



Critical Insights Into Nonclinical Toxicology And Real-World Evidence Essential For A Successful Rare Disease Product Launch

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Introduction

A well-designed clinical trial program requires both toxicological and epidemiological evidence to provide a solid foundation for the clinical phase of drug testing and regulatory review, whereas ineffective or inadequate toxicology and epidemiology data could halt the progress of a potentially promising new drug. In particular, successful drug development requires a thorough understanding of the drug candidates' pathophysiology and mechanism of action, as well as the targeted disease's prevalence and natural history. Elucidating the epidemiology of a rare disease through real-world studies is particularly important, as requirements for nonclinical toxicology studies to support rare disease clinical programs may vary, depending on the impact of the rare disease on quality of life and mortality.

This white paper highlights important evidence attained from both toxicology and epidemiology studies for a successful orphan drug launch. **ToxStrategies (www.toxstrategies.com) and EpidStrategies, a division of ToxStrategies (www.epidstrategies.com) have the necessary expertise to aid clients in their nonclinical and real-world data needs.**

Nonclinical Toxicology Studies

ToxStrategies scientists have developed rare disease products for more than 30 indications targeting genetic disorders, neurology, ophthalmology, oncology, and non-oncology using small molecules, ERTs, biologics, and gene therapies. **Our staff can help you optimize the nonclinical safety evaluation of your product to efficiently move into clinic trials (www.toxstrategies.com).**

Safety and Efficacy

Nonclinical studies are conducted to determine whether a drug is reasonably safe and suitable for testing in clinical studies. Well-designed nonclinical studies, including in vitro and/or ex vivo data, should contribute to a better understanding of a drug's

- Mechanism of action/efficacy
- Pharmacokinetics
- Toxicity

These parameters are then used to determine a potential efficacious and safe dose range in the clinical setting.

Nonclinical studies are critical to the design of early-phase clinical trials, particularly for selecting the

- Route of administration
- Starting clinical dose
- Dose escalation plan
- Dosing regimen (frequency and duration)

Patient Eligibility

A well-designed nonclinical toxicology program, coupled with an understanding of the epidemiology and natural history of a target indication, informs the patient eligibility criteria (e.g., age, sex, pre-existing conditions) and toxicological profile for establishing safety monitoring procedures and standards. Specific safety monitoring and/or clinical pathology assays to identify potential toxicities may be monitored in the clinic, and for immune modulating therapies, evaluation of anti-drug and antinuclear antibodies may be also necessary.

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Regulatory Guidance

While nonclinical toxicology studies are generally needed to support rare disease development, **there can be flexibility in the overall nonclinical toxicology package for indications with an unmet need, such as a severe, life-threatening, and rapidly progressing disease.** For example:

1. FDA Enzyme Replacement Therapy (ERT) Guidance (2019), allows shorter duration toxicology studies (3 months versus the standard 6- or 9-month studies) to support marketing for rapidly progressing diseases.
2. ICHS9 Nonclinical Evaluation for Anticancer Pharmaceuticals guideline also allows 3-month toxicology studies, genotoxicity studies with a marketing application, and a reduced reproductive toxicology assessment (i.e., embryofetal development [EFD] studies).
3. FDA's Severely Debilitating or Life-Threatening Hematologic Disorders guidance similarly allows 3-month-duration toxicology studies to support marketing, genotoxicity (only requiring a genetic mutation assay), carcinogenicity (not required prior to marketing), juvenile toxicity (usually not required), and reproductive toxicology (only EFD studies).

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Importantly, these guidances highlight that there is flexibility with setting the First in Human (FIH) starting dose based on the highest severely toxic dose (HNSTD) rather than a no-observed-adverse-effect level (NOAEL), which can be a high hurdle for potent drug products, especially when using healthy animals rather than an animal disease model.

These potential **timeline reductions** and opportunities for **reducing the number of nonclinical studies** can allow for resources to be allocated to other areas of clinical development and potentially accelerate the time to market for rare disease products. **ToxStrategies' familiarity and direct experience with these guidances across regulatory agencies can streamline the nonclinical program.**

Pediatric Populations

For rare diseases where the patient population is primarily or strictly pediatric patients, nonclinical studies in juvenile animals are expected prior to the conduct of FIH studies. Juvenile animal studies are substantially longer than traditional nonclinical studies conducted to enable FIH studies in adults. Alternatively, if an adult patient population can be identified for FIH studies, then shorter duration nonclinical studies could provide early safety data to support initiation of clinical studies in pediatric patients, and juvenile nonclinical animal studies may be waived. Juvenile toxicology studies can also be extended to include reproductive and development endpoints to satisfy the EFD study requirements earlier in the program.

