REGULATORY COMPARISONS FOR STARTING **FIRST-IN-HUMAN CLINICAL TRIALS**

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INTRODUCTION

Starting human trials of drugs in the EU and UK has become a more complex, resource-driven activity, considering the changes to the clinical trial application (CTA) preparation and submission process in the EU. Additionally, the Medicines and Healthcare Products Regulatory Agency (MHRA) is transitioning to a combined review process that is not fully implemented and therefore submission takes longer. As first-in-human (FIH) trials are the critical first step for the entire evolution of your drug development program, downstream planning and resource allocation depend heavily on the outcome of initial human safety trials.

Health agencies in the developed world are increasingly working together in a spirit of collaboration and innovation, to ensure that necessary medications are available for patients who need them. Reciprocal agreements exist between geographic regions, which facilitates more rapid and efficient global drug development. Generally speaking, these agencies follow technical requirements issued by the International Conference on Harmonisation, or ICH. Regional differences still exist, with each jurisdiction having its own timelines and set of requirements for CTAs.

Sponsors interested in **shortening their timelines by as much as six weeks** relative to the EU, and simplifying their drug development process over the long term, should consider conducting their Phase I research in North America (Canada or the U.S.).

FIH trials conducted in Canada or the U.S. can be used to support regulatory approval in the EU and UK. Depending on the specifics of your program, bridging studies or additional data may be required, which is why we recommend a consultation with Altasciences' experts.

ALTASCIENCES' INTEGRATED SOLUTIONS

We are an integrated CRO/CDMO with decades of drug development experience in North America (Canada and the U.S.). Our in-house, multi-disciplinary team of experts moves in unison, from preclinical studies, formulation and manufacturing, clinical pharmacology, to bioanalysis, to help shorten your FIH timelines, and allow you to make critical go/no-go decisions sooner.

We can support your new drug development with:

- gap analysis of existing preclinical data to the clinical trial application;
- strategic direction and solutions for gaps identified, including regulatory expertise;
- recommendation for whether a North American strategy is beneficial based on your unique program parameters; and
- North American (Canada or the U.S.A.) Phase I study design and conduct, potentially including drug formulation and bioanalytical analyses.

READ ON TO DISCOVER:

- Logistical considerations for timeline efficiencies
- Comparison of process and timeline differences per jurisdiction (EMA, UK, USA, Canada)
- More detailed review of certain key process differences
- Links to government guidance documents
- Additional resources

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LOGISTICAL CONSIDERATIONS SUPPORTING TIMELINE EFFICIENCIES

The EU and UK have reciprocal agreements with Canada and the U.S. so that FIH trials conducted in those countries can be used to support a CTA in the EU and UK. All four regions follow the International Conference on Harmonisation (ICH) M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals guideline, which provides thorough recommendations for the safety evaluation program and data required in ICH countries to enable a FIH trial.

Opposite are the ICH-recommended preclinical studies required to start your FIH trials, and the conditions under which each is required.

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Our experts can help you assess which studies you need to conduct and can provide the study solutions required.

Study Type	Small Molecule	Large Molecule	GLP Compliance Required
Pharmacodynamics			**No**
– *In vitro* (MOA)	x	x	
– *In vivo* (MOA and therapeutic effect)	x	x	
Safety pharmacology			**Yes**
– *In vitro* (concentration-effect relationship)	x	x	
– *In vivo* (dose-response for CNS, CV, respiratory effects)	x	x	
Pharmacokinetics			**No**
– *In vitro* metabolism (across species microsomal metabolism)	x	N/A	
– *In vitro* plasma protein binding	x	N/A	
– Toxicokinetics from repeat-dose GLP toxicity studies	x	x	**Yes**
Genotoxicity battery			**Yes**
– *In vitro* Ames test	x	Not typically required	
– *In vitro* and/or *in vivo* mammalian cell chromosomal damage evaluation	x		
Single-dose/dose range finding			**Yes for MTD**
– Rodent, single-dose (could be MTD study)	x	N/A	
– Non-rodent, single-dose (could be MTD study)	x	x	
Repeat-dose toxicity (duration and dosing route dependent on clinical trial design)			**Yes**
– Rodent, multidose	x	Optional	
– Non-rodent, multidose	x – species selection based on similarity in metabolism to humans	x – species selection based on the presence of the target and relative potency of the drug candidate against the target	
Other safety studies			**Yes**
– Immunotoxicity	x	x	
– Photo safety	x	x	
– Abuse potential (for drugs with abuse potential based on MOA/similarity to known drugs of abuse)	x	x	

