible solution for sponsors.

In externally controlled trials, the strength of evidence supporting effectiveness can be notably robust, particularly when:

1. The natural history of the disease is well-defined
2. The external control population closely mirrors the treatment group
3. Concomitant treatments affecting the primary endpoint exhibit minimal differences between the external control and trial populations
4. The results compellingly demonstrate a departure from the established disease progression

[3]The terms Externally Controlled Trials and External Control Arm reflect the terminology and regulatory scrutiny the FDA proposed in the dedicated draft guidance (2023). The FDA considers external control arms a prespecified use of RWE in the context of a pivotal trial, when all planning is done upfront, with the protocol finalized before initiating the externally controlled trial. We are not considering here other use cases of RWE to build a comparator cohort external to a trial that may be referred to as external comparator cohort (ECC) or external comparator (EC) study (for the terminology crf. Rippin, 2024)

Key considerations when employing ECTs

While there are clear opportunities for ECTs in regulatory submissions, the FDA has highlighted several key points in their guidance documents to consider.

One major theme stems from a lack of internal control in the single-arm trial, in which there is an absence of a randomized control group which consists of patients from the same population as the trial group but are assigned to a different treatment. In this case, ECTs using ECAs face numerous threats to internal validity, including lack of randomization, selection bias, and confounding bias, all of which can influence the study's results and interpretability.

Sponsors should consider these biases and be thoughtful in addressing them during the design and implementation of ECTs.

Lack of randomization is a major and well recognized limitation of ECTs that introduces bias and confounding in trial design. In well-designed RCTs, both trial arms are randomly assigned to treatment groups, ensuring that any observed differences in outcomes are likely due to the intervention itself and not to confounders such as differences in patient characteristics between the arms. While adjustment and weighting methodology may be used to statistically adjust for measured confounders in ECTs, unmeasured confounders will not be accounted for, thereby introducing bias for which the directionality will be difficult to ascertain. This is a limitation recognized by both regulators such as the FDA and European Medicines Agency (EMA), and health technology assessment (HTA) bodies.[3,4] Consequently, the inability to randomize generally restricts use of the external control design to situations in which the treatment effect is dramatic and the usual course of the disease highly predictable.

Another recognized challenge of ECTs is the limited ability to implement the same stringent study criteria across trial participants and ECA patients. For example, the difficulty in implementing an inclusion criterion in the external control arm because of limitations in data availability, particularly for data collected retrospectively such as during routine practice, may result in measurement error and confounding. This can ultimately weaken the ability to definitively establish causal relationships between the treatment and the observed outcome.

It is well documented that patients in a RW untreated control arm often have worse outcomes compared to participants in a randomized control group. Failure to address these discrepancies between the single-arm trial and the external control group may artificially inflate the perceived efficacy of a drug, even in cases where there is none. Such differences, if unaccounted for between the single arm trial and control group, may artificially result in a favourable drug response.[14] The greater the disparity between the groups, the weaker the study's internal validity becomes, therefore, it is critical for sponsors to ensure similarity between the trial arm and the ECA when conducting ECTs. Examples include inclusion/exclusion criteria, baseline characteristics such as demographic and clinical characteristics, treatment history, disease burden, and prognosis of patients between the two arms.

In the case where not all confounders or prognostic variables, known or unknown, are able to be captured in the external control arm, bias may be introduced between the arms. When using data collected from routine clinical care, attention should be directed towards biases that may arise from data collection, where issues such as missing data and misclassification are prevalent. These biases can significantly limit the utility of the data for an ECT, highlighting the importance of thorough examination of fit-for-purpose data at the design phase.

In light of these considerations, external controls should be used when the endpoints are objective and the impact of baseline and treatment variables on the endpoint are well characterized. Bias may be introduced when using surrogate endpoints that are not objective or well-defined. Such bias can introduce uncertainty into the risk/benefit assessment because clinical benefit is not measured directly and the quantitative relationship between the surrogate effect to the clinical effect may be unknown. For example, FDA guidance recommends using objective response

