THE GLOBALIZATION OF CLINICAL TRIALS FOR NEW MEDICINES INTO EMERGING ECONOMIES: WHERE ARE THEY GOING AND WHY?

by

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I. INTRODUCTION

The establishment and protection of intellectual property rights ("IPRs"), such as patents and copyrights, has a long global history.[1] Although legal and economic historians have devoted considerable efforts to assessing the very long-term impacts of intellectual property protection institutions on a nation's economic development,[2] there is also a growing literature on medium-term (say, between one and ten years) relationships among a country's IPRs, openness to foreign direct investment and imported technologies, ability to integrate and absorb external technology flows, domestic research and development ("R&D") efforts, and its productivity and economic growth.[3]

Findings from this literature are mixed. Lerner's [2002a] broad-based historical review found little evidence for a positive impact of strengthened patent protection on the pace of innovation, in part because of challenges in measuring IPR and innovation. In their analysis of the historical evolution of patent systems across the globe, Jaffe and Lerner [2004] note that there have been several common very long-term trends: patent office officials have been given less discretion in how they make grants, patent applications are being scrutinized more intensively, and patent awards are increasingly longer-lived. These trends all strengthen patents and make them more economically attractive. On the other hand, more recently there have also been exacerbations in conflicts and litigation involving patents, in part due to the apparent deterioration of examination standards at patent offices leading to weaker patents, which to some observers have had the unintended effect of undermining and inhibiting the innovation process. This leads Jaffe and Lerner to conclude, for example, that "The patent system seems increasingly to be a source of uncertainty and costs, rather than a mechanism for managing and minimizing conflict."[4]

The measurement of intellectual property protection and of innovation (not just patents) presents significant challenges. A seminal empirical study that quantified an index of patent rights protection for 110 countries at five-year intervals between 1960 and 1990 is that by Ginarte and Park [1997], who also went on to assess determinants of patent protection levels across countries and time. Among their principal findings were that measures of market freedom, lagged R&D investment rates, and lagged openness were strong determinants of patent protection levels. However, R&D was not an important predictor of patent protection unless an economy had reached a sufficiently high level of development, suggesting that threshold effects were present in that a country required a certain critical size of an innovating sector before it had an incentive to provide patent rights.

Causality in the reverse direction – from IPRs to economic and productivity growth – was the focus of their subsequent study, in Park and Ginarte [1997]. The key finding from that analysis was that the strength of IPRs did not appear to have any direct effect on productivity and economic growth, but rather IPRs stimulated the accumulation of factor inputs such as R&D and physical capital, which in turn contributed to explaining international variation in growth over time.

These findings suggest that it would be useful to examine links between R&D and IPRs more closely, preferably at a more disaggregated level of analysis. In the preliminary research findings reported here, we examine the role of several alternative measures of IPRs, among other factors, in affecting a particular form of "D" in the biopharmaceutical R&D sector, namely, clinical trial investigations on human beings for new medicines. We note that in terms of magnitude, private sector out-of-pocket expenditures on clinical investigations are two to three

times larger than pre-clinical expenditures, i.e., the sector's expenditures on D are two to three times larger than on R.[5] Hence, D is relatively much more important.

In a previous analysis we have documented that industry-sponsored clinical trials are increasingly being sited in emerging economies.[6] For example, based on data from a publicly available website, clinicaltrials.gov, we find that between 2002 and 2006 average annual growth rates ("AAGRs") in the global share of biopharmacuetical clinical trial sites averaged about 22% in emerging economies, with China (47%) and India (20%) exhibiting very high growth rates, although as of April 2007 still having minor global share participation levels (each about 1%). In contrast, over the same 2002-2006 time period, the US share has fallen at an AAGR of 6.5%, been stable, Canada's share has declined about 12% annually, while those for the UK, Switzerland, Sweden and Belgium declined at AAGRs between -5% and -10%, while those for Germany (12%) and particularly Spain (15%) were positive and substantial. This suggests that although IPRs may be playing a role in this increased globalization process, factors other than IPRs are also at work, and that a multifactorial analysis is required in order to identify and isolate the effects of various factors on globalization, including in particular various measures of IPRs.

The paper is organized as follows. In the next section we provide a background on clinical trials in the drug development process, and on recent efforts to make data on clinical investigations publicly accessible to patients, clinicians and providers. Then in Section III we draw on various literatures and outline a framework for modeling the decision of where geographically to locate a clinical investigation, and the ways in which various determinants affect this geographical siting decision. In Section IV we provide information on data sources and methods, and outline the basic elements of an econometric framework. We present

preliminary empirical findings in Section V, and summarize and outline future steps in Section VI.

II. BACKGROUND ON THE CLINICAL TRIAL DRUG DEVELOPMENT PROCESS

Unlike the case for many other products, for prescription drugs the time between original product development and product launch is very long, usually more than a decade. Most R&D projects fail, with the candidate medicine never making it to market. In Exhibit 1 we display the common sequential phases of drug discovery, development and approval, and the range of time intervals devoted to each phase.[7] The New Drug Application ("NDA") approval and post-launch Phase IV timelines in Exhibit 1 refer primarily to the U.S. environment and its regulatory body, the Food and Drug Administration ("FDA"). The pre-clinical phase has historically been more local, while the clinical phases are increasingly becoming global.[8] Incidentally, some recent evidence suggests early stage pre-clinical research is becoming more clustered in areas having research strengths in the life sciences and academic-industry linkages, such as in Boston, San Francisco, London-Cambridge, Uppsala, Singapore and Munich.[9]

Pre-clinical research – the "R" of R&D -- begins with basic discovery and research, and extends through animal testing; this basic research typically lasts one to five years, and when promising often simultaneously involves a sponsor filing one or more patent applications at the U.S. Patent and Trademark Office, and at similar agencies elsewhere. After carrying out extensive safety/toxicity, pharmacokinetic and pharmacodynamic studies in various animal models, the sponsoring organization can file an Investigational New Drug ("IND") application with the FDA, an Initiation Medical Technical Dossier ("IMTD") at the European Medicines

Evaluation Agency, or with analogous regulatory authorities elsewhere. In some cases, particularly for companies with headquarters outside the U.S., IND-type applications are initially