Once all your preclinical data is complete, you are ready to submit a regulatory request to start FIH trials. Depending on the specifics of your program and your commercialisation strategy, **up to SIX WEEKS can be saved** by conducting your FIH with Altasciences, in Canada or the U.S.

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SIGNIFICANT PROCESS DIFFERENCES PER JURISDICTION

For a deep dive into the CTA process in the EU and UK, including a detailed review of required documentation and comparisons to the Canadian and U.S. requirements, watch this presentation recorded in Cambridge, UK, in late 2023:

Review of Regulatory Landscape and Strategic Considerations

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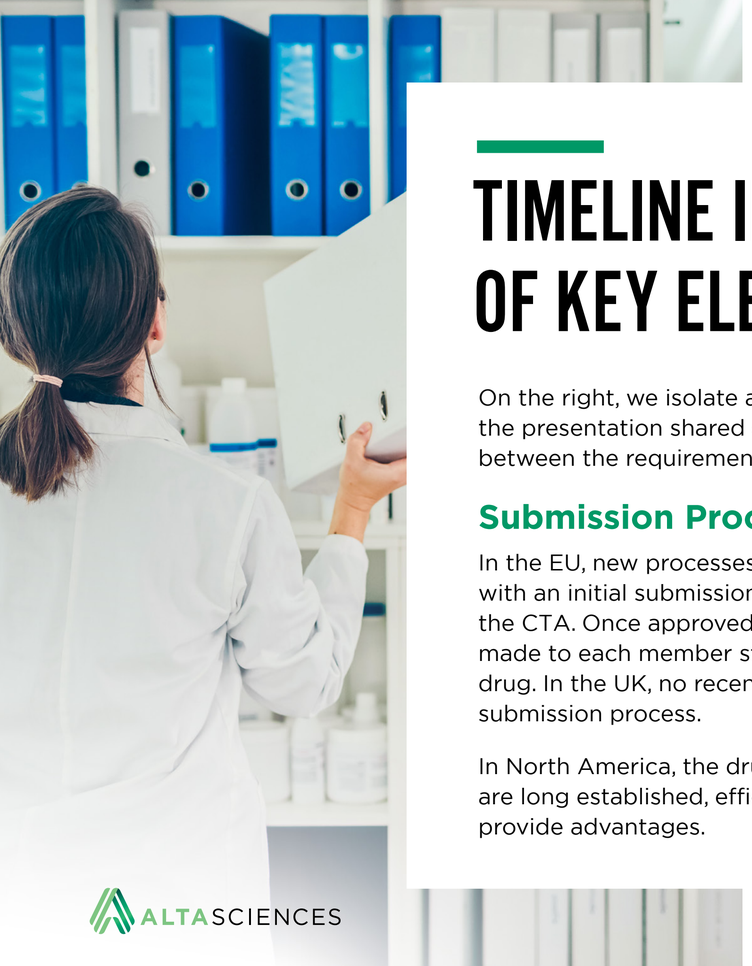
EMA—CTA	UK—CTA	FDA—IND	HC—CTA
Principle – A single CTA must be submitted to all MSCs (Member State Concerned) with harmonised dossier via the EU Clinical Trial Information System (CTIS) portal.	**Principle** – A single CTA per trial must be submitted to the MHRA and REC (Research Ethics Committee) via the UK HRA Integrated Research Application System (IRAS) portal.	**Principle** – A complete IND must be filed per product development program, submitted via portal or physical copy on DVD.	**Principle** – A CTA must be filed for each individual trial, submitted via email.
Review Time – 60 days for CTA (Part I and II) without any issues – 75 days for CTA (Part I and II) with validation issues – 91 days for CTA (Part I and II) with Requests for Information during the assessment – 106 days for CTA (Part I and II) with validation issues and Requests for Information during – Assessment (* + 50 days for ATMPs or biologics for the purpose of consulting with experts) – Request for a response extension is not allowed; standard response time is 12 days	**Review Time** – ~ 1 week for validation – 30 calendar days for initial outcome and RFI issued – 14 calendar days for applicant response to RFI – 16 calendar days for final outcome to be issued – 14 calendar days for applicant response to GNA	**Review Time** – 30-day default review for initial IND filing – Sponsor response to information requests to deficiencies identified by FDA are reviewed for an additional 30 days.	**Review Time** – 30 calendar days formal review for most trials – 7 calendar days administrative review for eligible comparative BA/BE studies (by policy) – Information requests–respond within 2 calendar days (extension request is permissible if granted)
