BUILD A LABELING EVIDENCE STRATEGY FOR TODAY'S APPROVAL AND TOMORROW'S INDICATIONS

AT QPS WE BELIEVE IN DEVELOPING CLOSE AND LONG-LASTING RELATIONSHIPS WITH OUR CLIENTS ON THE BASIS OF TRUST AND MUTUAL RESPECT.

This mutual trust, combined with the agile approach we offer as a specialty CRO, helps improve the quality of your outsourced clinical work and reduces the degree of required oversight.



QPS
CUSTOM-BUILT RESEARCH™

DRUG LABELING STUDIES

A drug development program that generates promising efficacy and safety results may still leave important questions unanswered, such as: How should the medicine be dosed in patients with impaired renal function? Could interactions with other medications affect treatment? What additional evidence is needed to support a new indication or expand use to another patient population?

When these questions are not addressed early, sponsors may face additional studies, delayed regulatory submissions or limitations in approved prescribing information. Planning backward from the intended label can help identify evidence gaps before they disrupt development.

Effective planning requires coordination across nonclinical research, clinical pharmacology, clinical trials, manufacturing, bioanalysis and regulatory affairs. Each study should answer a defined question and contribute evidence needed to support decisions about safety, efficacy and appropriate use.

This white paper outlines a framework for planning development from early research through initial approval and subsequent label expansion. It uses US regulatory terminology and internationally harmonized principles, with examples particularly relevant to orally administered small molecules. Study requirements vary by therapeutic modality, disease and jurisdiction. The objective is not to prescribe a fixed sequence of studies but to show how sponsors can align evidence generation with intended prescribing decisions.

1. DEFINE THE INTENDED USE AND EVIDENCE REQUIREMENTS

Begin with a target product profile

A target product profile (TPP) describes the proposed indication, disease severity, patient population, treatment setting, route, dose, frequency, duration and expected clinical benefit. It should also anticipate important safety limitations, monitoring and administration instructions. Early attributes are development hypotheses, not established claims. Although a TPP is not a regulatory requirement, it provides a common basis for planning across scientific and regulatory functions.

The FDA's prescribing information resources illustrate the range of topics an eventual label may need to address, including indications, dosage and administration, warnings, use in specific populations, clinical pharmacology and clinical studies. Sponsors can use these categories to identify questions that must be answered before submission.

Translate prescribing questions into an evidence plan

Create an evidence matrix that connects each proposed prescribing statement to the supporting study or analysis, the uncertainty it addresses and the decision it will inform. Distinguish evidence essential for initial approval from questions that can appropriately be investigated later. Regulatory discussion is needed before deferring an unresolved issue that could materially affect safe use.

For example, an oral treatment intended for older adults may require information about kidney function, common concomitant medications and administration with food. A program that routinely excludes such patients or medications could demonstrate efficacy while leaving practical prescribing questions unanswered.

Set decision criteria before data become available.

Specify what level of benefit, exposure, tolerability and uncertainty would justify advancing, modifying the regimen or stopping. These criteria help keep study decisions connected to the intended use rather than to individual positive findings.

2. BUILD A NONCLINICAL FOUNDATION FOR THE CLINICAL PROGRAM

Connect pharmacology and DMPK to clinical questions

Pharmacology studies should establish a plausible relationship among the drug target, the compound's activity and the disease process. Assess potency, selectivity, target engagement and the limitations of experimental models. An effect in a model supports a development hypothesis but does not establish clinical efficacy. Identify pharmacodynamic measures that may help test the mechanism in humans.

Drug metabolism and pharmacokinetics (DMPK) studies characterize absorption, distribution, metabolism and

QPS
CUSTOM-BUILT RESEARCH™

excretion (ADME), relevant metabolites, protein binding and possible drug interaction mechanisms. Integrate these findings with pharmacology and toxicology so dose decisions reflect both administered dose and systemic exposure. This work may also reveal questions that will later affect dosing instructions or use in specific populations.

