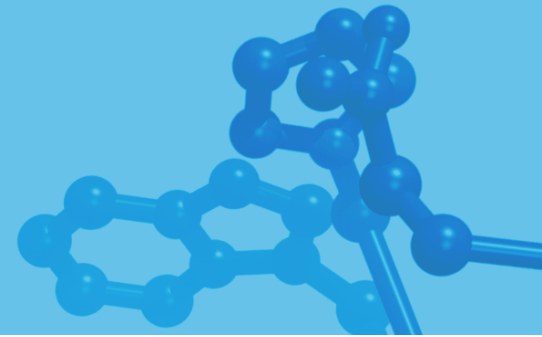


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April 17, 2008 South San Francisco, CA



Global Clinical Trials: Potential Pitfalls of Offshore Trials

**John Manthei, Latham & Watkins
Kent R. Thielke, PRA International
J. Ben Haas, Latham & Watkins**

Growth In Overseas Clinical Trials

- Over 40% of all US-regulated clinical trials are now conducted overseas, with most significant increase seen in CEE (according to Tufts Center for Study of Drug Development)
- Many top pharmaceutical companies project that, within the next 2 to 3 years, up to 65% of their FDA-regulated clinical trials will be conducted abroad (Tufts)



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Outsourcing & Investigative Site Trends

- Rising development costs and cycle times, combined with growing volume and scope of clinical trials, motivate drug sponsors to increase their reliance on foreign based investigators and patients.
- Demand for contract research organization (CRO) services is expected to grow by 16% annually over the next five years as drug developers increase their reliance on CROs for assistance with managing large, complex global clinical trials.
- Many top pharmaceutical companies project that, within two to three years, up to 65% of their FDA-regulated clinical trials will be conducted abroad, supporting strong annual growth of foreign-based clinical investigators.



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Outsourcing & Investigative Site Trends

- Building on recent trends, which saw the number of procedures per clinical trial protocol rise 6% annually during the past decade, protocol design complexity will continue to escalate as clinical trials involve a larger mix of diverse, globally-based patients.
- Over the next several years, drug sponsors, regulatory agencies, and human subject protection programs will increase training and oversight of foreign-based investigators in an effort to bring investigators into compliance with Good Clinical Practice (GCP) guidelines, in line with compliance rates among US investigators.



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Why Are Companies Looking Overseas?

- Harmonization of good clinical practice requirements (ICH)
- Strengthening of intellectual property protections
- Improved logistics (“world is flat”)
- Well-trained physicians and large number of patients willing to undergo experimental therapies
- Less competition from other studies
- Lower relative costs (particularly in CEE)



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What International Standards Should Apply to All Studies?

- ICH Good Clinical Practice Guidelines
- Declaration of Helsinki



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What Standards Apply in Europe?

- EU Clinical Trials Directives (2001/20/EC and 2005/28/EC)
- National laws and regulations in each country



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Comparison Between the EU and the US

- Regulatory Document Submissions
- Protection of Clinical Trial Subjects
- Investigational Medicinal Product (IMP) Issues
- Retention of Essential Clinical Trials (CT) Documents



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Regulatory Document Submissions

Application Submission

EU

- One Competent Authority (CA) submission per Member State
 - 27 countries
 - 27 authorities
- Remember, Europe is not one country!

US

- One regulatory authority at the federal level – the FDA
 - Single submission
 - Single authorization



Regulatory Document Submissions

Protocol

EU

- Stand alone submission to CA for each protocol
- Review timeframe:
 - 60 days (maximum), Member States can impose shorter timeframes per their national law

US

- New protocol submitted as an amendment to the IND of the investigational product
- FDA reviews the initial IND within 30 days
- No official review timeframe for subsequent amendments (protocols) to the IND



Regulatory Document Submissions

Protocol and/or Application Review

EU

- One opportunity for CA to request further information (clock stops)
- If CA does not find response satisfactory, the application is considered rejected