Review Decision: – Acceptable – Acceptance subject to specific conditions – Refusal (not acceptable)	**Review Decision:** – Acceptance – Acceptance subject to conditions – Grounds for non-acceptance	**Review Decision:** – Safe to Proceed letter for initial IND (usually) – Clinical hold (undefined period, depends on response to information requests)	**Review Decision:** – NOL (No Objection Letter) – Withdrawal without prejudice – NSN (Non-Satisfactory Notice)
EMA CTA Application Content (CTD Modules 1-5)/Divided in Two Parts – Part I contains scientific and medicinal product documentation: application form, protocol, cover letter, investigator's brochure (IB), GMP documentation, IMPD/Auxiliary medicinal product dossier, scientific advice, EU pediatric investigation plan (PIP) decision, example of investigational and auxiliary medicinal product labelling. – Part II contains the national and patient-level documentation: informed consent form and subject information leaflet, compensation arrangements, suitability of investigators and facilities, proof of insurance or indemnification, data protection rules, and proof of fee payment. Note: Precise content will be determined by each member state (e.g., QP Declaration)	**CTA Content** – Online IRAS application form – Cover letter – Protocol – Participant information sheet and informed consent form (PIS-ICF) and other patient-facing docs – IB/SmPC – IMPD and other GMP-related doc (e.g., manufacturer and import licenses, GMP certs, QP declaration(s)) – Label content for IMP(s) – Proof of insurance – Investigator CV/suitability – Site suitability docs – Copies of any scientific advice letters/PIP decisions	**IND Content** – Parts 1 to 10 or CTD Modules 1-5 (forms, protocol, IB, all pharmacology/toxicology, and clinical reports must be submitted). – Summaries (CTD module 2) are usually included for Phase II/III trials and are optional. – Full CMC required – Final audited preclinical reports required	**CTA Content** – Module 1: forms, protocol, submission rationale, IB, informed consent forms (ICF) – Module 2: quality overall summary (QOS) or IMPD – No preclinical reports are required
Annual Report – Development Safety Update Report (DSUR)	**Annual Report** – DSUR	**Annual Report** – DSUR	**Annual Report** – Not required