Match safety studies to anticipated exposure

The nonclinical safety program should reflect the planned route, exposure, treatment duration and study population. ICH M3(R2) provides principles for coordinating nonclinical studies with clinical development. Depending on the product, the package may include repeat-dose toxicity, safety pharmacology, genotoxicity, reproductive and developmental toxicity and assessment of carcinogenic potential. The timing and applicability of these studies differ, and not all are required before first human exposure.

Select scientifically relevant models and justify species selection when animal studies are used. Consider suitable nonanimal methods and whether they are acceptable for the intended regulatory purpose. Small molecules, biotechnology-derived products and anticancer therapies may require different approaches. Pivotal nonclinical safety studies supporting an investigational new drug (IND) application are generally expected to comply with applicable Good Laboratory Practice requirements.

Before clinical entry, the program should provide a defensible starting exposure, potential toxicity signals, monitoring needs and criteria for escalation or stopping. These findings should inform participant eligibility, safety assessments and follow-up.

3. ALIGN MANUFACTURING AND BIOANALYSIS BEFORE CLINICAL ENTRY

Keep clinical material and analytical controls ready

Chemistry, manufacturing and controls (CMC) activities must advance alongside study planning. Establish product identity, strength, purity, stability and suitable analytical controls. Secure enough clinical material for the proposed dose range and treatment duration, including matching placebo where needed. Evaluate whether materials used in nonclinical work adequately represent those intended for clinical studies.

Changes in formulation or manufacturing can alter drug exposure or product characteristics. Anticipate when comparative analytical testing, relative bioavailability studies or other bridging evidence will be necessary. A late formulation change could limit the relevance of earlier pharmacokinetic or food-effect findings if its consequences are not evaluated.

Build reliable measurement into study design

Validated bioanalytical methods help establish the relationship between dose, drug exposure and response. ICH M10 addresses validation and analysis of study samples for drug and relevant metabolite quantification. Biomarker methods need an approach appropriate to their intended use, with FDA's April 2026 guidance addressing bioanalytical method validation for biomarkers.

Distinguish exploratory biomarker measurements from methods used to determine enrollment, guide dosing or assess a pivotal endpoint. Define collection timing, sample processing, storage, shipping, stability and data traceability before a trial begins. Results must be linked reliably to each participant, dose, visit and sampling time. Inconsistent measurements can weaken otherwise well-designed studies and require additional work to interpret exposure-response relationships.

4. USE EARLY CLINICAL STUDIES TO ESTABLISH A CREDIBLE REGIMEN

Phase I: Investigate exposure, tolerability and early effects

First-in-human studies should explore a justified exposure range while protecting participants. Whether enrollment begins in healthy volunteers or patients depends on the mechanism, anticipated risk and disease context. Single- and multiple-dose assessments may characterize tolerability, pharmacokinetics, accumulation and early pharmacodynamic effects. Protocols should specify staged dosing, safety reviews, escalation criteria and stopping rules where appropriate.

Starting dose selection must integrate nonclinical toxicity, predicted human exposure, pharmacological activity and uncertainty. For higher-risk products, the minimum anticipated biological effect level (MABEL), an estimate of the exposure expected to produce a minimal biological effect in humans, may be especially relevant. The goal is to understand the relationship between exposure, biological activity and adverse effects rather than simply identify the maximum tolerated dose.

Phase II: Test proof of concept and dose selection

Phase II studies typically investigate whether a treatment produces clinically relevant benefit in the intended population and which dose and regimen warrant further evaluation. Examine dose-response and exposure-response relationships, treatment duration and variability among patients. When feasible, studying more than one dose can help avoid carrying an inadequately characterized regimen into confirmatory development.

Select endpoints that address the clinical question and are reliable and meaningful in the proposed population. A change in a biomarker may support the mechanism or dose selection without establishing a validated surrogate for clinical benefit. ICH E8(R1) emphasizes defining study objectives and factors critical to trial quality.

