Performing Phase I Clinical Trials of Anticancer Agents: Perspectives from within the European Union and Japan

Martin D. Forster¹, Nagahiro Saijo², Lesley Seymour³, and Hilary Calvert¹

Abstract

Drug discovery and early clinical development is an international endeavor, conducted in partnership between commercial entities such as biotechnology and pharmaceutical companies and academic investigators. Although once considered quite disparate, early clinical trials requirements and conduct are largely harmonized between the European Union, Japan, and the United States, increasing the opportunities for productive commercial-academic collaborations. Clin Cancer Res; 16(6); 1737–44. ©2010 AACR.

Cancer drug discovery and development is an international activity. Many of first-in-human studies of anticancer drugs are conducted in two sites in different countries, usually in North America (United States or Canada) and the other in Europe. Additional phase I studies including Japanese patients are often required for later marketing approvals in Japan. Phase I capabilities exist worldwide, including Australia, Asia, and South America. Although there are differences in attitudes between different countries in general, the concerns and approaches of phase I investigators are similar across the world. In particular there is emphasis on trial designs that minimize the number of patients treated with ineffective doses and maximize the possibility of eliciting therapeutic signals. We summarize here early clinical trial activities in Europe and Japan, highlighting key opportunities and challenges as part of this issue of CCR Focus, which examines the phase I clinical trial process (1).

European Union

In terms of organization, there is no overarching organization for European countries or even for one individual country. Rather, the tendency has been for potential sponsors to negotiate individually with individual centers. This has led to the focusing of many studies in relatively few centers where the expertise and the reputation for the conduct of these studies have been established. Of note, privately owned and commercially operated phase I clinical trials centers are emerging in Europe.

Marketing approval for new drugs within the European Union is the responsibility of the European Medicines Agency, which is a decentralized body of the European Union with headquarters in London. The agency is responsible for the scientific evaluation of applications for European marketing authorization for medicinal products using a centralized procedure. Companies submit a single marketing authorization application to the agency. Once granted by the European Commission, this authorization is valid in all European Union (EU) and EEA-EFTA states (Iceland, Liechtenstein, and Norway). In contrast, approval for clinical trials of new agents is the responsibility of each member state, with each country providing its own regulatory authority.

First in human trials are clinical experiments and are therefore governed by a number of regulations and guidelines. Patients who participate are given an intervention that they would not normally receive, with an unknown efficacy and toxicity profile, and often undergo additional clinical assessments and tests. It is therefore essential to protect their safety and well being, which is the primary role of the regulatory guidelines. Adherence to these guidelines is particularly relevant in phase I studies, in which the investigational medicinal product may have been administered to few, if any, humans previously. The regulations also aim to ensure that the clinical trial data produced are robust and accurately represent the activities of the Investigational Medicinal Product (IMP).

The first internationally recognized guidelines were the Nuremberg Code, developed in 1948, following the inhumane experimentation on subjects without appropriate consent during the Second World War (2). The Nuremberg Code formed the basis for the Declaration of Helsinki, first declared by the World Health Authority in 1964, which has undergone a number of subsequent revisions (latest in 2008: ref. 3). All clinical studies need to follow its guidelines, although it is not legally binding in international law, and it has formed the backbone to the Code of Federal Regulations (title 45, volume 46) in the United States (4) and the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) guidelines.

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International conference on harmonization

In 1996, the ICH guidelines were developed, in an attempt to harmonize the requirements for registering medicines across the European Union, the United States, and Japan and to allow data produced from one country to be accepted by another (5). The tripartite guidelines expand on the Declaration of Helsinki to advise on quality, efficacy, patient safety, and other miscellaneous aspects of clinical research. They focus on the core principles of Good Clinical Practice (GCP), which cover trial design, conduct, and analyses, with strict pharmacovigilance and thorough informed subject consent (6). Quality topics describe IMP production and evaluation to Good Manufacturing Practice (GMP) and there are extensive guidelines on preclinical safety evaluation and the training and responsibilities of trial staff. ICH GCP provides international guidelines to standardize the conduct of clinical trials, but their implementation has been variable between different researchers and countries.