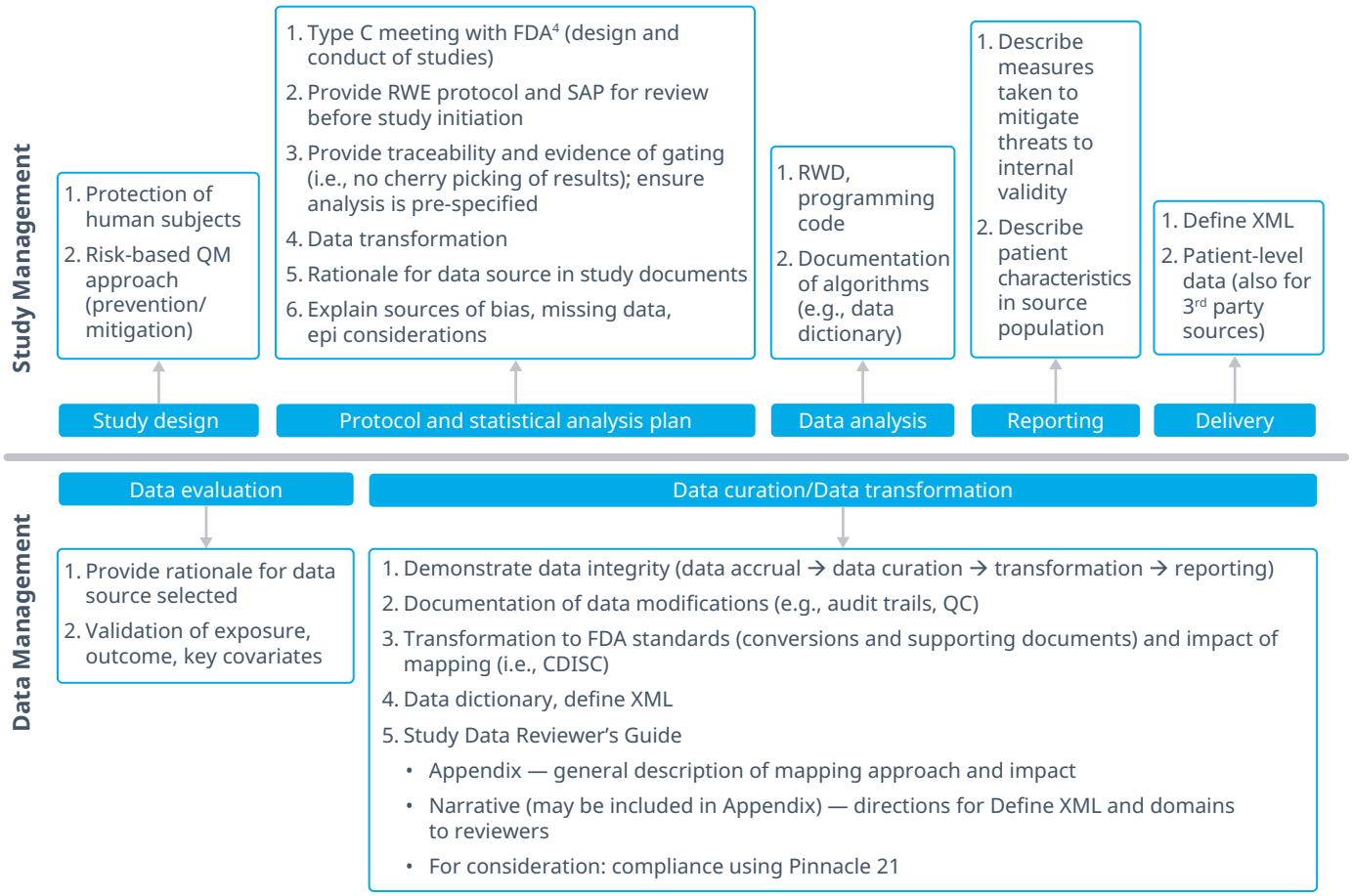
rate as an endpoint in single-arm oncology trials instead of time-to-event endpoints such as overall survival or progression-free survival. Utilizing time-to-event endpoints in an ECT is generally considered inappropriate by FDA, as highlighted in the agency's feedback on Y-mAbs's oncology drug Omblastys, where overall survival was used as the endpoint as the single-arm trial and ECA endpoint (see Section 4 below). If surrogate endpoints must be used, validation studies demonstrating the appropriateness of the endpoint should be conducted prior to initiation of the ECT. Finally, the analysis of endpoints across the external control arm and the trial should be blinded by investigators to reduce investigator bias.

Beyond the biases discussed above, other types of biases can reduce internal validity of studies. These include patient bias, analyst bias, and residual confounding. Collectively, consideration to each of these should be given and mitigated when implementing ECTs as substantial evidence to support marketing authorization.

Section 3. Best practices to meet FDA evidentiary requirements when using RWD/RWE as part of regulatory submissions

Key points highlighted in the FDA guidance documents span the entire study execution and range from study design to protocol and statistical analysis plan (SAP) development, data curation and transformation, and finally to delivery. When planning the use of RWE as part of regulatory submissions, sponsors should factor in all relevant aspects of these actionable recommendations with emphasis on study management and data management (Figure 2).

Figure 2. Regulatory considerations for RW study design elements



[4]Note that meetings with the FDA do not need to be limited to Type C meetings and communication with the agency should be as needed
QM = quality management. QC = quality control. CDISC = clinical data interchange standards consortium. XML = extensible markup language.

Sponsors should acknowledge that these recommendations may result in additional steps compared to RWE generated for non-regulatory purposes likely impacting overall study requirements and execution, and as a consequence potentially extending timelines for evidence generation. For example, a validation step may be required for key variables not previously validated. Similarly, data transformation of RWD into complaint data formats such as Clinical Data Interchange Standards Consortium (CDISC) may add time (and cost) to a study. Sponsors should consider these prior to study planning and incorporate additional steps into the timelines to ensure there are sufficient resources and time allocated to each phase of the study.

While the FDA's thinking is covered in a vast and evolving body of guidance, recurring themes have emerged, with FDA particularly emphasizing early engagement, data quality and fitness, and design robustness.

Table 1. Recurring themes in key FDA guidelines and frameworks

	EARLY ENGAGEMENT	DATA QUALITY	DATA FITNESS	DESIGN ROBUSTNESS
GUIDELINES/FRAMEWORKS				
Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products (Final) — 2023[5]	✓		✓	
Data Standards for Drug and Biological Product Submissions Containing Real-World Data (Final) — 2023[6]				✓
Framework for FDA's Real-World Evidence Program — 2018[7]		✓	✓	
Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products (Final) — 2023[8]		✓	✓	✓
Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products (Draft) — 2024[9]	✓	✓	✓	✓
Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products — 2022[10]				
Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices (Draft) — 2023[11]		✓	✓	
Considerations for the design and conduct of externally controlled trials for drug and biological products (Draft) — 2023[12]	✓	✓	✓	✓
Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision Making for Drug and Biological Products (Final) — 2024[13]		✓		✓

A. Early engagements with the FDA

The FDA recommends that sponsors coordinate on the use of RWE for regulatory submissions with the FDA prior to study execution. The sponsor should consult and ensure alignment with the FDA on study design and data management, including rationale for the data source(s) intended to be used, the method of data collection (e.g., retrospective or prospective data collection), and study design methodology.

Engagement with the FDA is an iterative, ongoing process for which the sponsor should prepare. General preparedness should include elements such as when to request the meeting, the type of meeting requested, and having appropriate documents such as observational study protocols (trial protocols in the case of an ECT), statistical analysis plans, or questions for the FDA prepared in advance. Sponsors should consider the following:

- Engagement with the FDA as an iterative process, and not simply a one-time meeting with the agency
- The initial engagement should consist of discussions with the agency on the rationale and intended use for the RWE in regulatory submissions

- Continued engagement with the FDA should generally include the following concepts:
  - » The sponsor should conduct feasibility assessment on all data sources that are considered to answer the research question and provide feasibility results for the data sources evaluated. If data sources were considered but not evaluated for feasibility, justification should be provided. Finally, the rationale for the final data source(s) selection should be provided to the FDA
  - » Additional details on the use of the intended RWE should be shared with the FDA including the study design concept (SDC), protocol, and statistical analysis plan
  - » The study design concept may be iterated based on feasibility results
  - » There may be multiple FDA interactions on the SDC and protocol based on feasibility results. Alignment on methodology stated in the SDC and protocol with the FDA should be ascertained prior to the initiation of data collection
  - » A prespecified protocol should be shared with the FDA to demonstrate transparency and ensure no preferential selection of results from the sponsor
- Importantly, sponsors should engage with the FDA regarding their intended use of the RWE before initiating the analysis

B. Study design recommendations

DATA SELECTION CONSIDERATIONS

The FDA has several recommendations related to data selection, including development of the research question prior to data selection, conducting thorough feasibility analysis, and providing clear justification of the data source(s) selected. Many of these considerations, as discussed in the preceding section on Early Engagement, should be discussed with the FDA early on. It is also recommended that sponsors align on expectations regarding patient-level data access for the FDA at an early stage. Engaging in these discussions during the design phase will ensure that the data selection and study design meet the FDA's expectations, thereby preventing the RWE from being excluded from regulatory review upon submission.