US

- Discussions with the FDA are not limited



Regulatory Document Submissions

EC/IRB Submission

EU

- 60 day review timeframe specified in Directive (parallel submission with CA filing)
- One EC opinion per country (regardless of the number of sites in the country)
 - 27 countries
 - 27 authorizations
- However, in some countries the system to obtain a single ethics outcome, includes consultation with the other ECs

US

- FDA Regulations do not define IRB approval timelines
- IRB approval required for each site
 - Many IRBs will assess the trials
 - However central IRBs speed the process



Regulatory Document Submissions

Amendments to the Protocol

EU

- Significant amendments require notification to CAs and ECs
- Significant amendments: “Substantial and likely to have an impact on the safety of the trial subjects or to change the interpretation of scientific documents in support of the conduct of the trial”
- Regulations define EC approval timelines (35 days)
- Although not specified, CAs are also expected to follow a 35 day timeline (may proceed if no grounds for non-acceptance are raised)

US

- Although submitted to the FDA, no official authorization required for protocol amendments “that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study”
- FDA Regulations require IRB approval of protocol changes, but do not define IRB approval timelines



Regulatory Document Submissions

End of Trial Notification

EU

- Each CA to be notified of closure of the trial in its' territory, and ultimately closure of the trial overall
- Closure notification to be done within 90 days of termination
- Early termination of trial requires notification within 15 days

US

- Notification of study closure to FDA in IND update, no particular timeframe specified
- Notification to FDA study closure due to safety reasons required immediately



Protection of Clinical Trial Subjects

EU

- Minimal detail on ICF requirements
- Minors & Incapacitated Adults
 - No incentives or financial inducements
- Some countries require insurance info to be put into ICF
- No provisions outlined for emergency consent
- European Commission Directive 95/46

US

- Detailed list of ICF requirements
- All subjects
 - Disclosure of anticipated prorated payment, if any, to the subject for participation
- No requirement for insurance info in ICF
- Provisions for emergency consent
- Local sites required to incorporate HIPPA regulations (privacy protection) into consent process



IMP Issues

Manufacturing and Import

EU

- Must be manufactured to a standard “at least equivalent” to EU GMP
- Import Authorization required via application to a CA
- Once within EU, shipment between MS does not require any further import authorization

US

- Phase II and Phase III supplies must satisfy US GMP (Phase I = compliance with certain aspects of GMP)
- Import of investigational product provided to a consignee as defined in the IND
- Unrestricted shipment between US states



IMP Issues

Labeling

EU

- Label samples may be required by ECs
- Must be in the official language(s) of the MS on the outer package, or where no outer package on the immediate packaging
- Labels require expiration date

US

- Label samples not required by IRBs
- Label must bear specific language (“Caution: new drug limited by United States law to investigational use”)
- Labels do not require expiration date



IMP Issues

Verification of Compliance with GMP

EU

- Inspections conducted by CA of the MS concerned, results to be recognized by all MS
- Qualified person (QP) to certify GMP compliance of each batch of IMP (includes placebo and comparators)

US

- GMP inspections can be performed by FDA
- No such function in the US



Retention of Essential CT Documents

EU

- The sponsor and investigator shall retain the essential documents relating to a clinical trial for at least 5 years after its completion
- Retention period may be extended under special circumstances

US

- ICH – 2 years after the last approval of a MA & no pending/contemplated MA in an ICH region or formal discontinuation of development of the product
- FDA – for 2 years after a MA is approved or 2 years after FDA notified that drug shipment/delivery is d/cd



IND v. non-IND

- Study under IND requires all sites worldwide to comply with FDA requirements (investigators must sign FDA Form 1572)
- Filing IND ensures prior review and comment on protocol by FDA, preventing later issues regarding study design
- On the other hand, FDA does accept data from non-IND studies, so long as certain international standards and local laws are met
- Non-IND may be appropriate where sponsor disagrees with FDA regarding protocol design, no US sites contemplated, etc.
- Non-IND may make it easier to engage sites and investigators (some investigators uncomfortable with signing 1572)



