Worldwide Clinical Trials

First-in-Human Studies: IND or CTA?

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Small to midsize pharmaceutical and biotechnology companies whose development efforts advance to the point of contemplating first-in-human (FIH) clinical trials frequently face a challenging decision: File a clinical trial application (CTA) with the intent of conducting FIH trials in a European Union (EU) member state and under the regulatory eye of the respective regulatory agencies and European Medicines Agency (EMA), file an investigational new drug (IND) application with the US Food and Drug Administration (FDA) with the intent of conducting FIH trials in the US under the umbrella of FDA regulations, or conduct clinical research in other regulatory jurisdictions that have unique corporate and operational advantages. Decision-makers often rely on variables involving funding, corporate milestones, and short-term opportunities and incentives when determining which path to take. An examination of the similarities and differences between CTA and IND regulatory pathways — and on the impact these decisions have on programmatic goals — showcases the opportunities that exist.

A number of strategies can lead to regulatory approval to conduct first-in-human (FIH) clinical trials. If a drug developer wants to conduct initial human trials in the United States, it would file an investigational new drug (IND) application with the US Food and Drug Administration (FDA), and, if cleared, the developer would conduct those FIH trials under the regulatory auspices of the FDA. If the developer wants to conduct initial human trials in the European Union, it would file a clinical trial application (CTA) with respective national regulatory agencies of member states under the European Clinical Trials Regulation coordinated by the European Medicines Agency (EMA), and, if approved, it would enable the developer to conduct its FIH trials under the regulatory oversight of the European parties.

Note that neither an IND nor a CTA preclude the developer from conducting trials in additional regions that may have additional or different requirements; nevertheless, the decision to file an IND or a CTA primarily determines the regulatory framework and expectations that will guide FIH trials, given that ICH and Good Clinical Practice (GCP) conventions are universally acknowledged. A developer filing an IND (or a CTA) and planning to conduct trials in other countries, whether that be Australia, Brazil, or the People's Republic of China, would still need to conduct those studies under established GCP conventions in order to satisfy the regulatory requirements of the FDA (or EMA).1 The nonclinical data required to enable that application would likely be consistent with International Conference on Harmonization (ICH) conventions. An application for FIH studies filed with the FDA or within Europe is a critical first step for most developers.

Different pathways, common destinations

The question is, which path — IND or CTA — should a developer take when only one initiative is possible? Even though, under the conventions of the ICH, the nonclinical data required for a CTA or IND submission do not differ materially across regulatory jurisdictions, the submission processes and the review procedures themselves differ substantially. Following both paths simultaneously is unrealistic for most companies.[1,2] Both applications can be complicated and time-consuming to complete. Compilation of a full IND application can require a concerted effort extending three to nine months, depending upon the complexity of the dossier to be assembled.

One distinction worth noting is that an IND submission is product-specific, whereas a CTA submission is protocol-specific. Once an IND is cleared, the sponsor amends the IND filing with updates to sections of the IND, and adding further protocols is akin to updating the IND on file with the FDA. Adding new protocols in the EU requires filing a new CTA for each protocol.

Pragmatic and financial considerations often hold more sway than the complexities of application processes, however: What will it cost to complete FIH trials within the EU under the guidelines of a CTA compared to the cost of running trials under the guidelines of an IND in the US? Are there differential financial incentives to encourage sponsors to initiate early phase clinical research under a CTA, and how do those incentives compare to incentives that exist to initiate that same research under an IND?

For example, countries within the EU offer a range of distinct incentives to those operating under a CTA (the Netherlands, for example, offers tax incentives, research and development credits, and more),[3] as do some countries outside the EU. In Australia, for example, developers can conduct FIH clinical trials without a US IND and may be able to recoup as much as 43.5% of their clinical research spend in government tax rebates.[4] For a small to midsize company with limited funding, such incentives can make the CTA pathway or an alternative stratagem attractive.