EU clinical trials directive

The variability in interpretation of ICH GCP led the European Union to develop the EU Clinical Trials and GCP Directives (2001/20/EC and 2005/28/EC, respectively), implemented from 2004. The directives formed a legal framework for clinical trial research, including phase I trials, and required incorporation into the legal systems of member states.

Directive (7) includes 24 articles required to be met, covering core areas including:

- The safety and well-being of clinical trial subjects,
- The procedures for independent ethical committee review and approval,
- The procedures to give regulatory approval before a trial starts recruitment,
- The procedures for authorities to inspect trial conduct to GCP standards,
- The standards for the manufacture and handling of IMPs,
- The procedures for reporting and processing adverse events.

In common with other EU directives, the Clinical Trials Directive (CTD) provides the principles, which are interpreted and converted to law separately by each member state. The interpretation and incorporation by individual states may be influenced by other laws already in place, such as the EU Data Protection Directive (95/46/EC). In addition subsequent rulings in individual states may also affect the implementation of the directive. An example would be the Human Tissue Act introduced to the United Kingdom in 2004 for studies involving clinical samples. This act was introduced following an event in which tissues and organs of children who had died were retained without parental consent, resulting in a very high-profile scandal featured in the media. The result is a series of stringent measures to control the acquisition, storage, and experimentation on human tissues of all kinds.

Differences in the existing national legislation and differing legal concerns within the different member states of the EU mean that cost, timelines, ease of setting up, and the conduct of new studies may vary significantly between different countries.

Trial set up and approval. ICH and EU CTD advise about preclinical evaluation and regulatory toxicology assessments following which a phase I protocol can be developed. An IMP dossier is also required, outlining the quality, safety, and use of IMPs in the study. This dossier forms the EU equivalent to the Investigational New Drug (IND) application required in the United States (requirements for the latter are discussed in this issue of CCR Focus; ref. 8). In parallel with the Investigational Medicinal Product Dossier (IMPD), an Investigator’s Brochure (IB) is required, which outlines all available preclinical and clinical data (6). Both the U.S. Food and Drug Administration (FDA) and Committee for Human Medicinal Products and competent authorities from each individual European country are available for consultation to discuss development strategy and the pathway to registration for an IMP.

Regulatory authorization. As noted above, each country has its own regulatory authority, such as the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom or the Ministry of Health in Italy and Germany, responsible for allowing a study to be conducted. Application requirements to gain regulatory approval differ a little between EU countries but the core documents for a Clinical Trial Application (equivalent to IND application in the United States) are listed in Table 1 (9), and regulatory approval is required for each country involved. EU regulatory authorities aim to assess applications within 30 days, extended up to 60 days if further details are required. The trial is then able to be registered onto an international clinical trials register, such as ClinicalTrials.gov.

Table 1. Europe: example of documents required for a clinical trial application

<table>
<thead>
<tr>
<th>Clinical Trial Application required documents</th>
</tr>
</thead>
<tbody>
<tr>
<td>EudraCT number</td>
</tr>
<tr>
<td>IB</td>
</tr>
<tr>
<td>IMPD</td>
</tr>
<tr>
<td>IND application (in the United States) if available</td>
</tr>
<tr>
<td>Information of investigators, recruiting sites, and analysis laboratories</td>
</tr>
<tr>
<td>Details of drug manufacturing and distribution</td>
</tr>
<tr>
<td>Trial production and sample consent form</td>
</tr>
<tr>
<td>Completed application form</td>
</tr>
<tr>
<td>Information from independent ethics committee</td>
</tr>
<tr>
<td>Fee</td>
</tr>
</tbody>
</table>

NOTE: From the Medicines and Healthcare products Regulatory Agency (9).
Although the authorization for clinical trials is done at a national level, all European Clinical IMP trials are required to be issued with a EU Drug Regulating Authorities Clinical Trials (EudraCT) number, which is issued by the European Medicines Agency (10).

EudraCT is the European Clinical Trials Database of all clinical trials commencing in the European Union from May 1, 2004 onwards. The EudraCT database was established in accordance with Directive 2001/20/EC. Each clinical trial with at least one site in the European Union receives a unique number for identification, the EudraCT number. The EudraCT number must be included on all clinical trial applications within the European Union and as needed on other documents relating to the trials (e.g., suspected unexpected serious adverse reaction reports).