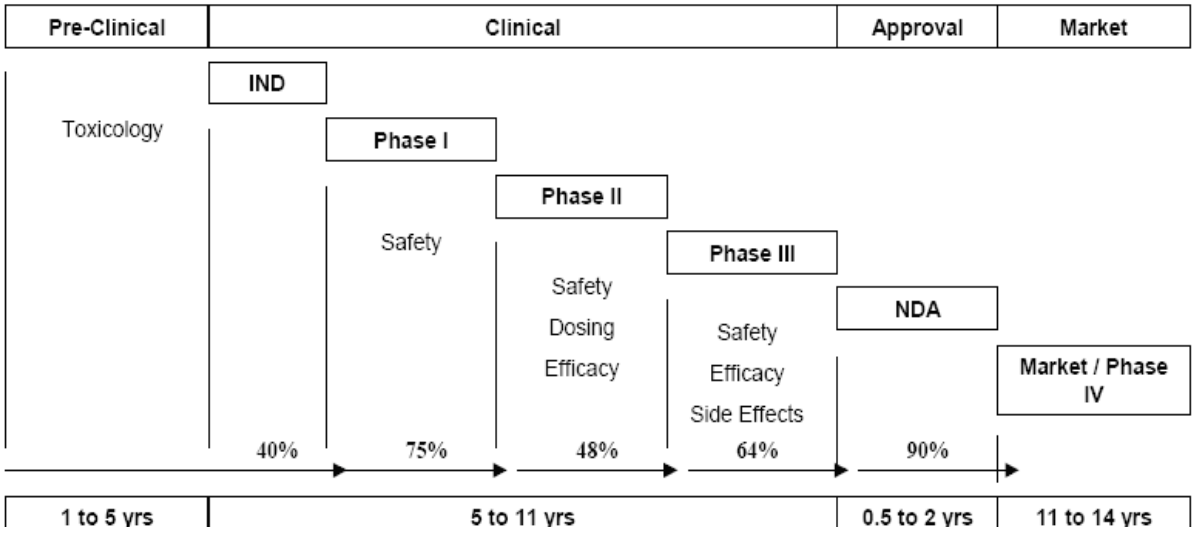

Exhibit 1: Duration and Transition Probabilities of Drug Development Phases

filed by developers in other countries, such as at the Medicines and Healthcare Regulatory Agency in the U.K., before they are filed in the U.S.[10] In the U.S., the pre-clinical phase ends when the IND clears the FDA, a prerequisite for allowing the sponsor to test the candidate drug in humans in the U.S. By convention, this is the point at which the "D" portion of biopharmaceutical R&D begins. As noted earlier, private sector out-of-pocket spending on D is two to three times larger on average than that on R.

Phase I trials follow the pre-clinical phase and are designed primarily to test for safety and tolerability of the drug in healthy volunteers (i.e., the ability of a patient to take a medicine, given its possible side effects and adverse interactions with other drugs). Phase I trials typically last one to six months. In Phase II, the preliminary efficacy of the candidate drug is assessed, as is safety and tolerability via continued monitoring within dose ranges established in the Phase I analyses. Phase II trials typically take from six months to two years to complete. In most cases,

by this time in the development process the sponsor has decided which particular illness or condition will be targeted for initial marketing approval by the FDA (the "primary indication"). Phase II trials often are multi-site trials, taking place concurrently in one or more countries.

Phase III trials, often called pivotal clinical trials, are designed to evaluate statistically the safety and efficacy of the drug compared to placebo or standard of care within a considerably larger and typically more diverse study population. In most cases the sponsor conducts several Phase III trials – possibly in a substantial number of global trial sites concurrently. Particularly when it is difficult to recruit appropriate patients, sponsors can employ a common clinical trial protocol and simultaneously contract with investigators at numerous sites in one or more countries. Although there is considerable variability, the average length of time of the entire Phase III process is approximately four years. Once the Phase III trial data are gathered and evaluated, the sponsoring organization can submit its application (called an NDA for synthesized molecules, or a Biologic License Application, "BLA," for biologicals) for review and approval by the FDA in the US, or at similar institutions in other countries.

A developer of a new drug may choose to initiate the drug development process in a country other than the U.S., conceive of and develop the evidentiary platform, and then undertake additional studies as needed to obtain regulatory approval in the U.S. and elsewhere. Often after or even before the pivotal Phase III studies have been completed in support of the original NDA/BLA, and during the time the national medicinal approval authorities are reviewing the NDA/BLA primary indication application, the sponsor may carry out additional studies. In some cases, the sponsor conducts additional Phase II and III studies as it seeks to obtain evidence in support of approval for additional medical conditions/diseases ("secondary indications") beyond the primary one(s) applied for in the original NDA/BLA. In other cases,

so-called Phase IV studies are undertaken as a condition required by the FDA when approving the original NDA/BLA, such as those assessing long-term effects of a drug in a larger and more heterogeneous population than studied in the Phase III trials, or in special sub-populations, such as pediatric patients.

There is now substantial evidence suggesting that in the context of prescription drugs, order-of-entry effects are significant, and that earliest entry provides substantial (although not insurmountable) benefits to the pioneer product within the therapeutic class.[11] One consequence of this is that the premium for speeding up drug development is becoming ever larger, implying that qualified clinical sites that can recruit patients quickly become very attractive to sponsors. Not coincidentally, sponsors have increasingly been outsourcing clinical trial management to contract research firms that specialize in rapid patient recruitment, and in the implementation and monitoring of clinical trials.[12]

Matching willing study volunteers with clinical investigators has become a critical issue in facilitating clinical R&D. Due in part to the perceived need to make information publicly available to potential patients seeking to volunteer for participation in a clinical study, and to facilitate patient recruitment by clinical investigators, in 1997 the US Congress passed the Food and Drug Administration Modernization Act ("FDAMA") which mandated that sponsors filing IND applications to the FDA and planning ultimately to apply for regulatory marketing approval be required to register publicly all trials for medical interventions to treat "serious or life-threatening diseases". The FDA's implementation of this legislation resulted in the 2002 creation of www.clinicaltrials.gov, a publicly accessible website maintained by the U.S. National Library of Medicine.[13]

A greater stimulus to public registration of clinical trials, however, emerged from a different source. In September 2004, members of the International Committee of Medical Journal Editors [2004] ("ICMJE", a consortium of major medical journals including the *Lancet*, the *Journal of the American Medical Association*, and the *New England Journal of Medicine*) jointly published an editorial stating:

> "The ICMJE member journals will require, as a condition of consideration for publication, registration in a public trials registry. Trials must register at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2005. For trials that began enrollment prior to this date, the ICMJE member journals will require registration by September 13, 2005, before considering the trial for publication".