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Study Organization / Vendors

- CROs
 - Logistics (site and vendor selection; coordination and administration)
 - Monitoring
 - Communication (local language / contract and budget negotiation)
 - Financial administration (payments to sites, investigators, and other vendors)
 - Data management
- Vendor for Clinical Manufacturing and Supply
 - Manufacturer
 - Kit assembly and labeling
 - Delivery (customs)
 - Returns
- Local Representative (legal agent in country)
 - Regulatory filings
 - Can be CRO



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Managing CROs and other Vendors

- CROs
 - Experience managing trials in indication and in countries where trial will be conducted
 - Control makeup of Project Team (contract)
 - Detailed budgets and services listings (prevent in-scope v. out-of-scope debates)
 - Regulatory updates (e.g., weekly teleconferences with study team)
 - Document all discussions and outcomes
 - Consider need for subcontracts (e.g., data management)
- Clinical Suppliers
 - Capacity? US GMP compliant?
 - Location of depot facilities



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Managing CROs and Other Vendors

- Avoid ceding too much authority
 - Transfer of obligations to CRO does not transfer ultimate responsibility for ensuring compliance of study with regulatory requirements
 - Participate in monitoring efforts
 - Regulatory submissions (translate, if necessary)
 - Contracts (translate, if necessary)
- Cultivate positive and transparent relationship with vendors, but protect your contractual and regulatory rights (e.g., budget management)
- Involve counsel in acrimonious discussions (insulate study team)



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Contracts

- Different than US, where one template agreement will typically be acceptable to all sites
- Sites will no longer sign template agreements because they want the work – anticipate negotiation and extensive comments
- No universal clinical trial agreement template – each country and site may be different
 - Use templates from counsel or CRO
- Sites/investigators may require execution of multiple agreements, e.g.:
 - Site agreement
 - Investigator agreement
 - Pharmacy agreement
 - Laboratory agreement



Contracts

- Expect idiosyncratic issues
 - Site and investigator relationship (disclosure of separate agreement)
 - Lead investigator agreements
 - Separate budgets for each participant
- Establish process for negotiation of agreements (involving counsel and CRO)
- Seek consistency among all sites in key provisions:
 - Compliance with laws (e.g., IND requirements)
 - Intellectual property and ownership of data
 - Confidentiality
 - Publication
 - Liability protection (accounting for statutory protections in certain countries)
 - Control of Study Drug
- Sites will require:
 - Governing law
 - Controlling language

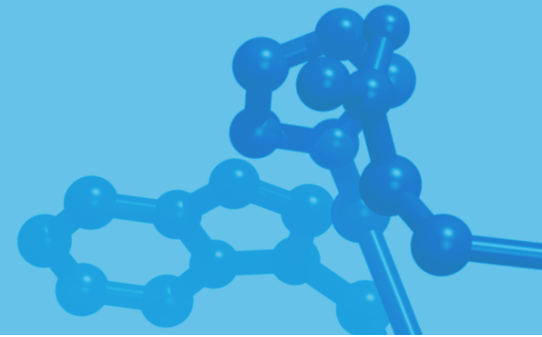


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Implication of the Globalization of Clinical Trials and Drug Development

Kent R. Thelke
Senior Vice-President
Scientific & Medical Affairs
PRA International

Current Clinical Trial Environment

- Today's clinical trial landscape is littered with trials that fail to meet their planned timelines and patient accrual
- ACT reports that 86% of clinical trials experience delays
- Centerwatch reports 94% of studies experience > 1 month delay
- 42% of major study delays are a result of poor patient accrual
- Any large Phase II/III program will require a global footprint
- Understanding where to go and what benefit each region can bring is critical to successful planning and implementation



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Patient Recruitment

- Recruitment is
 - 30% of overall clinical trial timeline
 - 40% of clinical trial costs
- 50% of all trial delays are caused by accrual issues
- Current accrual in the US is very poor with >70% of trials not finishing on time
- Accrual in emerging/developing countries can be 5x-10x that of the United States and Western Europe
- Faster accrual = shorter time to market = increased revenues
- Global is no longer a should but a must