STUDY DESIGN CONSIDERATIONS FOR RWE AS SUBSTANTIAL EVIDENCE

When using RWE as substantial evidence in regulatory filings, sponsors should consider the following additional elements:

- **Provide rationale for selection of appropriate exposure and outcome variables.** Considerations include whether these have been routinely used or are novel variables
- **Consider validation of surrogate variables (e.g., for exposure or outcome(s)), as appropriate**. Validation should be conducted prior to initiation of the RW study for which the validated endpoints intend to be used. The potential to impact timelines should also be considered
- **Provide rationale for selection of confounders and prognostic variables.** This should be done thoughtfully, and sponsors should be able to demonstrate diligence in selecting confounders. Sponsors should consider selecting confounder and prognostic variables prior to data source selection as not all variables identified will be available in a data source that has already been selected — confounder/prognostic variable selection ties into data source selection since key variables must be able to be measured and characterized from the selected data source
- **Demonstrate thoughtfulness on analytical approach and study population for main analysis, such as:**
  - » Ensuring comparability of comparator groups prior to modeling phase; for example through the study eligibility criteria
  - » Engaging with FDA on the main analysis and considering how sponsors want to demonstrate (i) how the selected analytical approaches reduce uncertainty and (ii) robustness of the analytical approach using additional methodology such as quantitative bias assessment (QBA) or negative exposure or outcome controls

» In oncology studies, for example, this may translate into:

- Preference to use objective response rate (ORR) in ECTs instead of time-to-event endpoints such as overall survival or progression-free survival, as the latter are not interpretable in single arm studies. This is discussed in detail in the Omblastys case study (Section 4).
- Conducting independent central assessment of response in the real-world study instead of relying solely on response assessment from routine care to measure response and mitigate investigator bias, as demonstrated in the Vijoice case study (Section 4).

C. Data management guidance

Marketing authorization applications (MAA) containing data from non-interventional studies intended to support regulatory decision-making should ensure that the electronic systems used to manage the data and produce the required records comply with 21 CFR part 11. Specifically, sponsors should ensure the following with regards to the design, conduct and oversight of the study:

- Compliance with final study documents (protocol, SAP)
- Appropriate study monitoring where applicable (i.e., additional data collection)
- Traceability of study records and ability of the FDA to access and verify study records (i.e., source data, study analysis)
- Maintenance and safe-keeping of study records to ensure inspection-readiness
- Demonstrated qualifications and experience of researchers by retaining a log of researchers involved in study design/conduct
- Data transformation according to FDA CDISC data standards

Special considerations for ECT

EARLY ENGAGEMENT

- As stated above, sponsors are encouraged to initiate early engagement and alignment with the FDA. For ECTs, sponsors should engage with the FDA before initiation of the ECT, and specifically, prior to initiation of the (single arm) trial. The FDA considers the single arm clinical trial and ECA to be complimentary and part of the same study, hence why alignment with the FDA should be done prior to the single arm trial initiation — not after the trial has completed. The sponsor should also align on the use of RW ECA for regulatory submissions with the FDA prior to clinical trial execution
- Sponsors must be prepared to provide the FDA with rationale for selecting an ECT design instead of a randomized control arm. Key points to consider may be a lack of SOC or an unmet medical need in the patient population
- Sponsors should ensure that they set up a Type B, C, or D meeting or repurpose already existing meetings with the FDA to discuss the intended use of the RWE

STUDY DESIGN

- Before initiating the ECT, sponsors should submit the complete study protocol (including detailing the single-arm trial and external control arm) and SAP to the FDA for review. This promotes transparency from the outset
- Any amendments to the ECT protocol or SAP should also be shared with the FDA to ensure transparency
- The ECT protocol should be posted on ENCePP and Clinicaltrials.gov
- Sponsors should also align on the data selection and submission requirement — for example, submitting patient-level data in the appropriate data format — for ECTs. The case study for Omblastys (Section 4) illustrates an example where the sponsor submitted the ECA data in a compliant format, allowing the FDA to conduct analysis of the data

TIMING CONSIDERATIONS FOR ECTS

- Sponsors should consider and plan for early engagement with the FDA
- Timelines for the ECA should be integrated with clinical development timelines given that the design considerations and data source selection for the external control arm should ideally be finalized prior to the single-arm trial initiation
- Timelines for ECA study conduct should consider the impact of regulatory key requirements for the ECA, such as analysis including sensitivity analysis, data conversion into compliant data format standards, and data delivery in XML format to the FDA
- Timeline considerations for the regulatory dossier and package submission should be conducted jointly between the sponsor's R&D and RWE groups to ensure that the RWE can be integrated into the filing package in a timely manner and as needed based on the development program, while conforming to key FDA recommendations

Section 4. Case studies

Several marketing authorization applications (e.g., NDAs and BLAs) have been submitted to the FDA containing real-world evidence as either supportive or substantial evidence.[3] Here, we highlight four case studies (Lumakras, Vijoice, Prograf and Omblastys). Some are considered exemplary in the implementation of best practices described above to highlight specific characteristics of RWE in regulatory decision-making and demonstrate the overall acceptability of real-world evidence by the FDA, while others faced challenges. The case studies were selected to illustrate RWE as both supportive and substantial evidence in the MAAs across a spectrum of traditional and innovative study designs (Figure 3). While some of these cases predate official guidance issued by the FDA, they nevertheless provide valuable insights into the FDA's approach in evaluating such evidence.