Although trials designed to study pharmacokinetics or major toxicity, such as certain phase I and bioequivalence trials are exempted, the ICMJE requirement is general and is based on a definition of a clinical trial "…as any research project that prospectively assigns human subjects to intervention or comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome".[14] The ICMJE editorial stated that the clinicaltrials.gov website met their eligibility requirements, and that in the future others might as well.[15]

We note in passing that considerable controversy exists concerning the timeliness of reporting of results of clinical trials, with understandable conflicts emerging between medical journal publication policies and public disclosure of findings on registries.[16]

III. TOWARDS AN ECONOMETRIC FRAMEWORK

We envisage biopharmaceutical firms as attempting to maximize the net present value ("NPV") of global profits. In turn, the NPV of global profits is comprised of NPV from global sales of currently produced products, the NPV from global sales of future products, and the NPV of global costs:

NPV Global Profits = NPV Global Sales Current Products

+ NPV Global Sales Future Products – NPV Global Costs.

Underlying this overall NPV global profit optimization are sub-functions, such as the production function for innovative output, and cost functions for R&D, manufacturing, marketing and other costs. Given the complexity of the overall optimization problem, global firms decentralize, delegate and carry out sub-optimization.

In making a decision on whether to site a clinical trial within a country i (i = 1,…,I), among other factors a firm will consider the country's capacity to produce clinical evidence, E_i, in a timely manner. We envisage E_i as being a function of a country's clinical input quantities and qualities (e.g., trained clinicians and researchers, workforce with tertiary education), number of patients with access to advanced medical care, communication capabilities (access to computers and the internet), intellectual property protection (patents, copyright and piracy), and market orientation (extent of government intervention, corruption). The firm will also consider the costs of inputs in country i relative to other countries; we denote these costs as C_i. In the next section we will discuss various measures of country-specific capacities and costs to produce E_i.

The decision on whether to site a clinical trial within country i will also depend on the NPV of potential sales of current and future products in that country. While we see no obvious reason why the R of R&D in country i would be linked to current and future sales in that country (indeed, as noted earlier, such basic research appears to becoming increasingly clustered geographically), such a link may exist between a country's D and sales of current and future products in that country. Specifically, a literature exists that links activities of clinicians involved in industry-sponsored clinical trials (particularly key opinion leaders) to their (and their peers') subsequent prescribing behavior.[17] Moreover, in interviews we have had with

biopharmaceutical clinical and regulatory personnel, we have learned that in the complex political economy of relationships among biopharmaceutical companies and public agencies, the siting decision of a BCT can be affected by a firm's view of a country's likely reimbursement policies, and by the involvement of clinical investigators in setting the fine details of those policies.

Given these considerations, we therefore envisage country i's capacity to produce sales, S_i, of current and future products as depending on its overall market size (population, gross domestic product per capita), and its willingness to pay for medical treatments (overall health care expenditures per capita, and the private-public mix of such expenditures).

In summary, we believe a reasonable basis for an econometric analysis is a framework in which the number of BCT sites in country i, BCT_i, is a function of its capacity to produce clinical evidence, E_i, the costs of clinical trials in country i relative to other countries, C_i, and its capacity to generate sales of current and future biopharmaceutical products, S_i, i.e.,

$$BCT_i = f(E_i, C_i, S_i), \quad i = 1,\ldots,I. \qquad \text{Eqn. (1)}$$

We now consider measurement issues and data sources for these variables.[18]

IV. DATA METHODS AND SOURCES

The data we employ in our empirical analyses come from a variety of sources, which we detail below. The dependent variables are the cumulative number of biopharmaceutical clinical trial sites over the 2002-2006 period ("BCTPOP"), and the average annual growth rate in the global share of trial sites over the same time period ("BCTAAGR"), each for country i. Explanatory variables include several measures of intellectual property protection, comparative costs of clinical trials, infrastructure capabilities, potential domestic market size, and free market environment.

A. NUMBER AND GROWTH RATE OF BIOPHARMACEUTICAL CLINICAL TRIAL SITES

A clinical trial site refers to a recruiting location for an individual clinical trial. The geographic allocation of sites across countries and regions was obtained from the clinicaltrials.gov website. This registry facilitates retrieval of information on the name and identification number of the trial, recruitment start date (when applicable), listings of locations of clinical trial sites, trial phase (I through IV, other), condition being treated, sponsor, and other trial characteristics.[19] Since the specific identity of the medical center in which the site is located is commonly not reported, a single recruiting hospital participating in, say, n distinct clinical trials, is counted as n trial sites.

An analytic data base spreadsheet was created, with the underlying data downloaded electronically from clinicaltrials.gov. Specifically, we developed an XML parsing software that retrieved detailed information on individual BCTs. Data was obtained only from "currently recruiting" or "completed" trials in which a recruitment start date was available. We excluded "not yet recruiting", "terminated" trials, studies funded and/or run by academic or public institutions, trials in which the clinical phase or information on clinical site locations was unstated, and studies of medical devices not relying on a drug for its therapeutic effect. The database used in our analysis consisted of 6,046 BCTs and 123,713 sites distributed globally. We also computed trial site data for active trials as of April 12, 2007 – the date at which the clinicaltrials.gov data were frozen.

Since many already ongoing and almost completed trials were retrospectively registered at clinicaltrials.gov by September 2005, and because in response to FDAMA others had been registered prior to the ICJME editorial, the comprehensiveness of coverage by clinicaltrials.gov

has likely increased substantially between 2002 and 2007. However, we are unaware of any published estimates of the coverage portion, or even of discussions on the nature of studies underrepresented in the registry. As discussed below, this complicates our modeling strategy.

As one dependent variable, for each country we compute the cumulative number of trial sites between 2002 and 2006 registered at clinicaltrials.gov.. Because the coverage rate of clinicaltrials.gov is unknown, we cannot establish absolute changes over time in the number of GCTs by country. We address this in several ways. Assuming that between 2002 and 2006 the geographical dispersion of BCTs reported and not reported to clinicaltrials.gov is similar, we can obtain a preliminary quantitative assessment of the changing geographical distribution of BCTs by computing growth rates in each country's *share* of total new trial sites by year.

Let s_{i0} and s_{i1} be country i's share of new global trial sites initiated in years 0 and 1, respectively. Accommodating the fact that in early years some countries have very small shares, we compute the annual growth rate in shares by taking the difference $(s_{i1} - s_{i0})$ and dividing by the arithmetic mean of shares in the two years, $(s_{i0} + s_{i1})/2$; to compute a country's average annual growth rate ("AAGR") between 2002 and 2006, we take weighted arithmetic means of the 2002-3, 2003-4, 2004-5 and 2005-2006 growth rates, using as weights the relative number of sites in year 1 of each bilateral year 0 and 1 intertemporal comparison.

Finally, we also compute regional aggregates. We designate the North America, Western Europe and Oceania regions as "traditional", and countries in Eastern Europe, Latin America, Asia, Middle East and Africa as being in "emerging" regions; for growth rates, we use the same weighted arithmetic mean procedure as noted in the previous paragraph.