**Patient information and consent.** There is strong emphasis on the protection of clinical trial patients in ICH GCP and EU CTD, leading to the generation of patient information sheets, which extensively explain the rationale of the study and possible risk of harm from the therapy. Although written in plain language these are often long and require careful explanation and time allowed to the subject for consideration, prior to informed consent being given. Patient information sheets may be required in multiple languages and within the European Union are submitted, along with the trial protocol, for independent ethical approval.

**Independent ethical review.** Ethical review is required to be done by an independent committee, but procedures depend on the number of sites involved and differ in different EU states. A single-center study may be reviewed by a local committee, whereas a national review may be possible in some countries (such as the United Kingdom or the Netherlands). A committee with particular expertise may be required for phase I trials and additional expert opinion may also be required if vulnerable adults and/or children are involved. This independent review differs from the Institutional Review Board (IRB) review required for trial registration within the United States. An ethics committee has a 60-day time limit to approve or decline a study, but applications may occur in parallel with the assessment of the scientific merit of the study and therefore need not add a time delay to trial initiation. It does, however, often allow easier subsequent amendments to be accepted either by chairman's review or formal committee reassessment.

In the United Kingdom, the Integrated Research Application System form has recently been introduced in an attempt to reduce the trial administrative burden. The regulatory applications are centralized to a single electronic form minimizing repetitive core data entry. Also in the United Kingdom, studies involving biomarkers on clinical samples are also required to comply with the Human Tissue Act. A Case Report Form is developed to gather data relevant to the study and individual site assessments, agreements, and approvals obtained prior to patient recruitment.

**Trial conduct and completion.** The ICH guidelines define GMP quality IMP production for clinical use and handling during trial evaluation (11). The procedures for drug labeling, supply, and distribution require implementation by sponsors, and differ between the European Union and United States. The EU regulations require a manufacturing authorization for the manufacturer or importers of an IMP, and one or more "qualified person(s)" to undertake responsibility for the quality assurance of each batch of unlicensed product. The qualified person needs to be based in the European Union and is therefore generally independent of the sponsor, who is able to do this role within the United States.

ICH GCP defines the documentation required to be collected in trial files, but there are several systems accepted for data storage, and the level of data monitoring and source data verification varies between studies in the European Union as it also does in the United States. Efforts to ensure data quality have been steadily increasing in all academic centers (12). Database systems validated in the European Union offer centralized statistical monitoring and automated data validation. These systems are often used in academic studies, thus requiring reduced source data verification thereby reducing monitor time and saving expense. Pharmaceutically sponsored studies often extensively monitor source data entry at added significant expense.

The EU CTD requires countries to have a system to independently inspect sponsor or participating trial institutions by regulatory bodies. Routine inspections can be preplanned or can be triggered by specific safety concerns. The EU CTD also allows for "urgent safety measures" to be taken by the sponsor before regulatory review if there are serious safety concerns.

A system for identifying and reporting adverse events is required by the EU CTD. Toxicity grades are usually standardized by the use of the CTCAE grading system and procedures, and reporting timelines are similar across the United States, the European Union, and Japan. The EudraVigilance Database contains safety data about all IMPs in EU clinical trials allowing information to be exchanged more easily between participating countries (13).

**Acquisition of drugs**

The advances in biology and in particular the advances in the understanding of the molecular biology of various different types of cancer have led to an exponential increase in the number of interesting anticancer targets for drug design. The concurrent advances in analytical technology, antibody development, and medicinal chemistry have enabled the discovery of agents with potential activity against these targets at an unprecedented rate. Potential new anticancer drugs are being developed by large pharmaceutical companies, smaller biotech companies, and academic groups, often supported by charitable funding. This increase in available agents has also led to efforts to improve clinical trial design to maximize efficiency and to
throughput directly to sponsors. This evolution led to a gradual reduction in the number of new agents being available to the cooperative group, which eventually led the EORTC to focus on its highly successful phase III programs.