The utility of reciprocity

Under the auspices of the EMA and the FDA, all clinical trials must be conducted in accordance with established GCP guidelines.[1] Accordingly, decision-makers considering whether to initiate FIH studies under a CTA or an IND may see no apparent distinctions from the standpoint of trial conduct. The data from FIH clinical trials taking place under the guidelines of a CTA will be admissible as part of any application to the FDA. Note that a developer seeking approval of a new drug in the US ultimately will be expected to have conducted some later phase trials in the US that involve a representative sample of the US patient population, and an IND would have to be submitted to conduct those trials. Similarly, the data from trials conducted under the guidelines of an IND will be admissible as part of any submission to the EMA or a national regulatory agency in Europe.

The prospect of reciprocity, particularly when combined with cost advantages, may make the CTA path for FIH studies appear more attractive than the IND application path, particularly when the required operational footprint for in country study conduct is considered. A US- or EU-based developer could file a CTA and conduct trials in a location where the cost of conducting a trial is low or where financial incentives offset the operational costs, yielding considerable savings in early-stage development costs.

	United States	Europe
Regulatory Approval Process	FDA requires a 30-day review period for the IND. After 30-day review period, sponsor company can initiate first Phase 1 clinical trial in any or all of the 50 states providing that no hold comments have been received and a "study may proceed" letter is received from the FDA.	Study initiation process is conducted under the European Clinical Trials Regulation (EU-CTR). Sponsor must submit CTA via the Clinical Trial Information System (CTIS). Sponsor selects one member state (MS) to perform functions of reporting member state (RMS), but sponsors can apply for authorizations in up to 30 EU and European Economic Area (EEA) countries at once. RMS will coordinate the review and can take up to 45 days to review a CTA for completeness and prepare an assessment report based on evaluation of scientific, therapeutic, and safety aspects of trial. Sponsor cannot initiate clinical trials until it receives approval for CTA.
IRB/IEC Approval Process	Approval from an institutional review board (IRB) must be obtained for each clinical trial. Clinical trial investigator obtains IRB approval for protocol, informed consent form, etc., related to trial to be conducted at specific study site Investigator submits study protocol and other required documents to his/her local IRB. No timeline for completion of local IRB's review and approval process. Interactions with local IRB through investigator, not sponsor.	Each MS has at least one central Independent Ethics Committee (IEC), approved by competent authority (CA), the regulatory agency/authority, of that country. However, sponsors can now obtain EC approval from each MS where trial is to be conducted through a single application to CTIS. Clinical trial approvals will be released as a single member state opinion following both the CA and IEC assessment per country. Unlike the US, interactions with central IEC are via sponsor, not investigator. Composition and responsibilities of an IEC are similar to those of IRB.

Table 1: Differences between US and EU process of gaining regulatory approvals for initiating clinical trials of a new drug.