Figure 3. Summary of case studies

	Lumakras *(sotorasib)*	**Vijoice** *(alpelisib)*	**Prograf** *(tacrolimus)*	**Omblastys** *(omburtamab)*
Sponsor	**Amgen**	**Novartis**	**Astellas**	**Y-mAbs Therapeutics**
Approved indication	KRAS G12C+ advanced NSCLC	PI3KCA-related overgrowth spectrum	Prevention of rejection in lung transplantation	Neuroblastoma with CNS/Leptomeningeal metastasis
Filing purpose	First indication	Expanded indication	Expanded indication	First indication
Application type	NDA	NDA	sNDA	BLA
Approval date	May 28, 2021	April 05, 2022	July 16, 2021	Not approved *(submitted March 2022)*
RWE use	Supportive evidence	Primary evidence	Primary evidence	Primary evidence
Study design	Retrospective cohort studies; systematic literature review	Retrospective single-arm study	Retrospective treatment arm with historical comparator; literature review	Pivotal phase I with ECA; systematic literature review
RWD Type	EMR[1], literature review	EMR[2]	Registry[3], literature review	Registry[4], literature review
Adult or pediatric	Adult	Both	Both	Pediatric
Rare disease?	N	Y	Y	Y
Orphan disease designation granted?	Y	Y	Y	Y
FDA Feedback on RWE	**Positive**	**Positive**	**Positive**	**Negative**

[1]Flatiron Health EMR dataset and American Association of Cancer Research (AACR)
[2]Compassionate use program chart review
[3]STRT Registry
[4]Central German Childhood Cancer Registry (CGCCR)

Lumakras (sotorasib)

Amgen submitted a marketing authorization application (MAA) for Lumakras (sotorasib) for the treatment of patients with locally advanced/metastatic non-small cell lung cancer (NSCLC) that harbor the KRAS G12C mutation. As part of Amgen's early engagement with the FDA, they requested that Amgen conduct a natural history study to characterize the disease and outcomes among KRAS G12C mutated-patients, because the natural history and outcomes for NSCLC patients with this mutation were not well characterized at the time of drug development (see Figure 4).

Amgen conducted three retrospective cohort studies to characterize patient demographics, clinical characteristics, co-mutations, treatment patterns and outcomes among advanced/metastatic NSCLC patients with KRAS G12C. Two data sources were used:

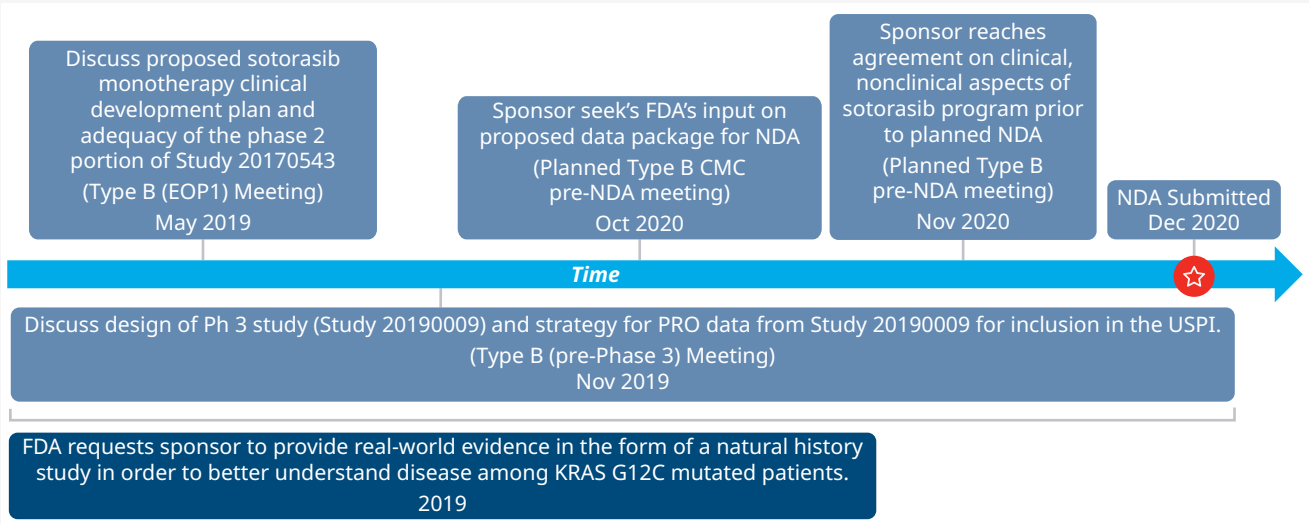
1. The Flatiron Health — Foundation Medicine Clinicogenomic Database (FH-FMI CGDB), an EHR database linked to genomic data among patients that had full-panel sequencing from the Foundation One panel to characterize 1) advanced NSCLC patients and 2) the subset of these patients with the KRAS G12C mutation; and
2. American Association of Cancer Research (AACR) Project GENIE database to characterize 3) metastatic NSCLC patients with the KRAS G12C mutation

The studies demonstrated similar clinical characteristics and outcomes (real world overall survival and real world progression-free survival) among patients with the mutation to that of the overall aNSCLC population. The FDA agreed with Amgen's description of the natural history and outcomes in the MAA. Furthermore, the FDA found Amgen's description of the natural history and outcomes in the MAA to be aligned with their understanding, and provided a positive recommendation for accelerated approval based on the totality of the body of evidence.

Overall, the RWE studies conducted by Amgen were compliant with the recommendations laid out by the FDA for such studies, indicating several key learnings when using RWE:

- Multiple data sources and cohorts were used to characterize the patient population
- Data were fit-for-purpose and described patient characteristics and demonstrated unmet need
- Key methodological and statistical considerations, such as addressing immortal time bias in this biomarker-tested population, were addressed in the analysis phase of the studies
- The three individual study reports with demonstrated consistency of results across the data sources

Figure 4. Lumakras FDA Engagement summary



Note: figure is not to scale.
RWE = real-world evidence. SAP = statistical analysis plan. sNDA = supplemental new drug application. NDA = new drug application. EOP1 = end of phase 1. PRO = patient-reported outcome. CMC = chemistry, manufacturers and controls.