This pattern is now common in most European countries. There a large number of capable and active phase I centers in most European countries that are negotiating and conducting trials on a case-by-case basis with the sponsors, most of whom are pharmaceutical companies. Many of the previously Eastern European countries now have expanding and robust clinical trials activities and compete effectively with the longer established Western European operations. Some of the better known organizations are highlighted below and play a valuable role in coordinating activity and providing a collaborative and educational platform. Much of the actual phase I–II activity, however, takes place by direct negotiation of the sponsor (or Clinical Research Organization) with the centers.

**Cancer Research UK (formerly Cancer Research Campaign – UK).** In 1981 the Cancer Research Campaign set up a phase I committee of oncologists with an interest in early studies of investigational cancer agents with translational scientists, chemistry and formulation expertise. This group gradually transformed into the Cancer Research UK Drug Development Office and a funding committee called the New Agents Committee. The New Agents Committee is able to consider drug candidates at any stage of their development and can organize and fund bulk synthesis, formulation, and toxicology as well as phase I–II clinical trials. Phase I clinical trials are managed by the Drug Development Office, which can handle all the requirements for a GCP trial, including sponsorship, monitoring, and reporting. This is an unusual, if not unique facility, because it can take a drug from concept stage to clinical trial entirely within the charitable and/or academic arena. It has been instrumental in developing a number of

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**Table 2. Factors contributing to “Lag” for approval of new oncology therapeutics in Japan**

<table>
<thead>
<tr>
<th>Stage in approval process</th>
<th>Causes of delays</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in the start of development</td>
<td>Concerns about cost and delays</td>
</tr>
<tr>
<td></td>
<td>Requests for additional data unique to Japan</td>
</tr>
<tr>
<td></td>
<td>Slow review and/or consultation times</td>
</tr>
<tr>
<td></td>
<td>Preference for positive phase II data prior to initiating</td>
</tr>
<tr>
<td>Prolonged trial conduct</td>
<td>Lack of protected time for clinical research, high clinical workload</td>
</tr>
<tr>
<td></td>
<td>Lack of reimbursement and/or recognition for investigators</td>
</tr>
<tr>
<td></td>
<td>Inexperience in clinical research, limited support staff</td>
</tr>
<tr>
<td></td>
<td>Infrequent IRB meetings</td>
</tr>
<tr>
<td></td>
<td>Additional paperwork and/or requirements unique to Japan (J-GCP)</td>
</tr>
<tr>
<td></td>
<td>Patient reluctance (strong national healthcare system; concerns about safety; negative media releases; expectations about a positive outcome)</td>
</tr>
<tr>
<td>Prolonged J-NDA review</td>
<td>Limited number of reviewers</td>
</tr>
<tr>
<td></td>
<td>Inconsistency in reviews and/or requirements</td>
</tr>
</tbody>
</table>

Abbreviations: J-GCP, Japan Good Clinical Practice; J-NDA, Japan New Drug Application.

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understand whether the presumed drug target has been affected (14, 15).

Numerically by far the largest proportion of new drugs undergoing phase I trials are sponsored by the pharmaceutical industry, but some notable drugs have had their origins in academic institutions. Examples are carboplatin (Institute of Cancer Research (ICR) and Bristol-Myers Squibb), raltitrexed (ICR and AstraZeneca), and temozolomide (University of Aston and Schering Plough).

**Phase I trials groups and networks**

Working under the regulatory framework outlined above, a number of different organizations have been set up to conduct or promote the trials of innovative new cancer agents within the EU countries. The list below is not a comprehensive list, as many countries have phase I capabilities or networks, including Germany, Scandinavia, and Italy.

**European Organization for Research on the Treatment of Cancer.** Anticancer drugs of the 1970s and 1980s were usually toxic and expertise in the conduct of phase I studies with them was confined to a few centers. The Early Clinical Trials Group of the European Organization for Research on the Treatment of Cancer (EORTC) was very successful in bringing European expertise together and formed a valuable point of contact for the pharmaceutical industry. This group (which later became the Early Clinical Studies Group) conducted a large number of phase I trials on agents that are now in common use. However changes in the environment eventually led to the disbandment of this group in 2004. As oncology products became mainstream, the pharmaceutical industry acquired in-house expertise in conducting these trials. A number of centers developed a high level of specialization in phase I cancer trials and therefore could offer local expertise and a high throughput directly to sponsors. This evolution led to a
licensed drugs, including temozolomide (16). The conduct of early clinical studies in cancer in the United Kingdom has also been greatly facilitated by the Experimental Cancer Medicine Network (17), which provides competitively allocated infrastructure funding to 19 centers around the United Kingdom.