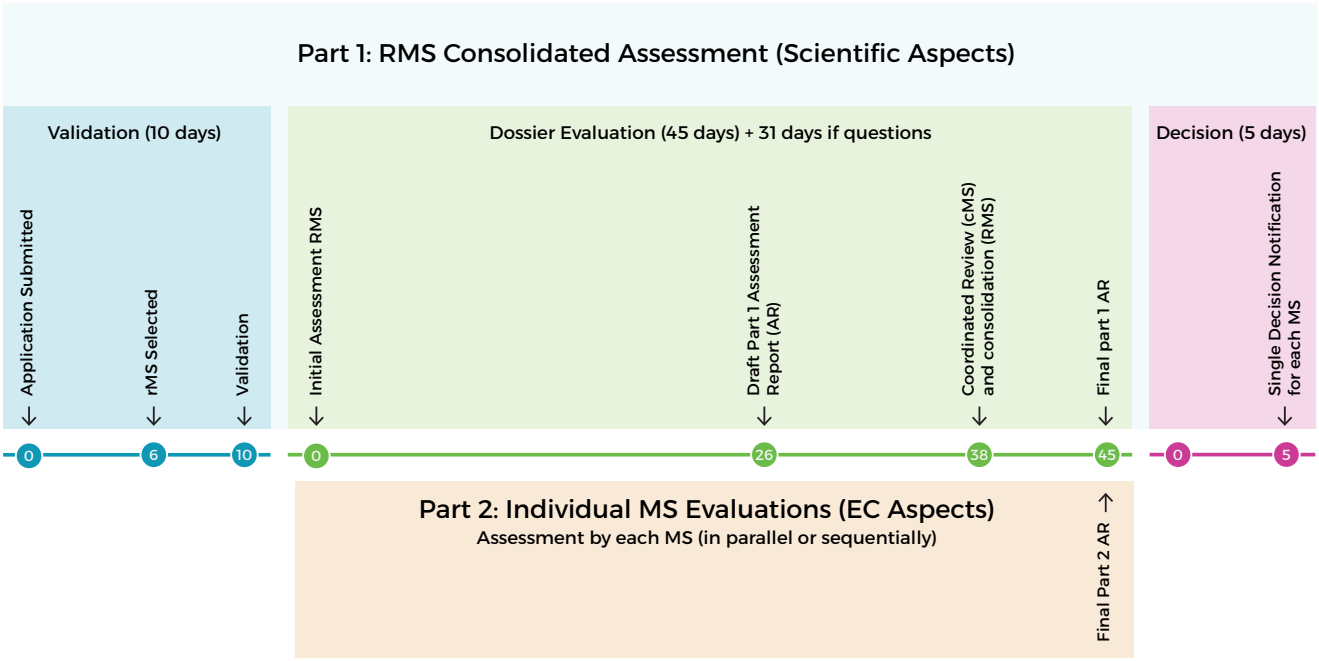

Figure 1: CTA approval timeline

Additionally, a CTA may permit a sponsor to exploit regional expertise or patient availability that would not otherwise be easily accessible in the US, given the competitive environment that often exists in particular therapeutic areas. As long as studies under a CTA are conducted in accordance with GCP principles, the developer would be able to position results in subsequent applications with the FDA — as, for example, when the developer filed an IND to perform a Phase 3 trial in the US. The developer might then complete a New Drug Application (NDA) at a lower overall cost, and shorter overall timeline, than would be incurred if it were to take the IND path and conduct its entire program, including FIH studies, in the US under the auspices of the FDA.

When geography counts

Reducing the calculus to solely one of cost, however, may discount the importance of other considerations. When a FIH study involves patients, as would studies encountered within oncology or with compounds characterized as advanced therapy medicinal products, a study conducted under a CTA in the EU (especially in Eastern and Southern Europe) may offer an advantage due to a generally lower density of clinical trials. Subject matter experts that have a research pedigree comparable to those present within other geographies may be more accessible. This can translate into brisk patient accrual rates, reducing the overall duration of time spent in an early phase trial, while ensuring the integrity of trial data.

A sponsor's site and corporate relationships within the EU are other important factors to consider when weighing the advantages of a CTA for FIH trials in a specific region. Sponsors who conduct their FIH trials locally — that is, in the EU under a CTA for EU-based sponsors or in the US under an IND for US-based sponsors — can benefit from their relationships with investigators and local academic or commercial trial networks. These investigators will be familiar with the local culture and regional standards of care, which may influence the feasibility of trial design and the pragmatics of study conduct specific to each region. In some cases, investors may request that the sponsor conduct its FIH trials locally — even if the cost is higher — because geographic proximity to trial sites will ensure that the sponsor and other stakeholders have better accessibility to the site and a closer control of a study execution.

Finally, if a sponsor's primary intention is to market a drug in the US, even with supporting trial data obtained outside of that jurisdiction, there is value in conducting FIH studies under an IND because the sponsor gains

the ability to engage with the FDA even before starting the clinical trial process to determine possibilities or restrictions regarding product labeling. The IND path enables the sponsor to incorporate the technical, scientific, and clinical oversight gleaned through pre-IND meetings and other methods of regulatory engagement (such as INTERACT, Type C and D meetings under the Prescription Drug User Fee Act [PDUFA VII], and more) into an overall development program that will anticipate the scrutiny expected when the dossier is reviewed for subsequent studies.