Expanded Indications

Another regulatory pathway for drugs that treat rare diseases is the identification of other indications where the drug could be efficacious. In this case, a complete nonclinical package may be warranted. Additionally, while most drugs that treat rare diseases benefit from global approval, challenges may arise when different regulatory agencies require further nonclinical studies or larger clinical studies. Early interactions with regulatory agencies can inform on the adequacy of the overall nonclinical and clinical plans. Working with ToxStrategies and EpidStrategies can facilitate productive interactions with these agencies.

Relevant Regulatory Guidances

FDA

1. [SDLTHD Guidance](#)
2. [ERT Guidance](#)
3. [Draft Guidance Rare Diseases: Common Issues in Drug Development Guidance for Industry](#)
4. [FDA Real World Evidence](#)
5. [Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drugs and Biologics Guidance for Industry](#)

ICH

1. [ICH S6\(R1\)](#)
2. [ICH S9](#)
3. [ICH M3\(R2\)](#)
4. [ICH S1B](#)

FDA Resources:

[FDA Office of Orphan Products Development \(OOPD\)](#)

Epidemiology and Real-World Studies

Elucidating the prevalence and natural history of a rare disease is important for regulatory submissions, particularly in understanding clinical endpoints and potential safety signals. **EpidStrategies has determined the prevalence for more than 40 different indications and conducted more than 20 natural history studies of rare diseases or genetic subsets of less rare diseases to support clinical trials and for use in regulatory submissions (www.epidstrategies.com).**

Prevalence

Analyzing the prevalence of a condition can support the product development process by providing the sponsor with an estimate of the target population size and as a basis for orphan drug regulatory submissions. EpidStrategies has used multiple rigorous methods accepted by regulatory bodies to calculate prevalence, including systematic literature reviews and meta-analyses, electronic health records, Markov modeling, publicly available data resources such as SEER, and the linked health records systems in Denmark. Our calculations have been incorporated into orphan drug applications for the FDA and EMA and presented in conference abstracts, published manuscripts, and internal reports.

Natural History Studies

Prognostic Enrichment

Understanding the target disease's natural history enables a more comprehensive and thorough definition of the disease population, including identification of important disease subtypes. This is critical, as it may allow for better characterization and selection of patients who are more likely to progress to endpoints (e.g., mortality) that will be assessed in the context of a clinical trial, thus reducing clinical trial timelines.

Trial Design

A comprehensive understanding of the relevant natural history aids in the development and implementation of critical elements in clinical trial design, such as trial duration and entry criteria. Other important components of a trial that can be elucidated from a natural history study include:

- Selecting clinical endpoints
- Having sensitive, specific outcome measures
- Identifying new biomarkers or validating existing ones
- Screening for possible responders (predictive enrichment)
- Recognizing safety concerns early
- Providing supportive evidence of efficacy

Selected Prevalence Studies

Cancer

- ▶ Thyroid cancer subtypes (papillary, follicular, medullary, anaplastic)
- ▶ Langerhan's cell histiocytosis
- ▶ Genetic subsets of:
 - Infantile fibrosarcoma
 - Soft-tissue sarcoma
 - Gastroesophageal junction adenocarcinoma
 - Gastrointestinal stromal tumor
 - Non-small-cell lung cancer
 - Lung squamous-cell carcinoma
 - Salivary gland carcinoma
 - Mammary analogue carcinoma of the salivary glands
 - Astrocytoma
 - Glioblastoma
 - Diffuse intrinsic pontine glioma
 - Cholangiocarcinoma
 - Colorectal cancer

Other Indications

- ▶ Cold agglutinin disease
- ▶ Idiopathic pulmonary fibrosis
- ▶ Myelofibrosis
- ▶ Essential thrombocythemia
- ▶ Polycythemia vera
- ▶ X-linked hypohidrotic ectodermal dysplasia
- ▶ Familial hypercholesterolemia
- ▶ Prader-Willi Syndrome

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External Comparators

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved submissions that use real-world evidence (RWE) for comparison populations in clinical trials, rather than traditional controls. Using external comparators or historical controls can be particularly useful for rare diseases or specific patient populations that are challenging to identify and characterize. However, a number of important factors must be considered when designing real-world studies, including:

- Development of study protocol and statistical analysis plan a priori
- Comparability of baseline characteristics between external comparators or historical controls and clinical trial patients
- Comparability of outcome assessments
- Completeness of important covariate data (particularly those related to study outcomes)
- Sufficient sample size for statistical comparisons between study cohort and external comparator or historical control

EpidStrategies scientists are skilled in the design, launch, and analysis of natural history studies using electronic medical record data, insurance claims data and primary surveillance for use in regulatory submissions.