However, it has become increasingly expensive to set up and conduct clinical trials, including early phase trials, largely owing to increased regulations and governance responsibilities. Phase I trial design has also evolved, expanding beyond simple toxicity evaluation to include multiple, often expensive, secondary and exploratory endpoints including predictive biomarkers, pharmacodynamic markers to show target inhibition in tumor or surrogate tissue, and preliminary efficacy outcomes. This means that the budget available to organizations such as CR UK will support far fewer trials than it would before the current regulations came into force. Similar budgetary considerations also apply to Clinical Development Partnerships (see below), which means that there are many interesting and potentially valuable new agents for which the clinical trials cannot be done.

The extraordinary success of modern drug development techniques, coupled with the increasing cost and complexity of clinical development, has resulted in many pharmaceutical companies having more promising agents in their pipeline than they have resources to develop. Acquisitions and mergers between these companies compound the situation often resulting in the pipelines of the merged company having several representatives of each class of drugs. The fact that many potentially useful drugs do not undergo clinical development is a potential loss to the oncology patient, because it is frequently not possible to make an accurate judgment of the clinical utility of a new agent without clinical data. Cancer Research UK Clinical Development Partnerships are designed to address this problem by offering to undertake early clinical development at the expense of CR UK. The collaborating company has an option to continue development with the drug if it looks successful in exchange for a revenue sharing agreement (18).

Southern Europe New Drug Organization. Southern Europe New Drug Organization (SENDO) was founded in 1997 to promote and coordinate transnational research and early clinical trials in Southern Europe with the aim of boosting research on new anticancer drugs using modern up-to-date methodology. It is a not-for-profit organization with centers in Switzerland, Italy, and Barcelona. It has all the expertise necessary for early clinical cancer drug development and a good network of collaborators for preclinical development (19).

Central European Society for Anticancer Drug Research. Central European Society for Anticancer Drug Research
(CESAR) was founded in 2001 with a focus on research into identifying new anticancer agents, the development of new agents, and fostering the translation of laboratory research into the clinic. CESAR comprises scientists from basic research and preclinical and clinical oncology in Austria, Germany, and Switzerland. In addition, the CESAR has created a network of study centers experienced in oncology of solid tumors in a number of Central and Eastern European (CEE) countries with the aim to foster international cooperation between oncologists and study centers in this area. CESAR has a portfolio of phase I and translational studies open and organizes meetings to promote and coordinate research (20).

Phase I–II cancer trials in France. The French National Federation of Cancer Centers has established a group (“Essais précoces”) coordinating early phase cancer trials in a number of French centers. The Institut National du Cancer (INCa) has also set up an agreement with U.S. National Cancer Institute Cancer Therapy Evaluation Program (CTEP) permitting a number of French centers to be selected for phase I–II trials sponsored by CTEP. The new French Cancer Plan has identified a need to establish a funded network of cancer centers for phase I–II trials.

Phase I–II cancer trials in Spain. There is substantial amount of phase I activity in Spain but no single overarching organization. A number of Spanish centers undertake a significant number of phase I trials and some of them receive governmental support as part of the Cooperative Network of Cancer Centers.

Phase I–II cancer trials in Switzerland. Within the SAKK group (the Swiss national group for clinical studies in cancer) there is an independent phase I group.

Japan

Despite Japan’s leadership role in basic research and discovery, its prominence in early clinical research is less established, although separate trials have often been required because of the differing pharmacology of drugs in Asian patients. In recent years polymorphic variations in proteins involved in drug clearance have been identified that begin to explain these differences (21). Marketing