B. INTELLECTUAL PROPERTY PROTECTION

In a series of papers, Park and Ginarte [1997] and Ginarte and Park [1997] constructed and then employed in their analyses an index of patent rights ("IPR") for 110 countries at five-year intervals between 1960 and 1990. The IPR index was subsequently extended to several Eastern European countries and updated to 1995, as discussed in McCalman [2005]; the most current version of the index covers 121 countries including additional countries from the former Soviet Union and from Asia, contains additional details within its sub-components, and has been updated further to 2000.[20] We note in passing that because of the staggered implementation of the TRIPS Agreement (the World Trade Organization's agreement on Trade Related Aspects of Intellectual Property Rights) for developing and least developed countries, the actual implementation and enforcement of patent protection may lag behind legislated changes.

The IPR index ranges from 0 to 5.00, and is the unweighted sum of five categories, each of which ranges between 0 and 1.00; higher values indicate greater patent protection. The five categories are: (i) extent of coverage (patentability of seven items – pharmaceuticals, chemicals, food, plant and animal varieties, surgical products, microorganisms and utility models, such as tools); (ii) membership in international agreements (Paris Convention of 1883 and subsequent revisions, Patent Cooperation Treaty of 1970, International Convention for the Protection of New Varies of Plants of 1961, and a signatory to the World Trade Organization documents on Trade-Related Aspects of Intellectual Property Rights– "TRIPS"); (iii) provisions for loss of protection (from three sources -- "working" requirements, compulsory licensing, and revocation of patents); (iv) enforcement mechanisms (availability of preliminary injunctions, contributory infringement pleadings, and burden-of-proof reversals); and (v) duration of protection (fraction of the 20 years provided from date of application). In 2000, values of IPR ranged from 0.00 (Burma,

Mozambique, New Guinea) to 5.00 (United States), with China having a value of 2.48, India 2.18, and Australia, Germany and Italy each having an IPR index of 4.52. Since it is more highly focused on patentability of specific products including pharmaceuticals, we also examine empirically the role of the coverage sub-component of IPR, which ranges between 0.00 and 1.00.

For the purposes of this study, we refine the overall IPR measure in several ways. First, we focus only on whether pharmaceuticals were covered by patents, as recorded in the Parks data set. This yields 0-1 dummy variables at each five-year interval, e.g., RX2000 for year 2000. We also calculate whether for each country there has been any change between pharmaceutical patent coverage; in the empirical analysis reported below, we calculate $\Delta RX = RX2000 - RX1990$.

Second, a slightly broader measure of patentability of medically-related products involves not only patentability of pharmaceuticals, but also of chemicals and surgical tools and instruments. We construct BIOMED at five-year intervals as a weighted average of 0-1 dummy variables for whether pharmaceutical products are covered by patent policy (weight of 0.5), whether chemical products are covered (weight of 0.25), and whether surgical tools and instruments are covered (weight of 0.25). Finally, we compute a change measure as $\Delta BIOMED = BIOMED2000 - BIOMED1990$.

An alternative measure of intellectual property protection has been published by the Business Software Alliance [2005] based on a survey conducted by the International Data Corporation. Called the personal computer software piracy rate ("PIRACY"), the measure is computed as the estimated percentage of the total packaged software base that is "pirated", based in part on a comparison of software licenses sold relative to personal computer shipments; we note that considerable controversy exists regarding the interpretation of such a measure. This

PIRACY measure has been published for 2003 and 2004 covering 87 countries, and is also aggregated into six global sub-regions.[21] In 2004, the mean PIRACY value was 35%; regional values were 53% for Asia Pacific, 35% for the European Union, 61% for Rest of Europe, 66% for Latin America, 58% for Middle East/Africa, and 22% for North America.

C. COSTS OF CLINICAL TRIALS

Data on costs of clinical trials per patient, by country and therapeutic area, were obtained from Fast-Track Systems, based in Fort Washington, Pennsylvania. Fast-Track obtains clinical trial contract information from small and large pharmaceutical companies, biotechnology firms and contract research organizations, and uses this contract data to construct comparative cost data by country, therapeutic area, and phase of clinical research. The data product is called Fast Track Grants Manager, and it contains "Information on investigator fees, clinical trial design and other core costs …from over 20,000 protocols and 200,000 investigator contracts worldwide."[22] We have obtained data from Fast-Track on the cost per patient in each of these trials by country, expressed in US dollars using concurrent exchange rates, from 2000 to the present.[23] The distribution of counts of trials by country in the Fast-Track data largely mirrors that in the cllinicaltrials.gov database, though the total number of trials in Fast-Track falls in 2004 and 2005, due to lags in data collection. Counts in some countries are very small, and unfortunately no data is available for a number of countries of interest such as Japan.[24] Fast-Track has an adjusted cost per patient measure, which for each country we average over all trial phases (I through IV) and therapeutic areas, over the years 2000 and 2001. We designate this cost per patient variable as COSTPP.

D. *INFRASTRUCTURE CAPABILITIES*

A number of measures of national innovative capabilities have been constructed, some of them relying on subjective criteria, others more on objective and quantifiable sources. As part of a large study on global investments by transnational countries, recently the United Nations Committee on Trade and Development [2005] ("UNCTAD") has published the UNCTAD Innovation Capability Index ("ICI"), which in turn is an unweighted average of two separately calculated measures, a Technological Activity Index ("TAI") and a Human Capital Index ("HCI"). The TAI is an unweighted average of R&D personnel per million population, US patents granted per million population, and scientific publications per million population. The HCI is a weighted average of national literacy rate as percent of population (weight of 1/6), secondary school enrolment as percent of age group (weight of 1/3) and tertiary enrolment as percent of age group (weight of ½). In UNCTAD [2005, ch. III and Annex A], values of TAI, HCI and ICI are given for 117 countries, for years 1995 and 2001. For 2001, the ICI index ranges from 0.019 (Angola) and 0.028 (Djibouti) to 0.977 (Finland) and 0.979 (Sweden); other 2001 values include 0.927 (U.S.), 0.906 (U.K.), 0.804 (Israel), 0.863 (France), 0.850 (Germany), 0.746 (Italy), 0.354 (China) and 0.287 (India).