Before proceeding, review efficacy, safety, exposure and operational feasibility together. An encouraging average response may conceal poor tolerability at the proposed dose or uncertainty about treatment duration. Development phases can overlap or be combined when justified; what matters is whether the evidence supports the next decision.

5. GENERATE EVIDENCE FOR INITIAL PRESCRIBING INFORMATION

Initial prescribing information draws on evidence collected throughout development. It should not be treated as an activity that begins only after the pivotal efficacy trials. Clinical pharmacology investigations help explain how a medicine should be administered, what changes drug exposure and which precautions or dose adjustments may be necessary.



For an oral small molecule, the program may include food-effect assessments, drug interaction studies, renal or hepatic impairment evaluations, relative bioavailability studies and characterization of elimination pathways. Human radiolabeled mass-balance studies may help clarify disposition and metabolites when appropriate. Population pharmacokinetic modeling and exposure-response analyses can integrate information across studies, although whether they can replace a dedicated study depends on the available data, regulaory question and agency agreement.

FDA guidance addresses food-effect studies and the assessment of pharmacokinetics in patients with impaired renal function. ICH M12 provides a harmonized approach to enzyme- and transporter-mediated drug interactions. These investigations should be timed to influence the clinical program. If an interaction substantially changes exposure, it may affect eligibility, concomitant medication restrictions, dose selection or safety monitoring in pivotal trials. Food-effect data may also need reassessment if the intended commercial formulation changes.

Interpret pharmacokinetic differences in the context of exposure-response, safety margins and clinical relevance. Not every difference in exposure warrants a dosing restriction, and an absence of evidence should not be described as evidence of safety. Product-specific questions may also involve cardiac electrophysiology, immunogenicity, pharmacogenomics, pregnancy and lactation or pediatric use. Each needs an evidence strategy appropriate to the medicine and population.

6. DESIGN CONFIRMATORY STUDIES AROUND THE PROPOSED INDICATION

Confirmatory studies, often conducted in Phase III, must provide evidence of efficacy and characterize safety in a population relevant to the intended use. Define the treatment setting, comparator, regimen, treatment duration, primary endpoint and magnitude of benefit considered clinically meaningful. Eligibility criteria must protect participants without making the findings unnecessarily difficult to apply to the proposed population. Evaluate recruitment, competing studies, visit burden and retention before finalizing the design.

QPS
CUSTOM-BUILT RESEARCH™

Define the treatment effect the trial will measure

An estimand is a precise description of the treatment effect a trial intends to evaluate. It specifies the population, outcome and how events such as treatment discontinuation, use of rescue medication or death are considered. ICH E9(R1) provides a framework for aligning these choices with the clinical question. Data collection, statistical methods and sensitivity analyses should support the same objective. Missing data and events that occur after treatment begins require related but distinct planning.

Plan an evidence package, not a fixed trial count

Sponsors should discuss the proposed confirmatory package with regulators rather than assume a set number of pivotal trials. FDA's June 2026 revised draft guidance explains circumstances in which one adequate and well-controlled investigation plus confirmatory evidence may establish substantial evidence of effectiveness.

Plan safety follow-up around expected exposure, treatment duration, mechanism and plausible risks. Integrated analyses should examine adverse events, laboratory findings, discontinuations and clinically relevant subgroup patterns. Before submission, reconcile the intended label with the actual evidence, including limitations. The nonclinical, clinical, manufacturing and labeling components should present consistent conclusions about benefit and risk.

7. DISTINGUISH POST-APPROVAL RESEARCH FROM LABEL EXPANSION

Address post-approval safety and evidence obligations

Approval may be followed by pharmacovigilance, required postmarketing studies, agreed commitments and other research. These activities can assess longer-term safety, remaining uncertainties or the medicine's use within its approved indication. FDA distinguishes postmarketing requirements imposed under law or regulation from commitments sponsors agree to conduct.