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More Patient's Than Ever Needed

- Patient accrual is critical factor to trial success
- Number of trials increased 250% in last 15 years
- 2007 – 100,000 clinical trials were underway with approximately 2 million patients needed
 - Oncology Trials
 - 2006, 679 trials in all phases for lung, breast and prostate would need 238,000 patients – corresponds to ½ of all cancer incidence
 - However, current participation rates in trials are roughly 3-5% NOT 50%
- Average NDA requires 4500 pts



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So Many Trials, So Few Patients

- Currently there are >5,000 Oncology clinical trials, >3,000 CNS trials, > 2000 Infectious Disease trials*.
 - Common tumor types are particularly competitive
 - >600 breast cancer trials
 - >800 lymphoma trials
 - >400 NSCLC trials
 - 300 brain cancer trials
 - 170 mantle cell lymphoma trials
 - 3300 MCL/yr, 5% =165 pts

* Based on trials posted on clinicaltrials.gov as of 3/2007



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So What's The Answer?

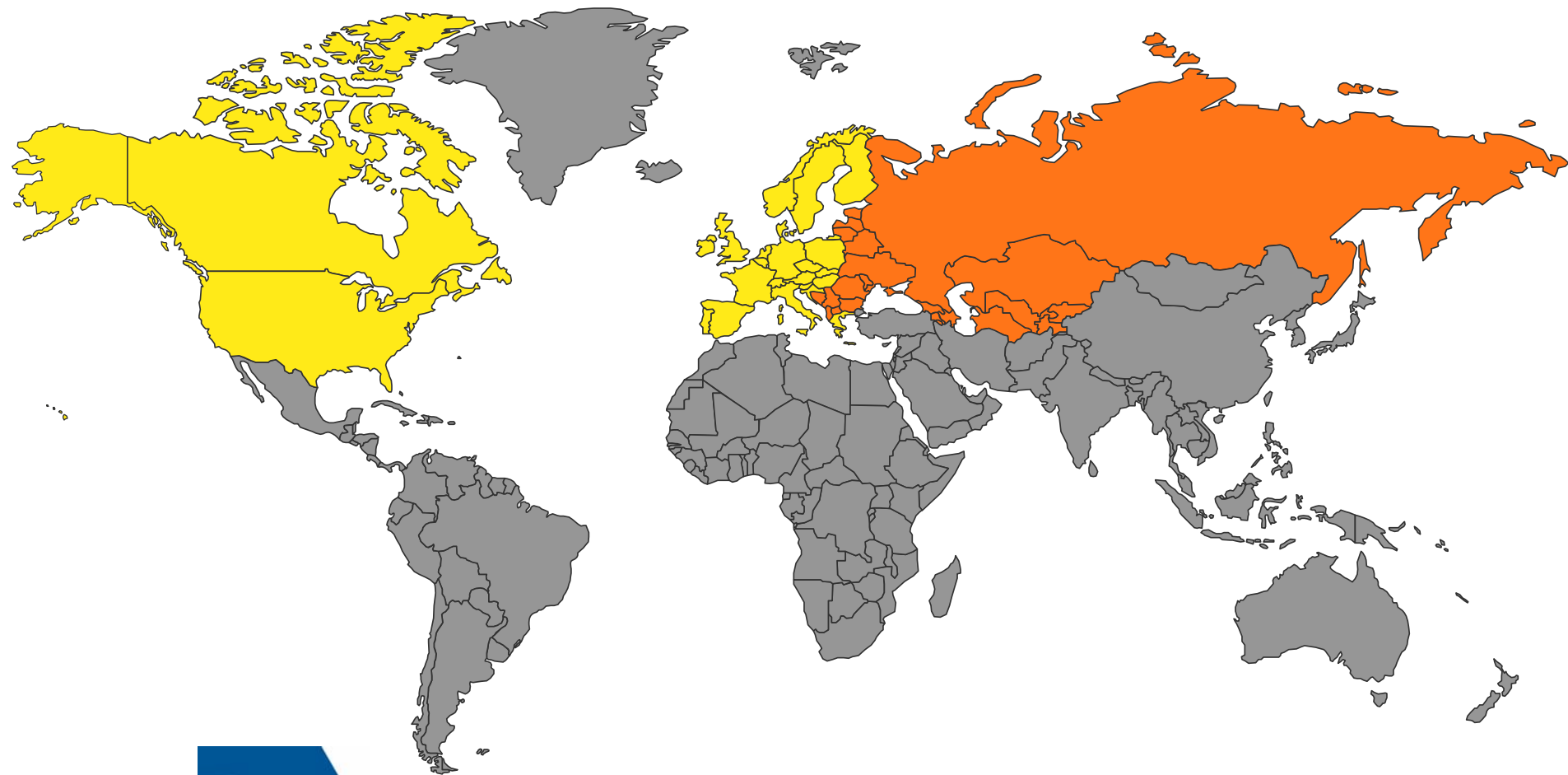
- Go Ex-US
 - Pick the right region
 - EU/EEU, Latin America, Asia, India, Africa
- Know your limitations
- Find a CRO Partner with global experience and footprint