Vijoice (alpelisib)

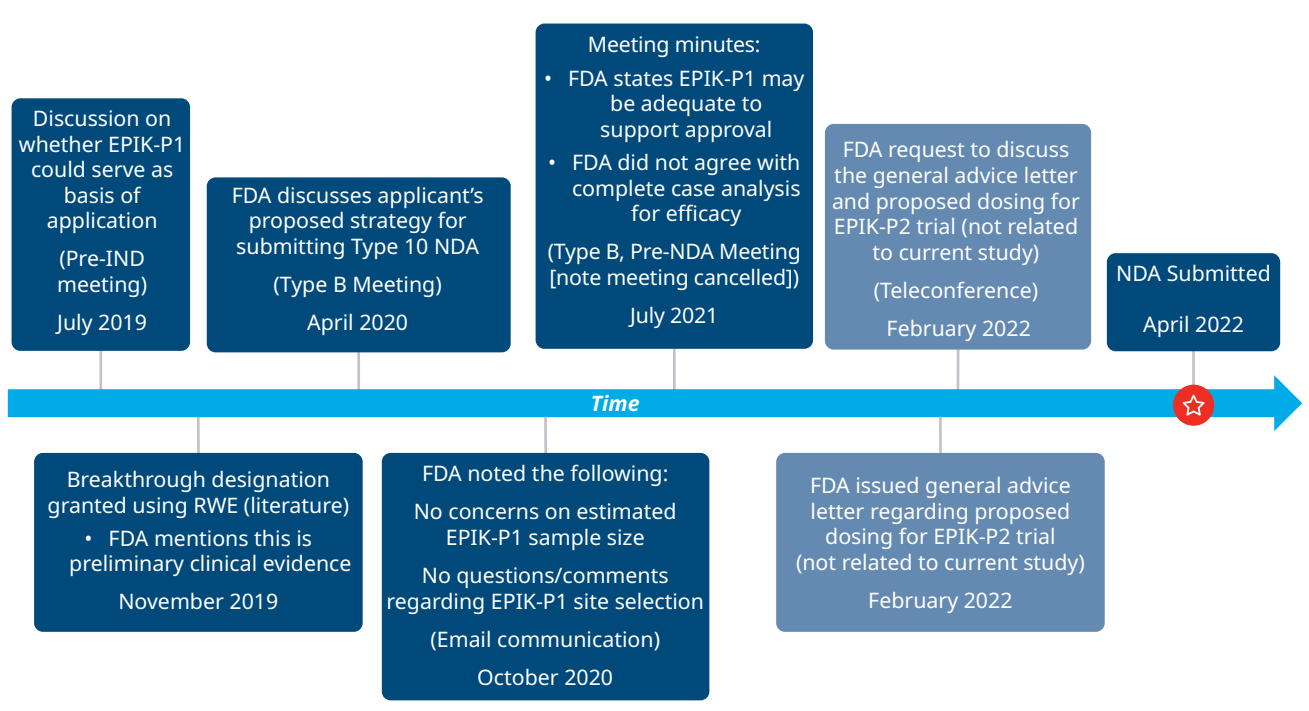
Novartis applied for an expanded indication for alpelisib under the brand name Vijoice for the rare disease PIK3CA-related overgrowth spectrum (PROS). Alpelisib was previously approved for HR+/HER2- PIK3CA-mutated advanced/metastatic breast cancer under the brand name Piqray. RWE was used as substantial evidence in the NDA.

Due to the rarity of PROS (~4,700 PROS patients estimated in the US), coupled with an absence of FDA-approved treatment in this patient population, Novartis employed a novel study design: a retrospective single-arm cohort of alpelisib-treated PROS patients in a compassionate use program (EPIK-P1). Data were collected using chart review from 7 sites across 5 participating countries. The study outcome was response (yes/no) defined by tumor reduction of ≥20% from baseline and assessed at Week 24 per independent central radiology review. A safety assessment was also conducted in the study.

Novartis frequently engaged with the FDA throughout the product development to ensure alignment on the use of RWE in this patient population with high unmet need. For example, in a pre-IND (investigational new drug) meeting, Novartis discussed whether this study could serve as basis of application with the FDA. Subsequent multiple engagements with the FDA included topics such as whether these data would be adequate to support approval, site selection, and appropriateness of statistical analysis (see Figure 5).

The study demonstrated compliance with FDA Good Clinical Practices (GCP). For example, data management processes were prespecified in the data management plan, the electronic data capture platform for data capture of the eCRF was compliant with 21 CFR Part 11, the RWD was converted to CDISC data standards, and the submission contained all required portions of the electronic Common Technical Document (eCTD). Onsite inspections were conducted for 2 of the sites. Importantly, the FDA determined the data provided in the submission to be complete and reliable.

Figure 5. Vijoice FDA Engagement summary



Note: figure is not to scale.
RWE = real-world evidence. SAP = statistical analysis plan. NDA = new drug application.

The results presented were well received by the FDA, although they disagreed with the sponsor's approach in analyzing missing response data. Of note, the FDA re-analyzed the efficacy data — made possible because the sponsor submitted patient-level data in a compliant format with its submission — conducted additional subgroup analyses, and reviewed patient narratives. The re-analyzed results were found to be consistent with those conducted by the sponsor. The FDA also determined that the sponsor demonstrated mitigation of investigator bias and measurement bias. Ultimately, the totality of evidence submitted in the NDA was determined to meet the statutory evidentiary standards for accelerated approval.