Some postapproval findings support updates to warnings, precautions or other prescribing information. However, a study does not establish a new indication simply because it occurs after approval. The purpose of the study and the regulatory claim it is intended to support must be clear, even when a single study can inform more than one question.

Reassess the evidence for a proposed expansion

For label expansion, define precisely what would change: the disease, stage, age group, line of therapy, combination partner, regimen, route or treatment duration. Review existing evidence and identify what can reasonably be carried forward. Prior approval may reduce uncertainty about manufacturing, pharmacokinetics or certain risks, but it does not automatically establish efficacy or an acceptable benefit-risk balance in a different population or disease.

A new indication may require further Phase II dose or endpoint exploration before confirmatory trials. Additional early clinical or nonclinical work may also be needed when the proposed use changes exposure, duration or anticipated risks. An applicant generally pursues a new indication for an approved product through an efficacy supplement to its existing new drug application (NDA) or biologics license application (BLA). FDA describes supplemental applications supporting new uses of approved therapies in its Split Real Time Application Review (STAR) program.

Consider a hypothetical medicine approved for a short course in adults but proposed for chronic treatment of another disease. The expansion plan should revisit long-term toxicity, cumulative exposure, concomitant medications and safety follow-up. If children are included, pediatric dose selection and development requirements need separate consideration. A second indication should build on existing knowledge without assuming that the original study package is sufficient.

8. USE REAL-WORLD EVIDENCE FOR A DEFINED REGULATORY QUESTION

Real-world data (RWD), including information from routine clinical care, can help characterize patient populations, disease history, treatment patterns and longer-term outcomes. Analyses of these data may generate real-world evidence (RWE) relevant to safety, postapproval requirements or a new indication in appropriate circumstances. FDA's RWE framework does not treat routinely collected data as an automatic substitute for a controlled trial.
Begin by defining the regulatory question and determining whether the available data are fit for that purpose. Assess completeness, outcome validity, exposure measurement, follow-up, potential confounding and selection bias. Prespecify the protocol and analysis, verify data provenance and discuss a proposed regulatory use early. A large dataset cannot compensate for systematic bias.

A randomized study embedded in routine care can address a different question from an observational database analysis. Select the design that can credibly estimate the treatment effect of interest. FDA's final ICH M14 guidance, issued in March 2026, outlines principles for noninterventional studies using RWD, primarily for assessing medicine safety. Its methods can also inform broader planning, but regulatory acceptance depends on the specific question and design.

9. KEEP THE DEVELOPMENT PLAN CURRENT

A development plan should remain a working decision document, not a schedule that is updated only after a study ends. Assign ownership to each major evidence gap and maintain a shared view of dependencies across functions. For each study, record:

- Purpose: The question it is designed to answer and its relationship to the proposed label.
- Prerequisites: Required assays, clinical material, regulatory feedback and earlier results.
- Decision criteria: The results that would justify advancing, adapting or stopping.
- Timing: Recruitment, sample analysis, follow-up, data review and reporting milestones.
- Next action: The consequences of an inconclusive result or emerging safety concern.

Use regulatory interactions to address consequential uncertainties before they become embedded in costly protocols. Pre-IND, end-of-Phase II and pre-submission discussions can help clarify expectations, while the advice received and unresolved questions should feed directly into the working plan.

Update the TPP and evidence matrix after significant findings. Reassess the intended indication, regimen, patient population and evidence still required for approval. This approach also creates a stronger starting point for future labeling changes, because the sponsor can identify what the original program established and which questions remain open.

Update the TPP and evidence matrix after significant findings. Reassess the intended indication, regimen, patient population and evidence still required for approval. This approach also creates a stronger starting point
for future labeling changes, because the sponsor can identify what the original program established and which questions remain open.

Planning for Approval and Beyond

Drug development planning requires more than selecting the next study. Sponsors must consider how each investigation contributes to the evidence needed for clinical decisions, regulatory approval and safe and effective use. Starting with the intended prescribing information helps identify critical questions early, coordinate research activities and prepare for potential label expansion.