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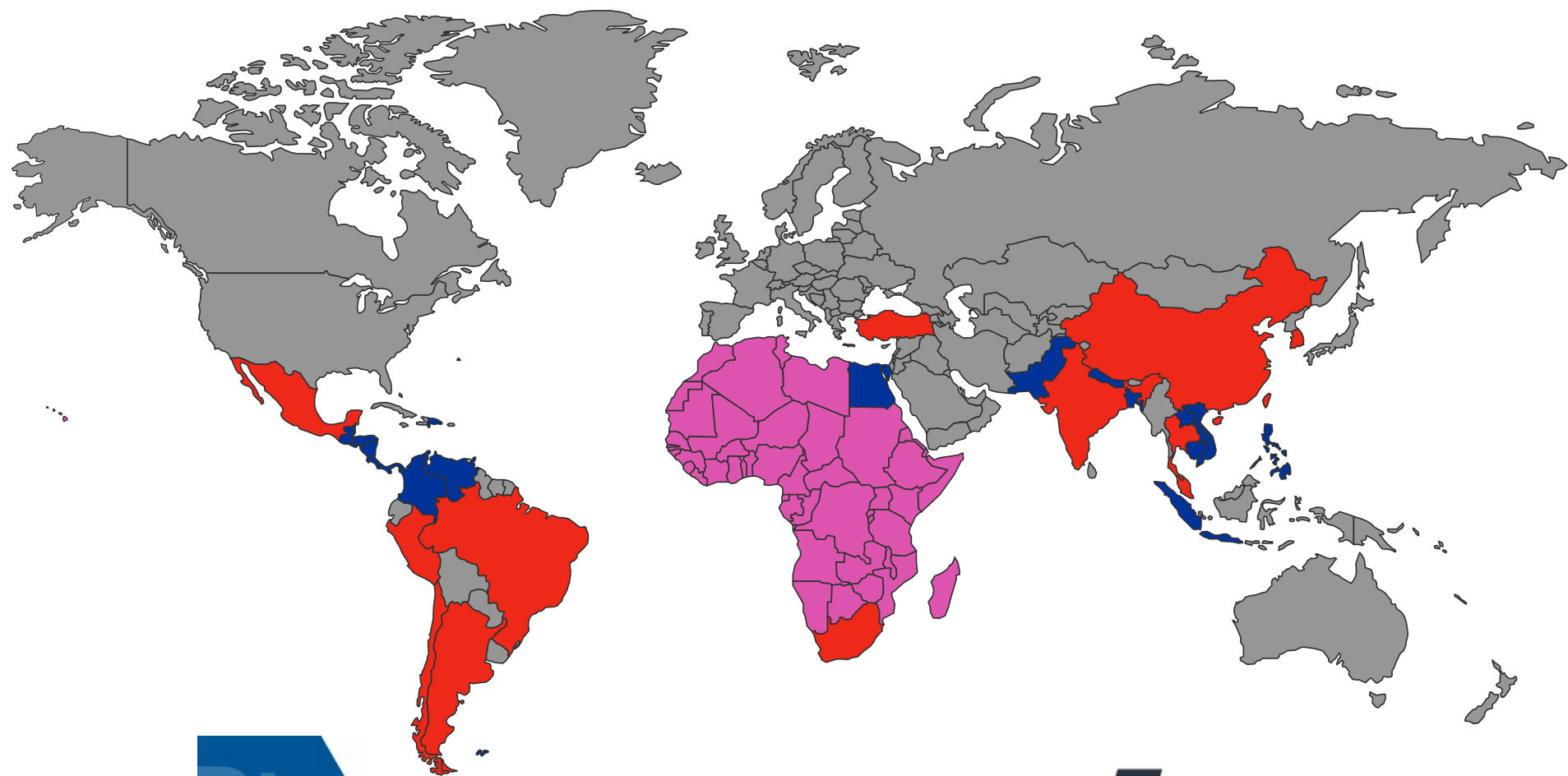
Current “Standard” Regions