One problem with the UNCTAD TAI measure is that it incorporates technological capabilities in non-medical areas such as software and electronics. As an alternative measure of research capabilities, we have obtained data on counts of randomized controlled trials ("RCTs") from the PubMed database maintained by the National Library of Medicine (www.pubmed.gov). This database was searched for all papers reporting randomized clinical trials using human subjects published in PubMed's "core clinical journals" between 1990 and 2000. These were then assigned to countries based on an algorithm that parses the AD field in

the PubMed database. This field reports, in principle, the institutional affiliation and address of the article's first author and we were able to identify the country of the first author of almost all of these publications. Fewer than one percent of papers had incomplete or missing address information, and in most of these cases we were able to infer the country from the domain name of the corresponding author's email address. We name this variable RCT.

We also have sought to employ other infrastructure measures that are more specific to health care. These include number of physicians, nurses, acute care hospital beds[25], and installed magnetic resonance imaging units[26]; unfortunately, these data are not available for a good number of countries in our sample.

Finally, since clinical trials increasingly involve global communications over the Internet, we employ as an indicator of infrastructure capabilities a component of the Economist Intelligence Unit's national measure of e-readiness, published in 2006 (for 2005) and in 2003 (for 2002), covering 68 and 60 countries, respectively. Information available at the Economist Intelligence Unit website http://www.eiu.com indicates that approximately 100 quantitative and qualitative criteria, organized into six distinct categories, feed into their aggregate national e-readiness rankings, with most of the data sourced from the Economist Intelligence Unit and Pyramid research. For each of the categories, scores range from zero to ten, with a higher score indicating greater infrastructure capabilities. The six categories and their weights are: (i) connectivity and technology infrastructure (25%); (ii) business environment (20%); (iii) consumer and business adoption (20%); (iv) legal and policy environment (15%); (v) social and cultural infrastructure (15%); and (vi) supporting e-services (5%).

Since most of these categories overlap with other indexes, for the purposes of this study we only employ the connectivity and technology infrastructure component, which measures the

access that individuals and businesses have to fixed and mobile telephone services, personal computers and the internet. In 2006 the category criteria included narrowband, broadband, mobile phone, internet, PC and WiFi hotspot penetration, as well as Internet affordability and security of telecom infrastructure.[27] To facilitate interpretation, we have taken the ordinal rankings of this variable (e.g., 1 for the highest ranking country, 100 for the 100th ranked, etc.), and subtracted it from 100, so that increases in the measure are interpreted as relatively greater connectivity capability. We call this index EREADY.

E. *HOST COUNTRY POTENTIAL DOMESTIC MARKET SIZE*

As measures of the potential size of the host country domestic market for biopharmaceutical products, we examine several variables: (i) gross domestic product ("GDP") for years 2002 and 2005, in billions of US dollars using purchasing power parity transformations[28]; (ii) population in millions, for 2004/2005[29]; (iii) health care expenditures per capita, in U.S. dollars, 1999 and 2003, using concurrent U.S. exchange rates[30]; and (iv) percent of population living in urban areas, for 2005.[31]

F. FREE MARKET ORIENTATION

A number of organizations have created and published indexes or rankings that purport to quantify the market environment in which private sector firms operate. Typically these measures cover the entire economy, and are not disaggregated to specific sectors such as health care or biopharmaceuticals. Among these are the 2006 Index of Market Freedom Index published by the Heritage Foundation, the 2005 Economic Freedom Index from the Cato Institute, and the 2005 Corruption Perceptions Index from Transparency International.

The Economic Freedom of the World Index, co-published by the Cato Institute, the Fraser Institute, and over 50 think tanks around the world, purports to measure the degree to

which national policies and institutions support economic freedom.[32] The summary index is derived from the assessment of thirty-eight components and sub-components which capture measures of economic freedom in five areas: (i) size of government; (ii) legal structure and protection of property rights; (iii) access to sound money; (iv) international exchange; and (v) regulation. Economic freedom scores are scores are out of ten, with ten corresponding to the highest attainable degree of economic freedom.

The 2006 Index of Economic Freedom, co-published by the Heritage Foundation and the Wall Street Journal, is created from a set of 50 distinct variables divided into ten broad categories contributing to economic freedom.[33] These categories include trade and monetary policy, banking and finance, property rights, pricing and wages, and activity in the informal sector. A total of 161 countries are assessed using the index. Scores range from one to five;, scores between 1-1.99 are interpreted by the authors as representing a "free" country, 2-2.99 a "mostly free" nation, 3-3.99 a "mostly unfree" country, and 4-5 a "repressed" nation

The Corruption Perceptions Index is published by Transparency International, a civil society organization who identify themselves as being focused on combating corruption around the world. The index is based on a composite survey reflecting the perceptions of both country analysts and business persons who are residents and non-residents of the assessed countries. A total of 16 different polls from ten independent institutions were drawn upon in the scoring process. All countries included in the index feature at least three polls. The index ranges from one to ten, with a score of ten corresponding to a country perceived to be least corrupt. The 2005 index reflects data collected between 2003 through 2005.

Finally, various forms of price controls on biopharmaceutical products have existed for quite some time in most countries other than the U.S. Lanjouw [2005, Table A3] contains price

control data on 68 countries (excluding, however, China and countries from the former Soviet Union) for two time intervals – an early period (1982-1992) and a late period (1993-2000); for each period, she records whether there was an increase, decrease or no change in what she calls "any price controls" or "extensive price controls" on biopharmaceutical products. She labels price controls as extensive if prices of "...all drugs are regulated, rather than just a subset of the market, or if a country's price regulation is identified by commentators as being particularly rigorous."[34]

G. *ECONOMETRIC SPECIFICATIONS*

One important feature of the clinicaltrials.gov registry is that while it has undoubtedly experienced increasing coverage over time, we do not know what the time path of that coverage ratio is. Below we report on two different ways of dealing with this measurement issue. Our research to date is still in its preliminary stage, and additional work remains to be done.

The first econometric specification we employ is mostly log-linear model in which the dependent variable is the log of BCT ("LBCT"), the logarithm of the 2002-2006 cumulative number of BCT sites. As regressors in our base case specification, we include the log of gross domestic product ("LGDP"), the log of population in millions ("LPOP")), the log of cost per patient ("LCOSTPP"), the log of the cumulative 1990-2000 number of published RCT articles with lead author in that country ("LRCT"), as well as the UNCTAD Human Capital Index ("HCI") and the Economist's e-readiness measure ("EREADY").

We then employ three alternative measures of changes in intellectual property protection between 1990 and 2000. In our base case model, we include as a regressor the 1990-2000 change in Park's overall IPR index, $\Delta IPR = IPR2000 - IPR1990$. In Model II, we instead utilize the change in the pharmaceutical only component, $\Delta RX = RX2000 - RX1990$. Then in Model

III we use the change in the slightly broader weighted average of the pharmaceutical, chemical and surgical tool and instrument coverage indexes, ΔBIOMED = BIOMED2000 – BIOMED1990.