How QPS Supports Drug Labeling Studies

QPS is a global, full-service CRO providing expertise in pharmacology, toxicology, DMPK, bioanalysis, translational medicine, central lab and kitting services, clinical trial units, as well as clinical research services.

QPS services support preclinical, early-phase clinical trials and Phase II–IV clinical research, supported by regulatory affairs, data management, biostatistics and medical writing. This breadth of services helps sponsors plan and conduct research that addresses development questions and generates evidence to support regulatory submissions.

Planning your next drug development program or evaluating opportunities for label expansion? Contact QPS to discuss how its research capabilities can support your development objectives.



QPS
CUSTOM-BUILT RESEARCH™

REFERENCES

1. US Food and Drug Administration. Prescribing Information Resources. https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources. Accessed 18 November 2026.

2. US Food and Drug Administration. M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. January 2010. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m3r2-nonclinical-safety-studies-conduct-human-clinical-trials-and-marketing-authorization. Accessed 18 November 2026.

3. US Food and Drug Administration. IND Applications for Clinical Investigations: Pharmacology and Toxicology (PT) Information. https://www.fda.gov/drugs/investigational-new-drug-application-ind/ind-applications-clinical-investigations-pharmacology-and-toxicology-pt-information. Accessed 18 November 2026.

4. US Food and Drug Administration. M10 Bioanalytical Method Validation and Study Sample Analysis. November 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m10-bioanalytical-method-validation-and-study-sample-analysis. Accessed 18 November 2026.

5. US Food and Drug Administration. Bioanalytical Method Validation for Biomarkers. April 2026. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/bioanalytical-method-validation-biomarkers. Accessed 18 November 2026.

6. US Food and Drug Administration. E8(R1) General Considerations for Clinical Studies. April 2022. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e8r1-general-considerations-clinical-studies. Accessed 18 November 2026.

7. US Food and Drug Administration. Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Content and Format. December 2016. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-pharmacology-labeling-human-prescription-drug-and-biological-products-content-and-format. Accessed 18 November 2026.

8. US Food and Drug Administration. Assessing the Effects of Food on Drugs in INDs and NDAs—Clinical Pharmacology Considerations. May 2026. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-effects-food-drugs-inds-and-ndas-clinical-pharmacology-considerations. Accessed 18 November 2026.

9. US Food and Drug Administration. Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing. March 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-patients-impaired-renal-function-study-design-data-analysis-and-impact-dosing. Accessed 18 November 2026.

10. US Food and Drug Administration. M12 Drug Interaction Studies. August 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m12-drug-interaction-studies. Accessed 18 November 2026.

11. US Food and Drug Administration. E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials. May 2021. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e9r1-statistical-principles-clinical-trials-addendum-estimands-and-sensitivity-analysis-clinical. Accessed 18 November 2026.

12. US Food and Drug Administration. Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products. Revised draft guidance. June 2026. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products. Accessed 18 November 2026.

13. US Food and Drug Administration. Postmarketing Requirements and Commitments: Frequently Asked Questions (FAQ). https://www.fda.gov/drugs/postmarketing-requirements-and-commitments-introduction/postmarketing-requirements-and-commitments-frequently-asked-questions-faq. Accessed 18 November 2026.

14. US Food and Drug Administration. Split Real Time Application Review (STAR). https://www.fda.gov/drugs/development-resources/split-real-time-application-review-star. Accessed 18 November 2026.