<table>
<thead>
<tr>
<th>Study component</th>
<th>Requirements</th>
<th>Japan</th>
<th>EU</th>
<th>United States</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical data and starting dose</td>
<td>ICH Guidelines for safety (S3, S4, S6, S7, S9, M3)</td>
<td>In Japan, ICH S9 is at Step 4; May use data from other phase I studies; level at which no DLT reported. If no ethic difference in metabolism and/or safety suspected, phase I data from other countries may be acceptable to support phase II studies</td>
<td>One species (rodent) acceptable</td>
<td>Two species (one nonrodent) required</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>ADME defined, Assays developed and available</td>
<td>Required</td>
<td>Desirable</td>
<td>Desirable</td>
</tr>
<tr>
<td>Facilities and Personnel</td>
<td>Adequate knowledge of preclinical data, Investigators knowledgeable in clinical pharmacology and oncology therapy, Number of centers, single center preferred; if multicenter, good communication channels must be in place</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>Usually cancer patients unless minimal toxicity (volunteers may be acceptable); Patients with poor performance status (ECOG 3 or 4) excluded, No standard options known to prolong life, Hospitalization? Hospitalization may be required by PMDA</td>
<td></td>
<td>May be treated as inpatients or outpatients</td>
<td></td>
</tr>
<tr>
<td>Design and conduct</td>
<td>May include multiple tumor types or be tumor specific if appropriate, Criteria for organ function and/or eligibility, Must evaluate more than a single dose, Pharmacokinetics, Independent data monitoring committee, Especially for combination studies, May be required</td>
<td></td>
<td>Recommended</td>
<td>Not mandated</td>
</tr>
</tbody>
</table>

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; ECOG, Eastern Co-operative Group.
approvals for Japan have lagged a number of years behind approvals in other jurisdictions (22), owing to a number of factors, summarized in Table 2 (23-25), including the requirement for data from Japanese patients, especially in later phase studies, as well as prolonged regulatory approval times, despite Japan being one of the largest markets for pharmaceuticals. Often, these considerations have resulted in development plans for Japan being implemented only after positive signals in phase II studies conducted in other regions, further delaying the availability of new agents for cancer patients in Japan and resulting in scientifically unattractive confirmatory trials. Other factors cited in the late inclusion of Japan in early clinical trials have included prolonged timelines (26) and high costs.

A number of major initiatives have been implemented since 2004 (Fig. 1) involving the Pharmaceuticals and Medical Devices Agency (PMDA; refs. 27-29), JMACCT (an organization of the Japan Medical Association; ref. 30), and Ministry of Health, Labor and Welfare (31), including initiatives to improve the infrastructure for clinical trials in Japan by supporting clinician researchers (investigators) and medical institutions in conducting clinical trials and developing clinical trials networks. Early data suggest that these initiatives have had an impact, with an increase in the numbers of clinical trials conducted in Japan and faster accrual times.

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In addition to the changes noted, increasing understanding of ethnic differences in pharmacokinetic, pharmacodynamic, and pharmacogenetics has streamlined development plans. For example, phase I data for new therapeutics metabolized by CYP 1A2, 2E1, and 3A4/5, which are independent of ethnicity (32), may thus be derived from Japanese patients, include Japanese patients, or be used to allow the early initiation of phase II studies in Japan. Higher rates of mutations in the epidermal growth factor receptor have been documented in the east Asian population. In some instances, data from other Asian countries may be used to support early trials in Japan. Nonetheless, in some instances, phase I data from studies including Japanese patients may be mandatory.

**Phase I studies in Japan.** The requirements for the conduct of phase I studies are summarized in Tables 3 and 4, and, since the development and adoption of ICH S9 (Nonclinical Evaluation for Anticancer Pharmaceuticals), these requirements are now congruent with those in Europe and the United States. To date, relatively few first in human studies have been conducted in Japan, for the reasons described above with the majority using data from first in human studies from other countries to support starting doses. Although there are some cultural differences in the reporting of adverse event data (for example, the reporting of any laboratory changes >grade 1 as adverse events, or the attribution of causality), the conduct and design of phase I studies mirror those in Europe and the United States. When appropriate, and included as objectives of the study, patients and researchers are comfortable with biopsies or use of archival tissue for correlative studies.

**Conclusions**

Both the European Union and Japan are major markets for pharmaceuticals, and as such are important participants in early clinical trials. Although each jurisdiction was traditionally considered somewhat unique in terms of early drug development, major initiatives in the last decade have aligned drug development in Japan, Europe, and the United States. Although many new agents are developed in collaboration with the
pharmaceutical industry, many academic drug discovery and development organizations exist, offering many opportunities.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

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Reference

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