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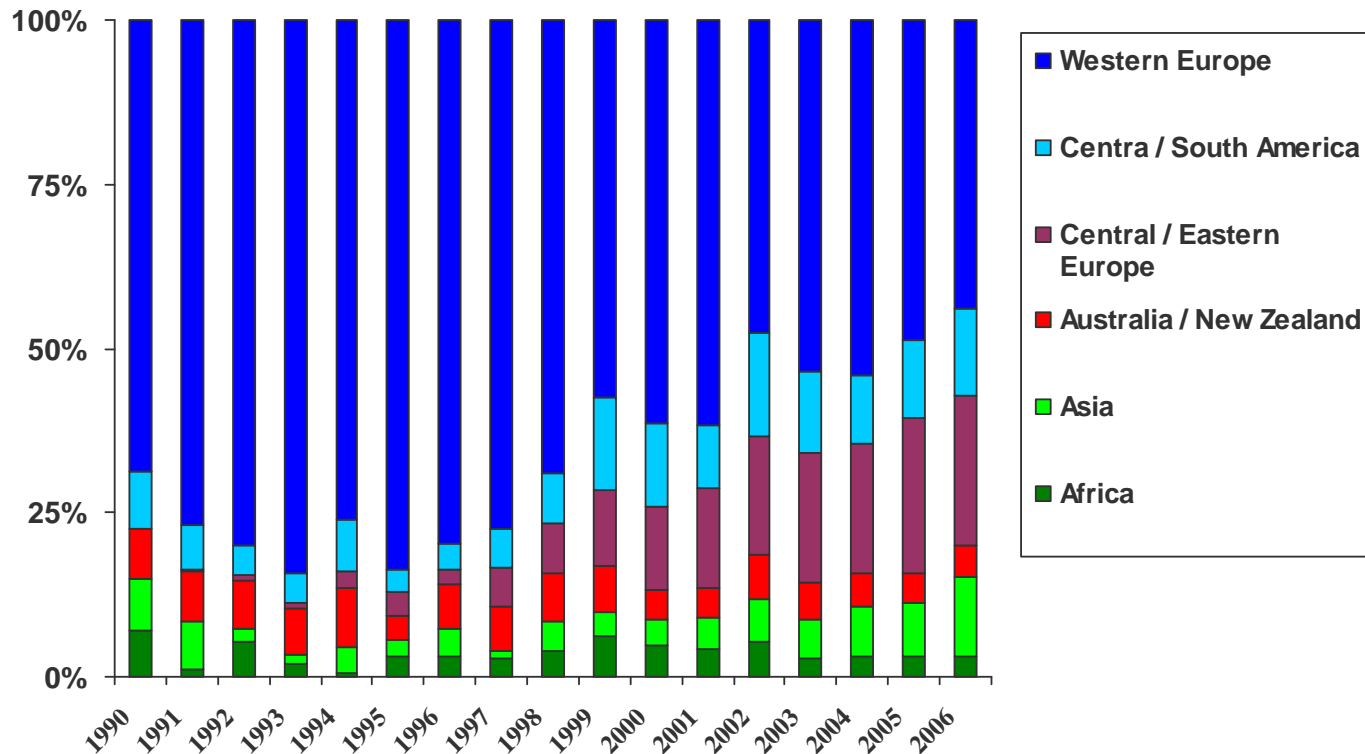
Critical Emerging Regions