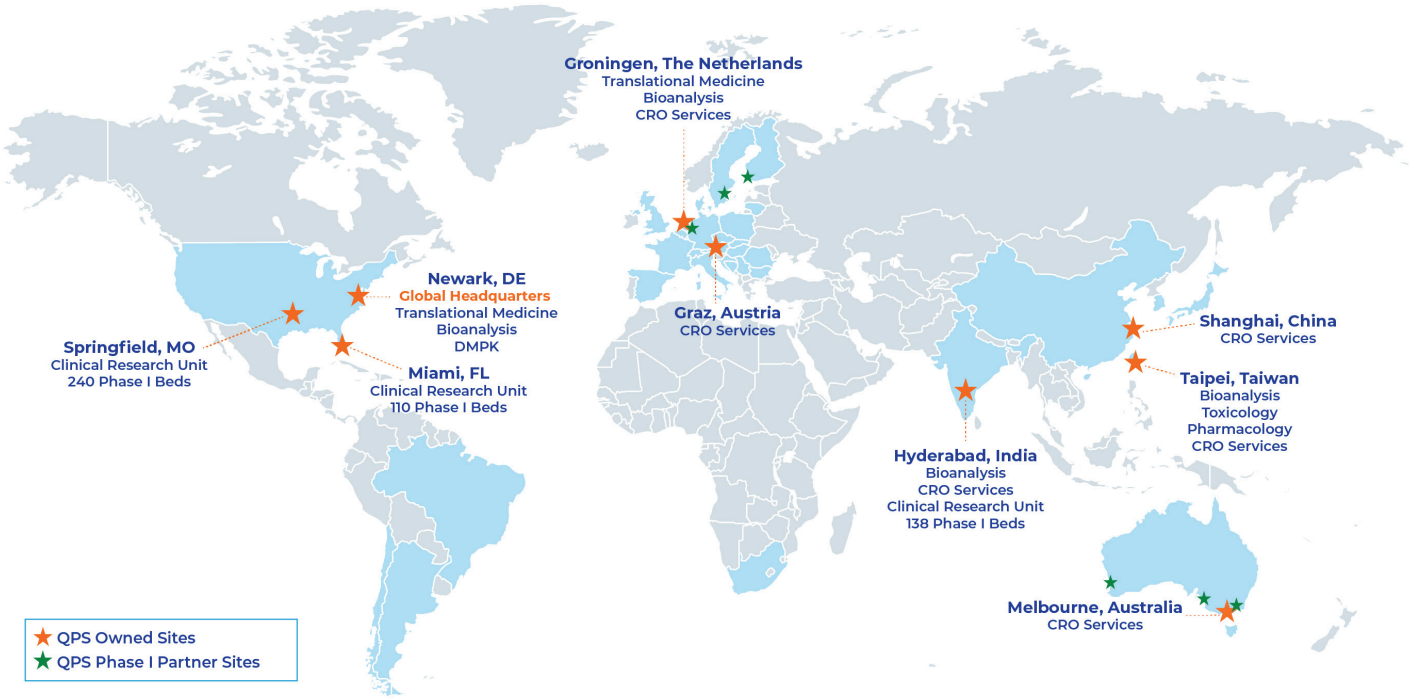
15. US Food and Drug Administration. Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products. August 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug. Accessed 18 November 2026.

16. US Food and Drug Administration. M14 General Principles on Planning, Designing, Analyzing, and Reporting of Non-interventional Studies That Utilize Real-World Data for Safety Assessment of Medicines. March 2026. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m14-general-principles-planning-designing-analyzing-and-reporting-non-interventional-studies-utilize. Accessed 18 November 2026.

QPS
CUSTOM-BUILT RESEARCH™

TIME IS OF THE ESSENCE IN DRUG DEVELOPMENT. CONTACT THE QPS BUSINESS DEVELOPMENT TEAM TODAY!

Call +1 512 350 2827 Email infobd@qps.com



NETWORK LOCATIONS USA / Austria / Australia / Argentina / Belgium / Bosnia / Brazil / Bulgaria / Chile / China / Croatia / Czech Republic / Denmark/ France / Finland/ Germany / Hungary / India / Italy / Lithuania / Netherlands / Poland / Romania / Serbia / Slovakia / South Africa / South Korea / Spain / Sweden / Taiwan / United Kingdom

QPS
CUSTOM-BUILT RESEARCH™