Overall, the Vijoice RW study conduct and FDA review highlight a number of key learnings which may be used in future RWE applications, particularly for substantial evidence:

- The sponsor sought early engagement with the FDA to ensure alignment on data selection, study design and concept, endpoints, and viability of study to address the research questions
- The study protocol and statistical analysis plan were predefined: the protocol was finalized prior to patient recruitment and the analysis plan was finalized prior to data abstraction
- Consideration was given to appropriate and objective endpoints; in this case, lesion reduction. For example, selection of endpoints such as overall survival or progression-free survival would be inappropriate given the difficulty in contextualizing these endpoints in a single-arm study
- Independent response assessment of radiographic scans was conducted to mitigate investigator bias
- The sponsor ensured compliance with GCP and demonstrated inspection-readiness for audits. This includes ensuring that all study documents were in place and considerations for the delivery of source data (in this case study, imaging reports) and patient-level data. This applied to sponsors, data providers, and contract research organizations
- The sponsor submitted analysis datasets in compliant data standards that allowed the FDA to replicate analyses. Sponsors should enable and expect the FDA to conduct additional analysis with data (e.g., redefining the efficacy population)

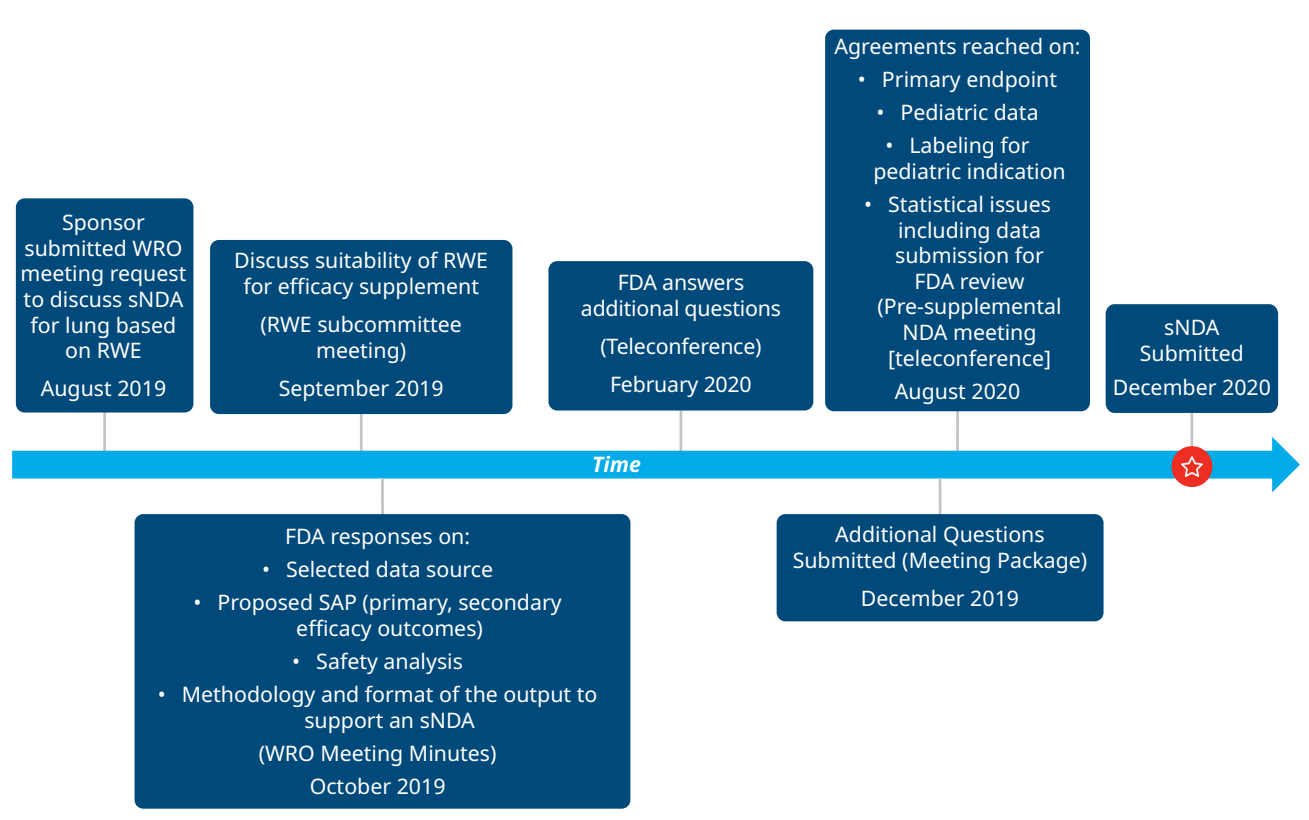
Prograf (tacrolimus)

Prograf (tacrolimus) is an immunosuppressive agent originally approved in 1994 for use in transplant recipients for the prevention of kidney, liver and heart organ rejection. More recently, Astellas submitted an application to the FDA for indication expansion to patients with treatment-resistant end stage lung disease for whom lung transplant is the only option (see Figure 6).

At the time of the study, no approved immunosuppressants were available for lung transplant recipients. Calcineurin inhibitors (CNIs) are necessary for transplant patients for the prevention of graft rejection, with tacrolimus as the CNI of choice and the standard of care in organ transplants. As a result, off-label tacrolimus had become the standard of care for lung transplant recipients. The sponsor was therefore able to show that conducting an RCT of tacrolimus for lung transplant recipients was not ethical in the current treatment era. Astellas also demonstrated that because alloimmune response to transplanted organs is mechanistically similar regardless of the organ, lung transplant patients would react in a similarly positive way to tacrolimus as patients undergoing other organ transplants (and approved indications).

Both of these elements lay the groundwork for conducting a non-interventional study in which RWD was used for both arms: the treatment arm was comprised of tacrolimus used in routine clinical care among patients in the Scientific Registry for Transplant Recipients (SRTR), and the control arm was comprised of historical controls identified from literature review. Data collection for the registry was well documented and previously

Figure 6. Prograf FDA Engagement summary



Note: figure is not to scale.
WRO = written response only. RWE = real-world evidence. SAP = statistical analysis plan. sNDA = supplemental new drug application. NDA = new drug application.

published. Outcomes collected included graft failure, re-transplant, and all-cause death for all lung transplant recipients. Astellas engaged with the FDA early to determine the suitability of RWE as the primary basis for the expanded indication. Of note, the RW study had gaps which were supplemented by literature: because dosing regimen and trough concentration were not recorded in the registry, a literature review summarized the dosing regimen and targeted whole blood trough concentrations used by different transplant centers. Data from prior tacrolimus approvals for other solid organs were also used. The prior published information and prior label information used for the new indication were not recognized as a limitation by the FDA.