Our second equation is a "change" rather than "levels" specification, in which the dependent variable is a country's AAGR in the global *share* of BCT sites between 2002 and 2006. Recall that we employ the AAGR in growth of share of BCT sites, since the clinicaltrials.gov registry likely has achieved increased coverage over time, so that simply looking at AAGR in the absolute number of BCT sites would confound changing shares with changing coverage.

As regressors in this AAGR equation, we include LCOSTPP (cost per patient), log of GDP per capita (LGDPPOP), LRCT (cumulative 1990-2000 number of RCT publications with lead author in that country), as well as the UNCTAD Human Capital Index (HCI) and the Economist's measure of e-readiness (EREADY). We then examine three alternative measures of intellectual property protection in 2000 (the last year for which Park's data are currently available): IPR2000, RX2000 and BIOMED2000.

For both equations, estimation is by ordinary least squares, with heteroskedasticity-robust standard errors. The data sample is from the top 50 countries in number of cumulative 2002-2006 sites; the lack of available data for four countries reduces our cross-sectional sample to 46 cross-sectional observations.[35]

V. EMPIRICAL FINDINGS

We now move on to preliminary empirical findings. We first present descriptive ranking data based on the absolute number of active trial sites as of April 12, 2007 for the top 50 countries, then in terms of average annual growth rates ("AAGRs") in share of BCT sites

between 2002 and 2006, and finally rankings based on density (number of active trial sites as of April 12, 2007 per million 2005 population). We then report econometric results regarding factors affecting the absolute number of BCT sites, and AAGRs of shares of global BCTs.

A. ABSOLUTE NUMBER OF ACTIVE TRIAL SITES AS OF APRIL 12, 2007

The ranking of BCT sites by country is presented in Table 1 for the top 50 countries. We also display them color coded, with countries in traditional regions (North America, Western Europe and Oceania) labeled in blue (and in regular font), and countries in emerging regions (Eastern Europe, Latin America, Asia, Middle East and Africa) in green (italics font).

Table 1 Somewhere Near Here

The top five countries are all in traditional regions and together account for 66% of all active trial sites as of April 12, 2007. With 36,281 sites (48.7% of total), the US dominates by a large margin, having more than eight times the number of active trial sites than second place Germany (4,214 sites, 5.7% of total). Countries in emerging regions are mostly small players when analyzed individually (each with less than 2% global share), but as a composite group they are hosting 17% of all actively recruiting trials as of April 12, 2007.

It is useful to divide the top 50 countries into approximate thirds. Among the top 17 countries, 11 are in traditional regions, while three of the six from emerging regions are in Eastern Europe (Poland, Russia, Czech Republic). The only two countries from emerging regions in the top 13 are Poland and Russia, while the remainder are from North America (two), Western Europe (seven), and Oceania (two). While India is ranked 16th, as of April 12, 2007 it accounted for only 1% of all trial sites (757).

In the middle third of the country rankings (#18 to #34), the relative shares flip – now ten of the 17 are in emerging regions (four from Eastern Europe, three from Asia, and one each from

Africa (South Africa) and the Middle East (Israel), while seven are in traditional regions (all from Western Europe). Notably, with 533 active sites, China is ranked #23 as of April 12, 2007.

In the bottom third of top 50 country rankings, 14 of the 16 are in emerging regions (five in Asia, four each in Eastern Europe and Latin America, and one from the Middle East) and only two countries (New Zealand and Ireland) are in the traditional regions.

B. RANKINGS BY GROWTH RATES IN SHARE OF BCT SITES

Before presenting country-specific AAGRs, in Figure 1 we first plot the 2002-2006 evolution of the regional shares of BCT sites. Participation shares of traditional (blue tones) and emerging (green tones) regions for trials beginning in each year between 2002 and 2006 are shown. AAGRs between 2002 and 2006 by region are -6.9% for North America, 3.5% for

Figure 1 Somewhere Near Here

Western Europe, 9.3% for Oceania, 24.0% for Eastern Europe, 19.8% for Latin America, 20.4% for Asia, 27% for Middle East, and 0.0% for Africa.

As Figure 1 shows, the evolution of the BCT share distribution reveals a continuing share growth in emerging regions, growing from less than 8% starting to recruit in 2002 to 20% of BCT sites that became active in 2006. While the AAGRs in shares of clinical trial participation have grown 21.3% of the unknown underlying growth rate of overall number of BCTs, the traditional regions combined have experienced a negative AAGR of -2.9%. As seen in Figure 1, the most notable decline for Western Europe occurred between 2002 and 2004, while the decrease in North America occurred mostly between 2004 and 2006.

The ranking of countries in terms of AAGRs of BCT sites is presented in Table 2; again, countries in traditional regions have blue tones (regular font), while those in emerging regions have green tones (italics font).

Table 2 Somewhere Near Here

A number of findings are striking. First, among the 25 countries with the largest AAGRs, only one (Portugal) is from a traditional region – the top half of Table 2 is almost entirely green. Second, the bottom half of Table 2 is almost entirely blue – of the slower half of countries in terms of AAGRs of BCTs, only six are from emerging regions (Taiwan, Bulgaria, Chile, Singapore, South Africa and Puerto Rico). The ten countries with the slowest growth rates, including all eight with negative AAGRs, are from traditional regions. Third, the range in growth rates is remarkably wide – from 47% for China and 34.6% for Estonia, to -12.0% for Canada and -14.7% for Norway.

It is useful to divide the top 50 countries into five approximate quintiles. In the top are the nine countries having AAGRs greater than 30%, with all of these being in emerging regions: four from Eastern Europe (Estonia, Russia, Ukraine, Lithuania), three from Asia (China, Malaysia and the Phillippines), and one each from Latin America (Peru) and the Middle East (Turkey).

In the second top quintile are ten countries having AAGRs between 20% -30%. Both Latin America (Colombia, Argentina and Mexico) and Eastern Europe (Slovakia, Czech Republic and Hungary) each have three countries in this group, Asia has two (Hong Kong and Thailand), while the Middle East has one (Israel). The only country with this high an AAGR coming from a traditional region is Portugal, with an AAGR of 25.3%.

In the middle quintile are 12 countries having AAGRs between 10% and 20%. Nine of these countries are in emerging regions – four from Eastern Europe (Romania, Greece, Poland, and Bulgaria), three from Asia (India, South Korea, Taiwan), and two from Latin America

(Brazil and Chile); only three are in traditional regions, two from Western Europe (Spain at 14.9%, and Germany at 11.7%), and one from Oceania (Japan at 10.3%).