For sponsors eyeing future opportunities to market a drug in the US and the EU, these early meetings with the FDA can also offer input and set expectations for next steps, such as the need for a parallel scientific advice meeting where regulators from the FDA and EMA jointly provide input about the drug in development from both agencies' perspective.

For sponsors planning to commercialize a product exclusively for use in the EU, a CTA may be the obvious choice for the same reasons. Comparable early phase scientific advice meetings are also offered by the EMA and member state regulatory agencies (e.g., the IRIS platform).

The de-risking effect of scientific advice

As noted, one reason decision-makers may be inclined to pursue the CTA path is rooted in the cost of developing a new drug, particularly when the FIH studies that are critical to defining product attributes are to be conducted within a single country outside the US. Managing commercial interest within current and realistically anticipated opportunities for future funding is important. A caveat often noted in the forward-looking statements section of biopharma and biotech press releases reminds readers that a drug may falter not because it does not work but because sufficient funding to complete development, clinical trials, and commercialization is not guaranteed.[5-8]

Both the IND and CTA pathways offer innumerable opportunities for accruing a portfolio of scientific advisory opinions (generally consistent, with some exceptions) that can materially enhance the value of an asset in the course of clinical development. Because the IND is product-specific rather than protocol-specific, though, early review and encouragement from the appropriate FDA division carries significant weight within the development community that may view a program through prism of key inflection points. An FDA-vetted discovery/development program bolstered by pre-IND meeting minutes and subsequent FDA engagements may attract considerably more investment attention than a program lacking such input. In an appropriately granular exchange, agreements or deficiencies in chemistry, manufacturing, and controls, safety pharmacology, toxicology, pharmacokinetics/bio disposition, and the proposed FIH study may be vetted. Though input on the envisioned strategic clinical program is often difficult to secure at an early stage, as the agency may regard questions about a proposed program as speculative, the FDA does occasionally opine with sufficient detail to be informative.

With FDA input of this nature, the investment community may be more likely to place a higher valuation on an asset in development that it otherwise might in the absence of such input, as this input can significantly "de-risk" the decision process. This particularly is valuable when there is a lack of regulatory precedent for a proposed clinical indication, as it can increase stakeholder confidence in the developer adhering to projected developmental timelines and estimated expenditures.

An informed early development process facilitates market access

There is an oft-quoted adage that the regulatory authorities dictate approval, physicians dictate adoption, but payers are ultimately responsible for access. The importance of the FDA's comments on program design — accessible within the framework on an IND — is not lost on the payer/provider community, either. If a developer's efforts continue to show promise and continue to have the encouragement of the FDA, demonstrated through appropriately disseminated regulatory exchanges, the payer/provider community will take note and be more likely to recommend — and reimburse — a new drug or device when it becomes available in the US at levels commensurate with the development effort. Frequent interactions with regulatory authorities, whether the EMA or the FDA, particularly in the early stages of drug development, specifically may enable one to deduce likely measures and/or outcomes that should be included within the planned development program, and thus potentially impactful on policy decisions regarding formulary placement and reimbursement.

Summary

Small to midsize pharmaceutical and biotechnology companies frequently must decide whether to conduct FIH clinical trials under the auspices of a CTA, an IND, or under the jurisdiction of another regulatory authority that shares some, but not all, features of each of the application processes. As with most strategic decisions, the process is multivariate, considering timelines, costs, and overall strategic objectives. Provided clinical research is conducted under all jurisdictions under a clinical development program (CDP), data indeed may be fungible.

The unambiguous regulatory advice received in the context of a pre-IND meeting through the use of clearly articulated questions and position statements enables a FIH study to inform development program, as it is product- and not protocol-specific. Comparably structured scientific advice accessible in the EU as a complement to the CTA process likewise facilitates the integration of an international perspective in strategic program development. CTA and IND registration pathways are characterized as different processes with common destinations. Both provide a framework for clinical development that transcends the ability to initiate a single study.

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