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Distribution of Ex-US FDA-Regulated Investigators Initiating Clinical Trials



Opportunity in Asia

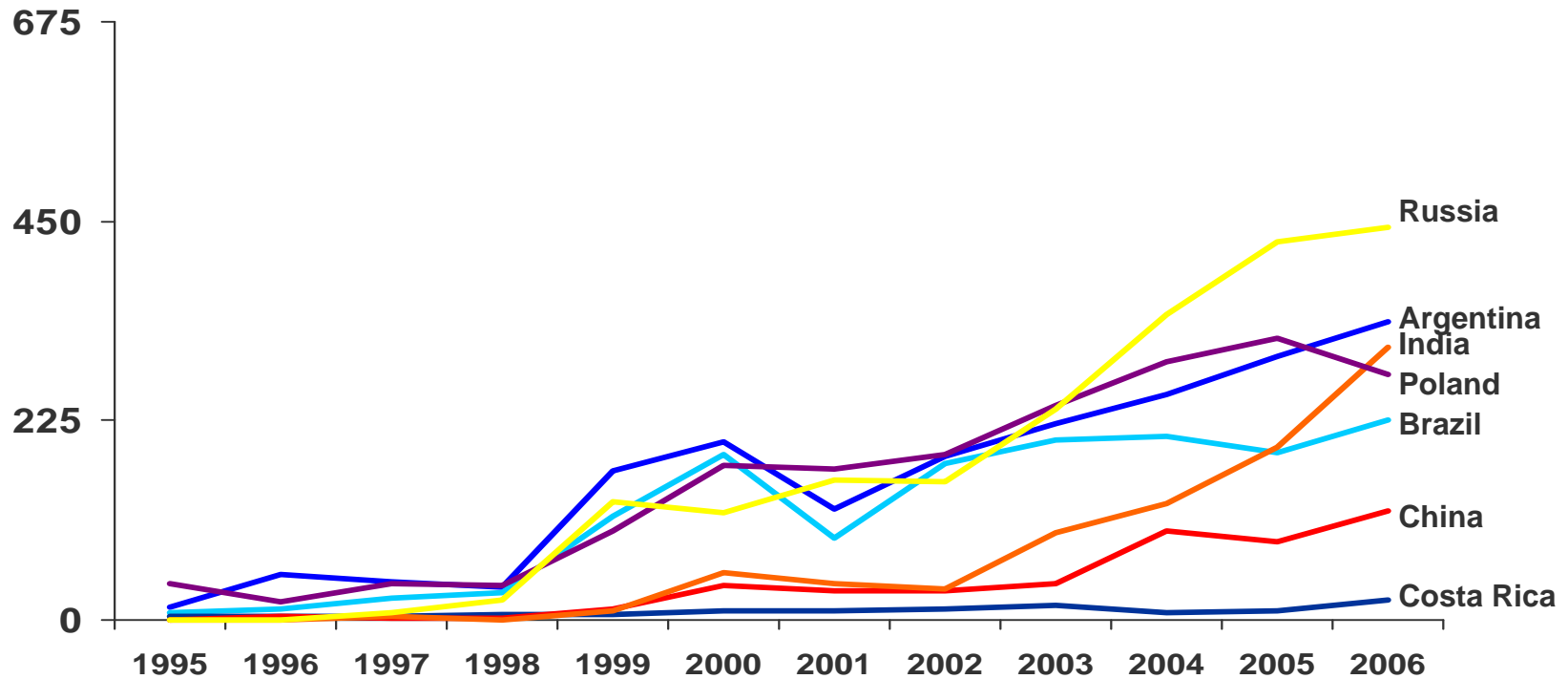
Source: Tufts CSDD Analysis of FDA's Bioresearch Monitoring Information System File (BMIS)