In the fourth quintile are 11 countries with positive AAGRs but less than 10%. Countries from Western Europe dominate this with six entries (Austria, Denmark, Italy, Ireland, Finland and the Netherlands), two are in Oceania (Australia and New Zealand), and one each are in Africa (South Africa), Asia (Singapore) and Latin America (Puerto Rico).

Finally, the eight countries in the bottom approximate quintile each have negative growth rates, ranging from -4.0% for France to -14.7% for Norway; among these eight countries, six are in Western Europe (France, Switzerland, Sweden, Belgium, the U.K., and Norway), while two are in North America (the U.S. and Canada). While the US share has fallen at an annual rate of -6.5%, that for Canada has fallen more sharply, at -12.0% annually. It is worth emphasizing, however, that these negative growth rates are in shares, not absolute numbers. If the unknown overall annual growth in BCT sites globally is greater than 6.5%, then even though the U.S.' and Western Europe's shares are falling, the absolute number of BCT sites would be growing.

C. POPULATION DENSITY TRIAL SITES RANKINGS AS OF APRIL 12, 2007

Since it is reasonable to assume that the population of a country affects the number of active BCT sites and the share growth rate, we now describe variation across countries in trial site density, which we measure as the number of active trial sites as of April 12, 2007 per million 2005 population.

As seen in Table 3 and as depicted in Figure 2, the density ranges widely – from highs of 120 in the U.S. and 95 in Belgium to lows of 1 in India and 0 in China (excluding Hong Kong).

Table 3 and Figure 2 Somewhere Near Here

Of the 25 countries having the highest density, 17 are from traditional regions – in blue tones, while eight are from emerging regions (green tones). Among those relatively high density countries from emerging regions, most are from Eastern Europe (Czech Republic, Estonia, Hungary, Slovakia, Lithuania and Greece), while one is from the Middle East (Israel) and the other from Latin America (Puerto Rico). In the bottom half of Table 3 are countries with the lowest density; here all except three (Ireland, the U.K. and Japan) are in emerging regions (green tones).

In Figure 2 we color code countries' density with darker orange colors denoting a greater density of trials, white meaning close to zero number of trial sites per million population, and gray countries being ones with no actively recruiting BCT sites as of April 12, 2007. The darker oranges are primarily in North America, Scandinavia and Eastern Europe, the paler oranges are largely in Southern Europe and Oceania, while most of the rest of the globe is colored either gray or white, implying little or no actively recruiting sites as of April 12, 2007.

D. ECONOMETRIC FINDINGS

Parameter estimates of the log cumulative sites equation are given in Table 4, with the three columns corresponding to alternative measures of intellectual property protection.[36] Other things equal, a country's GDP is positively related to its number of BCT sites; the GDP elasticity is about unity. On the other hand, there is no significant relationship between a country's number of BCT sites and its population, holding other factors fixed. A very strong result we obtain is that the cumulative number of BCT sites in a country is negatively related to the cost per patient; the estimates of the elasticity are quite robust, ranging from -0.75 to -0.81, each with p-values less than 0.01.[37]

We obtain mixed results in terms of the effects of a country's infrastructure on its cumulative number of BCT sites. While the 1990-2000 cumulative number of authored papers in MedLine dealing with RCTs is negative but statistically insignificant, UNCTAD's Human Capital Index has a very large and statistically significant impact on number of BCT sites; this elasticity estimate is robust, ranging only between 2.67 and 2.72. Although positive, the estimated impact of the EREADY measure is not precisely estimated, and only trends to significance in Model III.

Finally, in terms of impact of intellectual property protection on the cumulative number of BCT sites, we see that in our base case specification involving changes in Park's overall IPR measure between 1990 and 2000, the impact is positive and small but not significant. When we use a much narrower measure – whether there was a change between 1990 and 2000 in coverage of pharmaceutical products – we obtain a larger but still insignificant estimate. However, when our measure of patent protection coverage encompasses a broader biomedical domain – changes between 1990 and 2000 in BIOMED (a weighted average of coverage of pharmaceuticals, chemical products and surgical tools and instruments), we obtain a positive and statistically significant estimate of around 1.10. However, in results not shown, when 1990 or 2000 levels of these intellectual property protection measures are included instead of the change measure, the resulting parameter estimates are not statistically significant.

These estimates are consistent with the view that while GDP, costs per patient and human capital capabilities have long affected the number of BCT sites by country, during the 1990s new developments in intellectual property protection also played an important facilitating role, attracting substantial clinical trial investments from biopharmaceutical companies.

We next turn to the AAGR equation. If developments in intellectual property protection and other factors brought about a major change in the geographical siting of BCTs, then what we observe in the 2002-2005 period may well not yet represent a new steady state equilibrium, but instead reflect catch-up behavior by emerging economies. As seen in Table 5, AAGRs by country do not appear to be significantly affected by cost per patient, but GDP per capita has a significant and negative effect. Interestingly, when LGDP and LPOP are entered as separate regressors (results not shown), the effect of LGDP is negative, while that of LPOP is positive; the absolute magnitudes of these effects are very similar, rationalizing use of the LGDPPOP (log GDP per capita) specification. Countries with larger populations, other things equal, are attracting clinical trial investments by biopharmaceutical companies, even though they have relatively low GDP.

In terms of infrastructure capabilities, we find that authored RCT articles in MedLine journals have a very small, albeit statistically significant impact on a country's AAGR in BCT share, a finding whose interpretation is unclear. While both a country's human capital index and its e-readiness have estimated positive effects, these estimates are generally insignificant.

Finally, in terms of intellectual property protection, in contrast to findings in Table 4 where changes but not levels of intellectual property protection affected the cumulative 2002-2005 number of BCT sites by country, here we find that certain 2000 levels of intellectual property protection impact a country's AAGR in share of BCTs. Specifically, in our base case estimates, we find that Park's overall IPR2000 measure has a small, positive but statistically insignificant impact on a country's AAGR. However, when the measure of intellectual property protection is refined to only whether there is patent coverage of pharmaceutical products in 2000 (Model II in Table 5), the estimated impact increases considerably, and becomes statistically

significant. This impact of intellectual property protection in 2000 becomes even larger when the domain is broadened to include not just pharmaceuticals, but also chemicals and surgical tools and instruments (Model III).