Selected Examples from EpidStrategies



Cold agglutinin disease burden: a longitudinal analysis of anemia, medications, transfusions, and healthcare utilization
Mullins M, Jiang X, Bylsma LC, Fryzek, JP, Reichert H, Chen EC, Kummar S, Rosenthal A
2017. Blood Advances 1:839-848



Long-term health outcomes in patients with Prader-Willi Syndrome: A nationwide cohort study in Denmark
Hedgeman E, Ulrichsen SP, Carter S, Kreher NC, Malobisky KP, Braun MM, Fryzek J, Olsen MS
2017. Int J Obes (Lond) 41(10):1531-1538



Increased Incidence of thromboembolic events in a large cold agglutinin disease (CAD) cohort: A 10-year retrospective analysis
Broome CM, Cunningham JM, Mullins M, Jiang X, Bylsma LC, Fryzek J, Rosenthal A
2020. Res Pract Thromb Haemost 00:1-8



Epidemiology of myelofibrosis, essential thrombocythemia, and polycythemia vera in the European Union
Moulard O, Mehta J, Fryzek J, Olivares R, Iqbal U, Mesa RA.
2013. Eur J Haematol 92(4):289-297



Prevalence of RAS and BRAF mutations in metastatic colorectal cancer patients by tumor sidedness: A systematic review and meta-analysis.
Bylsma LC, Gillezeau C, Garawin TA, Kelsh MA, Fryzek JP, Sangare L, Lowe KA
2020. Cancer Med 9(3):1044-1057



Epidemiology of systemic mastocytosis in Denmark
Cohen SS, Skovbo S, Vestergaard H, Kristensen T, Møller M, Bindslev-Jensen C, Fryzek JP, Broesby-Olsen S
2014. Br J Haematol 166(4):521-8



Clinical and economic burden associated with Stage III-IV Triple Negative Breast Cancer: A SEER-Medicare Historical Cohort Study
Schwartz K, Simon MS, Bylsma LC, Ruterbusch JJ, Beebe-Dimmer JL, Schultz NM, Flanders SC, Barlev A, Fryzek JP, Quek RGW
2018. Cancer 124(10):2104-2114.

Contact Information

For additional information on development of nonclinical and clinical study designs, please contact:

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Dr. Fryzek has 30 years of experience in the pharmaceutical industry and private consulting firms. He has led numerous studies based on Real-World Evidence, including descriptive incidence studies, disease treatment pattern studies, and co-morbidity assessments in support of drug development and safety. Dr. Fryzek has over 175 peer-reviewed manuscripts, book chapters, and scientific meeting abstracts.

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Ms. Movva manages numerous large- and small-scale real world studies in various therapeutic areas including oncology, infectious diseases, and heart disease in the United States and Europe. Further, she has led data analyses of primary and secondary data, systematic literature reviews and manuscript and regulatory document writing.

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Ms. Bylsma is experienced in elucidating the epidemiology of rare diseases. She has expertise in conducting systematic literature reviews and meta-analyses and developing epidemiology sections for regulatory submissions, particularly determining the prevalence of target populations and presenting to regulatory bodies.

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Dr. Welsh has more than 10 years of experience in the pharmaceutical and biotechnology industry, including 6 years consulting. He has overseen and participated in the study design, protocol development, conduct, study monitoring, data interpretation, and reporting of numerous nonclinical general, safety, and reproductive and developmental toxicology (GLP and non-GLP) studies in various animal species. In addition, he specializes in evaluating hazards and risks associated with exposures to a wide variety of biopharmaceutical and pharmaceutical products

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Ms. Mease has more than 15 years of experience in the pharmaceutical industry, focusing on nonclinical product development. She has accrued extensive experience in drug development, including rare disease drug products. She is skilled in all aspects of toxicology study conduct, as well as in providing innovative solutions to drug development challenges. Additionally, she has experience authoring regulatory documents and representing nonclinical at regulatory agency meetings.

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Dr. Wood is a toxicologist with more than 14 years of experience in drug discovery and development, including 7 years at the U.S. Food and Drug Administration and 4 years consulting. Her expertise includes developing nonclinical regulatory strategies for a wide variety of drug product types, routes of administration, and therapeutic indications, as well as addressing challenging scientific and regulatory issues. She also is experienced at overseeing nonclinical toxicology programs, authoring regulatory documents, and providing nonclinical expertise at regulatory agency meetings.