This design was well received by the FDA, which noted that the study met the regulatory requirements for an adequate and well-controlled study under 21 CFR 314.126 when considering the totality of the body of evidence, including confirmatory RCTs for other previously approved organ transplants and published literature on tacrolimus. The FDA also found the choice of data and study variables including outcomes to be relevant and reliable and the data to be fit-for-purpose. They did note potential misclassification of outcomes since implausible values were identified in the SRTR due to possible data quality issues. Post-hoc analyses conducted by the sponsor, such as reporting the primary endpoint with modifications not specified *a priori*, was not used in the product label. Overall, results demonstrated a large treatment effect for tacrolimus which the FDA noted as conclusive of the effectiveness of tacrolimus despite potential differences in patient characteristics between the two arms.

Despite a positive review, the study design had several limitations noted by the FDA, particularly around threats to internal validity including residual confounding, exposure and outcome misclassification, and selection bias. As a result, the FDA recommended several changes to the product label language, including eliminating comparative effectiveness language for tacrolimus and other indications due to residual confounding, as well as clarifying the study population and exposure definition to prevent exposure misclassification and selection bias.

The case of tacrolimus illustrates the strengths and opportunities of non-interventional studies being used for both the treatment and comparator arms:

- As seen in other positive assessments of RWE, the sponsor had early engagement with the FDA to align on the suitability of the RWE for the expanded indication
- Study protocol and statistical analysis plan were predefined
- The sponsor submitted patient-level data enabling FDA replication of analysis
- The sponsor used national registry data that enabled complete-case ascertainment of all lung transplant patients and resulted in no or minimal generalizability issues
- A large treatment effect of tacrolimus was observed, making differences due to other characteristics unlikely
- The gold-standard mortality data, the Social Security Death Master File, were used resulting in minimal risk of outcome misclassification
- The RWE submitted as substantial evidence for the label expansion was supplemented with confirmatory evidence provided from previously-approved indications

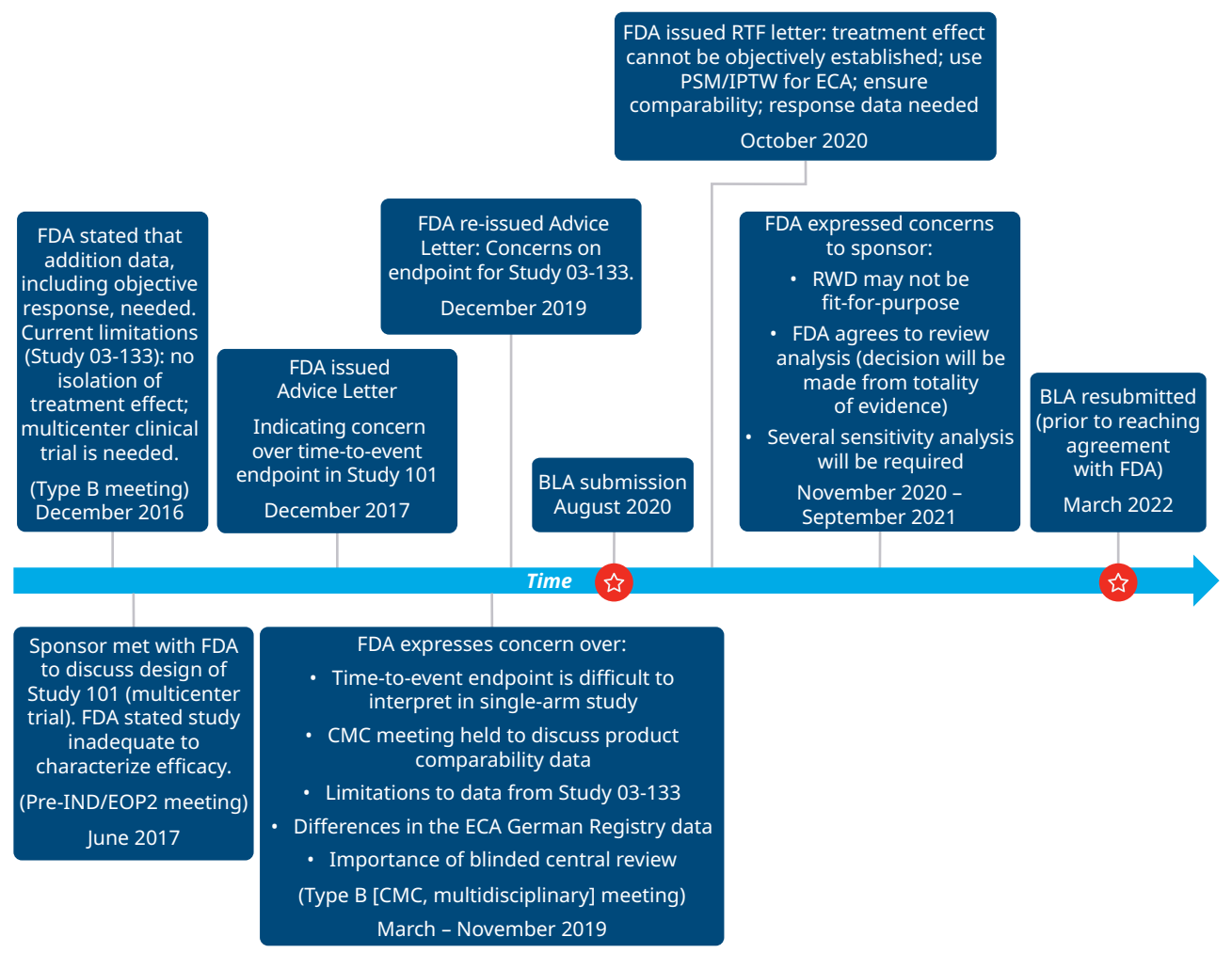
Omblastys (omburtamab)

Y-mAbs submitted a marketing authorisation application to the FDA for Omblastys (omburtamab) for neuroblastoma with CNS/leptomeningeal metastases. The BLA for the new indication was initially filed in 2020 and resubmitted in 2022 with subsequent rejection by the FDA, following a series of meetings and feedback from the regulatory body which remained unaddressed by the sponsor (see Figure 7).