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Growth in Ex-US FDA Regulated Investigators Initiating Clinical Trials



Opportunity in Asia

Source: Tufts CSDD Analysis of FDA's Bioresearch Monitoring Information System File (BMIS)



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High Growth Countries for New FDA-Regulated Investigators

	2001	2003	2006	5-yr Growth Rate	Most Recent 3-yr Growth Rate
Argentina	126	221	337	22%	15%
Brazil	92	203	225	20%	3%
Costa Rica	10	16	22	17%	11%
China	33	42	124	<u>30%</u>	<u>43%</u>
India	42	98	307	<u>49%</u>	<u>46%</u>
Poland	170	243	277	10%	4%
Russia	159	238	443	<u>23%</u>	<u>23%</u>

Opportunity in Asia

Source: Tufts CSDD Analysis of FDA's Bioresearch Monitoring Information System File (BMIS)



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Practical Considerations of Global Trials

- Maximize/Optimize the CRO benefit by leveraging corporate experience (SED, Feasibility Library, etc)
- Be REALISTIC in preparing timelines and milestone expectations
 - Accrual is not a straight lined exercise – Site Recruitment Months
- Understand the US Population first – IntrinsiQ, Marixa, In
- Conduct extensive feasibility to determine site/country selection
 - Prevalence of the target indication
 - Standards of Care
 - Availability of patients
 - BSC and placebo issues
- Greater competition requires more countries with fewer sites
- Maximize the public healthcare settings in developing countries
 - India, Brazil, Russia/Ukraine



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Savings vs Expense Ex-US

The Myth

- Accrual in these countries may significantly shorten time to market
- Investigator grants are lower but not for long
- Procedure fees are lower
- Labor costs associated with contract services are lower
- Laboratory fees are lower
- Everything associated with the trial may need to be covered by the sponsor
- Comparator drug must be supplied/reimbursed
- Equipment Costs (-70°, centrifuge)
- All other protocol meds must be reimbursed
- Tax implications on import of comparator drug can be significant
- Cash transfers may also be taxed
- Investigator travel – business class
- Global Infrastructure Required
- CHINA – CMC can cost you



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Contracts/Clinical Trial Agreements (CTAs) Are Not Universal

- A US contract is rarely directly transferable to a developing or ex-US region
- Contracts are usually 2-way or 3-way and in some cases 4-way
 - 2-way (Sponsor/Sponsor Rep + Study Institution/Investigators)
 - 3-way (Sponsor/Sponsor Rep + Institution + Investigator)
 - 4-way (Sponsor + Sponsor Rep + Institution + Investigator)
- Funds distribution should be stated in contract
 - % to sites vs investigator vs study nurse
 - Assigned bank account of the site/investigator/foundation
- Translational requirements are varied
- Several EU countries now require all contracts to be executed prior to Ethics submissions
- Use your CRO's template language and save time



We'd like to global but....

- Is the practice of medicine the same?
- Do they have the same medications available?
Supportive Care? Diagnostics?
- Is the quality of data as good as the US?
- Can they do EDC?
- What about Quality of Life? Endpoints?
- Will FDA accept the data? How many patients can come from ExUS?



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The Implications

- Not going ex-US can significantly delay timelines and time to market and cost Millions of dollars in potential revenue
- While going ex-US can cost more – the trade off in getting to market sooner can more than make up the difference
- The ethical obligations
 - Only go ex-US for studies that are ethical
 - Ex-US studies bring life saving medications to patients that have no other options
- After all bringing new drugs to patients and saving and changing lives is why we are all here.



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