TIMELINE IMPACT OF KEY ELEMENTS

On the right, we isolate and compare some key topics from the presentation shared on the previous page, to distinguish between the requirements of each jurisdiction more easily.

Submission Process

In the EU, new processes involve a centralised online portal, with an initial submission to one member state for approval of the CTA. Once approved to proceed, individual submissions are made to each member state where you intend to market your drug. In the UK, no recent changes have been applied to the submission process.

In North America, the drug development process and timelines are long established, efficient, and well understood, which can provide advantages.

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Submission Principles

EU	UK	U.S.	CANADA
A single CTA must be submitted to all MSCs with harmonised dossier via the EU CTIS portal.	A single CTA per trial must be submitted to the MHRA and REC via the UK HRA IRAS portal.	A complete IND must be filed per product development program, submitted via portal or physical copy on DVD.	A CTA must be filed for each individual trial, submitted via email.

In the EU and UK, submission of a CTA is via an online portal. In Canada, the application is submitted via email in non-eCTD format or a portal (CESG) for eCTD format.

Timelines for Initial Review

EU	UK	U.S.	CANADA
60 days for CTA (Part I and II) if no issues	~1 week for validation and 30 calendar days for initial outcome and issuing if the RFI	30-day default review for initial IND filing	30 calendar days for formal review for most trials and 7 calendar days for administrative review for eligible comparative BA/BE studies

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Response Extension Requests Permitted

Not all CTAs are processed immediately; it is not unusual for regulatory agencies to require additional information. Different situations may arise, and all agencies have a prescribed timeline for exchanges of information with drug development sponsors. Generally, the timeline for information requests is between 12 days and four weeks; in Canada, it is two calendar days. Canada is currently the only regulatory jurisdiction where an extension request will be considered.

In Canada, given the very short window for response, an extension can be requested by the sponsor, to ensure they have sufficient time to obtain the information. The short extension must be granted by Health Canada; if timelines do not allow, they do not permit the extension.

Under the **EU** process, if the sponsor does not respond in time, tacit abandonment of the file is considered to have occurred. By the same token, if the regulatory agency does not make a request for additional information in time, tacit approval is granted for the application.

In the **UK and U.S.**, per regulations, timelines are established in a manner that does not allow a request for an extension. As for the FDA specifically, in case of a clinical hold, the applicant will have sufficient time to prepare the answers to address the FDA's questions. This response will undergo another 30-day review, after which the FDA will render a decision on lifting the clinical hold.

Required Documentation for Your CTA Submission

The basic documentation requirements are similar, but not identical, between agencies (see Table on page 4). For example, in **Canada**, your CTA will consist of a single submission per individual trial, without full CMC (for Phase I) or preclinical reports, meaning that you can start quickly, and end a program with relatively low risk. CMC is summarised in a Quality Overall Summary (QOS) and preclinical data is detailed in the IB.

The **U.S.** FDA requires submission of the protocols for all the anticipated IND trials at the same time, including full CMC, draft toxicology reports, and SEND data—a significant time and resource investment. After approval of the IND, it can be amended to add additional study protocols or CMC information; however, these modifications require additional time.

In the **EU**, the initial submission to the Reporting Member State (RMS) is data and document-heavy, and once approved, an additional full submission per country may be required; and these may vary slightly per country. Responses and exchanges may happen with one or more of those additional countries, resulting in a significant administrative burden of managing documents, versions, correspondence, etc.

In the **UK**, a single CTA is submitted to the UK Health Regulatory Authority (HRA) via the Integrated Research Application System (IRAS) portal.

See **Table on page 4** and the webinar **Review of Regulatory Landscape and Strategic Considerations** for complete and detailed information on regulatory submission inclusions.

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REGULATORY GUIDANCE DOCUMENTS

Health Canada

- Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications
- Guidance Document - Quality (Chemistry and Manufacturing) Guidance: Clinical Trial Applications (CTAs) for Pharmaceuticals

U.S. FDA

- Investigational New Drug (IND) Application
- CFR - Code of Federal Regulations Title 21

European Medicines Agency (EMA)

- Revised Guideline on First-in-Human Clinical Trials
- Marketing Authorisation

UK

- MHRA Guidance for Industry

CONCLUSION

Thorough understanding of the regulatory requirements for each health authority is key to successful drug development. Early preparation and strategic planning help with appropriate resource allocation, and facilitate the efficient preparation of clinical trial applications, adapted to your unique program needs and marketing objectives.

Altasciences' mission is to apply our integrated, full-service drug development solutions to help get better drugs to those who need them, fast—without compromising on safety and quality. We can help you leverage the collaborative nature of the four Health Authorities to permit use of the same clinical trial data, avoiding duplication of efforts and saving development time.

Additional Resources

Podcast

- The Benefits of Conducting Clinical Trials in Canada

Webinar

- Review of the Current Regulatory Landscape and Strategic Considerations
- Determining the Right Regulatory Pathway for Your Drug
- A Hop Across the Pond: The Many Advantages of Conducting Early Phase Clinical Trials in North America

***The Altascientist:* Scientific Journal**

- The Advantages of Conducting Early Phase Clinical Research in Canada

ABOUT ALTASCIENCES

Altasciences is a forward-thinking, mid-size contract research organisation offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions.

Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customisable to specific sponsor requirements.

Altasciences helps sponsors get better drugs to the people who need them, faster.

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