Neuroblastoma is a rare paediatric condition (~650 incident cases in the US per year) among which only a small portion of patients develop central nervous (CNS) metastasis or leptomeningeal metastases (LM). At the time of drug development, no FDA-approved therapies were available for neuroblastoma with CNS relapse. Y-mAbs used a pivotal Phase 1 single-arm, single-center trial in the US with overall survival and progression-free survival as efficacy outcomes, supplemented with an external control arm utilizing European historical controls from Central German Childhood Cancer registry.

Over the course of the engagement with Y-mAbs, the FDA raised several concerns on the suitability of the single-center single arm trial, outcome selection, the selection of RWD for the ECA, and the methodology used to compare the external control

Figure 7. Omblastys FDA Engagement summary



Note: figure is not to scale.
CMC = Chemistry, Manufacturing and Controls. RTF = refusal to file. RWE = real-world evidence. SAP = statistical analysis plan. sNDA = supplemental new drug application. NDA = new drug application. IND = investigational new drug. EOP = end of phase 2. ECA = external control arm. BLA = biologics license applications. PSM = propensity score matching. IPTW = inverse probability of treatment weighting.

arm to the trial arm. These were highlighted both in the Refusal to File letter after the original BLA submission in 2020 and the Complete Response letter in 2022 that rejected Omblastys.

A critical concern raised by the FDA was on the use of time-to-event outcomes such as overall survival in single-arm trial. Guidance on clinical trial endpoints states that overall survival should only be used in randomized control trials because single arm studies are unable to adequately characterize time to event studies.[21] Appropriate endpoints in single-arm studies include objective response. Another limitation of the final submission included a lack of multi-center design and insufficiency of a single centre for the pivotal trail.

The FDA also flagged several concerns related to the RWE in the submission that ultimately led to a full re-analysis of the data by the FDA. For example, although the sponsor developed a statistical analysis plan in which several analyses were pre-specified, the rationale for analyses was not clear. Numerous limitations of the efficacy analysis were highlighted including immortal time bias, not accounting for temporal issues, internal validity, and issues with comparability between the trial and comparator arms. The FDA noted that the down-weighting of the external comparator arm appeared arbitrary and that the analysis introduced immortal time bias because patients in the trial arm had to have been alive up to the time of drug administration whereas those in the external control arm did not. Furthermore, potential differences in clinical care between the United States and Germany were not considered.

The FDA re-analysis of the trial and external control arm data addressed statistical issues such as the already mentioned immortal time bias and selection of appropriate index dates, and ultimately demonstrated null results of Omblastys efficacy. The FDA also conducted an onsite inspection at the ECA site used for the submission to verify the data quality.

There were several issues related to both the single-arm trial and the ECA in the Y-mAbs submission cited by the FDA, which led to the negative recommendation. These included a determination by the FDA that the RWD was not fit-for-purpose (control arm was not comparable), the demonstrated null results of the FDA-conducted sensitivity analysis, and the lack of reliable response data collected in the single-arm trial and external control arm. As such, the key learnings below should be taken into account when conducting an ECT:

- Early alignment with the FDA is critical. While Y-mAbs had early engagement with the FDA, the regulatory recommendations remained unaddressed up to the final submission
- Sponsors should demonstrate comparability of trial and comparator arm; for example ensuring that baseline characteristics are comparable and addressing differences through restriction of the study population prior to adjustment via modeling. Comparability of study arms is paramount when executing an ECT
- Considerations should be given to appropriate selection of outcomes for an ECT. As demonstrated above and indicated in the FDA guidelines, time-to-event outcomes are an inappropriate choice for single-arm trials
- Immortal time bias may be present in ECTs because participants must survive long enough in the trial to receive treatment, but this is not required for patients in an untreated external control population. This should be addressed via appropriate index date selection and methods considerations
- As demonstrated in this and other RWE case studies above, patient level data in a format compliant with FDA standards allows the FDA to conduct analysis

Learnings

These four case studies illustrate the importance of closely aligning with FDA and following their recommendations when conducting RW studies for use in marketing authorization applications for regulatory decision-making.

Finally, the real-world studies conducted for Vijoice and Prograf were novel and innovative in how the real world data were used and implemented in study design, highlighting the potential applications of RWE, particularly when the treatment effect is large and when there is a clear unmet medical need in the patient population.

ECT CONSIDERATIONS

Early engagement and alignment with the FDA for ECTs is critical, as seen in the Omblastys case study. Ensuring that the FDA is aligned and there is transparency around the study design and data management prior to ECT study execution is a key consideration for sponsors, as this can avoid unexpected feedback from the agency during the submission process and review.

Addressing sources of bias is a major concern for ECTs because the control group is not generated from the same population as the trial arm. The sponsor should follow FDA guidelines on single-arm trials and ECTs and demonstrate steps taken to mitigate such biases. For example, the RW arm used should be as trial-like as possible by ensuring the same inclusion and exclusion criteria (while taking into account challenges from RWD such as missing data), same/similar endpoints, unbiased methods of endpoint assessment, and preferably contemporaneous time periods as in the single-arm trial.

Conclusion

The collective body of FDA guidance and case studies highlight six key themes for sponsors to consider in the adoption of RWE for regulatory submissions to the FDA when using RWE for substantial evidence. Focus on these key points will help sponsors achieve regulatory acceptance:

- **Early engagement with the FDA** is critical for sponsors to provide transparency and ensure early alignment with the intended use of RWE
- **Select fit-for-purpose data** by summarizing feasibility work conducted during the data selection process to demonstrate why the final data source(s) was selected to answer the research question
- **Ensure that the study protocol and analysis plan are prespecified** — that is, completed prior to initiation of analysis — to ensure no preferential selection of results. Sponsors should also consider sharing these study documents with the FDA
- **Provide patient-level data to the FDA** according to compliant data formats
- **Demonstrate internal validity** through the implementation of rigorous methodologies aimed at identifying and mitigating biases
- **Demonstrate relevance** through the availability of key data elements related to the exposure, outcome(s), and covariates
- **Demonstrate data reliability** such as data accuracy, data completeness, provenance, and traceability, and be audit-ready

Industry and regulators will continue the collaborative journey to rethink how RWE can support regulatory decision making. Taking these key points and current guidance into account allows sponsors to effectively interact with the regulatory agency, equipped with the tools to successfully navigate this rapidly evolving environment.

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