

## US vs. EU: Differences in Initial Regulatory Applications for Phase 1 Studies

Requirements	US (FDA)	EUROPE (EMA)
<b>Laws &amp; Regulations</b>	<p>CFR Title 21 Food &amp; Drugs</p> <ul style="list-style-type: none"> <li>Part 312: Investigational INDs (IND)</li> <li>Part 314: New Drug Applications (NDA)</li> </ul>	<ul style="list-style-type: none"> <li>Directive 2001/83/EC (Medicinal Products)</li> <li>Directive 2001/20/EC (Clinical Trials)</li> <li>Each country must adopt laws and regulations to comply with the EU Directives</li> </ul>
<b>Application Required for Investigational Trial</b>	<p>Single Initial IND Application per Phase 1 Indication</p> <ul style="list-style-type: none"> <li>IND remains open</li> <li>New protocols for same indication sent as amendments to IND</li> <li>No application fee</li> </ul>	<p>Usually one (1) CTA for each study</p> <ul style="list-style-type: none"> <li>CTA submitted to the Competent Authority of the Member State</li> <li>EudraCT - Sponsor must register (database of trials occurring in Europe)</li> <li>Minor application fee</li> </ul>
<b>Pre-Application Meeting with Regulators</b>	<ul style="list-style-type: none"> <li>In the US, Sponsors can obtain scientific and regulatory advice on their IND package through a pre-IND meeting</li> <li>US regulators will provide feedback on their expectations for toxicology study designs as well as contents of the regulatory submission package (CMC, Clinical Protocol)</li> <li>This interaction will provide important information and will guide the development process in the US</li> </ul>	<ul style="list-style-type: none"> <li>There is a mixed response from the EU agencies with regard to meeting requests, and there are no meetings to obtain “buy in” with regard to the developmental path forward as there are in the US. Therefore, there is an expectation that sponsors closely follow ICH Guidance documents</li> <li>Strict scientific advice may be obtained at cost through the national regulatory agencies. Note, that these agencies are not responsible for making a decision on the Marketing Application.</li> </ul>
<b>Regulatory Timelines*</b>	<p>IND Review Time</p> <ul style="list-style-type: none"> <li>Study may begin 30 days from submission of IND unless notified by FDA of “clinical hold” (default system)</li> <li>IND Amendments: study could legally begin right away, but some sponsors wait 30 days for potential issues</li> <li>IND Annual Reports required</li> </ul>	<p>EU Directive</p> <ul style="list-style-type: none"> <li>Maximum of 60 day review period but generally shorter for Phase 1 studies</li> <li>Each country may set shorter timelines (BE and NL with parallel EC/CA submissions may receive approval within 15 days; FR is about 4 weeks (Phase I only))</li> </ul>
<b>Ethics Committee (EC) Review Timeline</b>	<p>Varies; depends upon the site:</p> <ul style="list-style-type: none"> <li>Phase 1 Unit: Healthy Volunteers: 1-2 weeks</li> <li>Clinical Trial Sites: 2-4+ weeks</li> <li>Academic Site: 2-8 months</li> </ul>	<ul style="list-style-type: none"> <li>Phase 1 Healthy Volunteer: 14-21 days (by law they have up to 60 days)</li> <li>Process is even longer than 60 days for gene therapy and somatic cell therapy</li> <li>The EU Directive has regionalized ECs within each of the EU member states, but it is still necessary to obtain local review and approval at the institution where the clinical study will take place (and this can only occur after EC approval has been obtained)</li> </ul>

\*Please note that these timelines/guidelines generally apply to drugs only; some biologics including gene therapy and somatic cell therapy products require additional review by other boards in the EU (but not in the US) (timelines up to 180 days) AND some countries have additional review boards with non-regulated timelines.



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<b>Toxicology</b>	<ul style="list-style-type: none"> <li>• Single-dose acute toxicology studies in two mammalian species</li> <li>• Repeated dose studies in two mammalian species (one rodent, one non-rodent) are often required</li> </ul>	
<b>Duration of Clinical Trials</b>	<b>Minimum Duration of Repeated Dose Toxicity Studies</b> <div style="display: flex; justify-content: space-around;"> <span><b>Rodents</b></span> <span><b>Non-rodents</b></span> </div>	
<b>Single Dose</b> <b>Up to 2 Weeks</b> <b>Up to 1 Month</b> <b>Up to 3 Months</b> <b>Up to 6 Months</b> <b>&gt; 6 Months</b>	2 Weeks** 2 Weeks** 1 Month 3 Months 6 Months 6 Months	2 Weeks 2 Weeks 1 Month 3 Months 6 Months Chronic
<b>Reproductive Toxicology Studies</b>	Not required before Phase 1 with appropriate precautions (use of contraception)	Assessment of embryo-fetal development required before Phase 1 if women of child-bearing potential are to be enrolled
<b>GMP Requirements</b>	Recent draft guidance released by FDA on 12 January 2006 referenced changes to the direct final rule of 21 CFR Part 211 which exempts most investigational “Phase 1” drugs from complying with GMP requirements	Must comply with GMP requirements

\*\* In the US, as an alternative to 2 week studies, single dose toxicity studies with extended examinations can support single-dose human trials