E. SUMMARY AND CONCLUSIONS

In this paper we have reported early stage findings from a long-term research program that seeks to understand factors affecting the increasing globalization of clinical trials for new medicines, particularly into emerging economies. This research is but a small part of a very large literature that deals with the effects of intellectual property protection on innovation, and that has historically been challenged by difficulties in measuring both intellectual property protection and innovation. Our relatively narrow focus – assessing impacts of several alternative measures of intellectual property protection on a country's level and AAGR of global share of clinical trial sites -- has the advantage of focusing on a specific type of investment. In particular, since by their nature multi-country global clinical trials have very similar protocols and design, they are relatively homogenous, and using them as a measure of R&D investment avoids ambiguities of other types of R&D that are customized to be market and country-specific. In addition, this narrow focus allows us to examine in detail the links between patent protection and a particular form of D – not just overall R&D.

Although the globalization of clinical trials into emerging economies has received considerable attention and is at the center of several controversies involving issues of outsourcing, ethics and nation building, surprisingly little attention has been devoted to quantifying its dimensions and modeling its variations. This paper begins to address these gaps. A major challenge we face is that data on the number of global biopharmaceutical clinical trial (BCT) sites reflects both increasing clinical trial activity globally and improvements in the ratio

of trials registered at clinicaltrials.gov, the latter spurred by FDA requirements and especially by the major medical journals who announced in 2004 mandated trial registry at time of trial inception. Thus the 2002-2007 data reflect in unknown proportions both increased global activity, and enhanced coverage of that activity.

Given this ambiguity, we have examined the BCT data from two complementary perspectives: the cumulative number of BCT sites in the top 50 countries, and 2002-2006 AAGRs in a country's *share* of BCT sites registered at clinicaltrials.gov. Although the US, Western Europe and Canada still dominate in terms of cumulative numbers of BCT sites, in general there has been rapid growth in BCT numbers and shares in Eastern Europe, Latin America, and Asia, at the expense of Western Europe and North America. While the U.S. and Canadian shares have been falling, if the unknown global AAGR in absolute number of BCT sites is greater than 6.5% between 2002 and 2006, then the absolute number of sites in the U.S. is still growing as well. In this sense, it is unlikely that trials are leaving traditional regions and moving into emerging regions. A more plausible scenario is that there is little or no growth in traditional regions, but impressive positive rates in emerging ones.

Our preliminary results from modeling this globalization process reveals that the elasticity of cumulative BCT sites with respect to GDP is about one, while the elasticity with respect to cost per patient is about -0.8, another important factor having a positive impact is the country's human capital index (constructed by UNCTAD has a weighted average of national literacy rate, secondary school enrolment rate, and tertiary education rate). While the 1990-2000 change in Parks' overall measure of intellectual property protection has a positive but insignificant impact on cumulative BCT sites, as does its 1990-2000 change in pharmaceutical product coverage detailed component, a slightly broader ΔBIOMED measure (encompassing

1990-2000 changes in patent coverage of pharmaceutical, chemical and surgical tool and instrument products) has a substantial and statistically significant positive impact. We interpret these findings as reflecting the beginning of a transition period as biopharmaceutical firms and countries adapt in response to changing intellectual property regimes and clinical trial economics.

With respect to results from modeling cross-country variations in 2002-2005 AAGRs in shares of BCT sites, our results are largely consistent with emerging economies catching up with slower growing countries traditionally involved in clinical medicine. In particularly, the AAGRs are negatively related to GDP per capita, and to the cumulative number of first authors of articles reporting results from randomized clinical trials (RCTs) in major MedLine journals. Regarding intellectual property protection, while the 2000 level of Park's overall IPR index has a small positive but insignificant impact on a country's AAGR, the 2000 level of the pharmaceutical product coverage has a considerably larger and significant effect, and this effect becomes even larger when the broader BIOMED coverage measure is utilized.

This study has a number of limitations, some of which we plan to address in subsequent research. Viewing globalization of BCTs as a diffusion process suggests that it would be useful to try and model ceiling or saturation effects, which could be envisaged as being country-specific, depending on characteristics of its health care system and economic geography. Our measure of clinical trial activity is the number of trial sites; while data on number of patients in the trial would be useful, such data are not available at clinicaltrials.gov, but may be at other data sources such as PharmaProjects. In future research we plan to examine number of patient issues, as well as variations by clinical phase, by therapeutic area and by type of industry sponsor (biotech, pharmaceutical, firm size, public/private, location of headquarters). Finally, from both

the existing literature and conversations with industry regulatory and clinical personnel, we understand that a critical consideration in choosing a clinical trial site is not only its investigator quality and its cost per patient, but also the speed with which patients can be recruited and the trial be completed. We are currently investigating the availability of such data.

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Table 1

Number of Active BCT Sites by Country and Ranking as of April 12, 2007

Ranking	Country	Region	Number of Sites	Share of Sites (%)	AAGR (%)
1	United States	North America	36281	48.7	-6.5
2	Germany	Western Europe	4214	5.7	11.7
3	France	Western Europe	3226	4.3	-4.0
4	Canada	North America	3032	4.1	-12.0
5	Spain	Western Europe	2076	2.8	14.9
6	Italy	Western Europe	2039	2.7	8.1
7	Japan	Oceania	2002	2.7	10.3
8	United Kingdom	Western Europe	1753	2.4	-9.9
9	Netherlands	Western Europe	1394	1.9	2.1
10	*Poland*	*Eastern Europe*	*1176*	*1.6*	*17.2*
11	Australia	Oceania	1131	1.5	8.1
12	*Russia*	*Eastern Europe*	*1084*	*1.5*	*33.0*
13	Belgium	Western Europe	986	1.3	-9.4
14	*Czech Republic*	*Eastern Europe*	*799*	*1.1*	*24.6*
15	*Argentina*	*Latin America*	*757*	*1.0*	*26.9*
16	*India*	*Asia*	*757*	*1.0*	*19.6*
17	*Brazil*	*Latin America*	*754*	*1.0*	*16.0*
18	Sweden	Western Europe	739	1.0	-8.6
19	*Mexico*	*Latin America*	*683*	*0.9*	*22.1*
20	*Hungary*	*Eastern Europe*	*622*	*0.8*	*22.2*
21	*South Africa*	*Africa*	*553*	*0.7*	*5.5*
22	Austria	Western Europe	540	0.7	9.6
23	*China*	*Asia*	*533*	*0.7*	*47.0*
24	Denmark	Western Europe	492	0.7	9.2
25	*South Korea*	*Asia*	*466*	*0.6*	*17.9*
26	*Ukraine*	*Eastern Europe*	*440*	*0.6*	*31.0*
27	*Taiwan*	*Asia*	*420*	*0.6*	*13.9*
28	*Greece*	*Eastern Europe*	*413*	*0.6*	*19.1*
29	*Israel*	*Middle East*	*399*	*0.5*	*25.2*
30	Finland	Western Europe	370	0.5	2.3
31	*Romania*	*Eastern Europe*	*354*	*0.5*	*19.4*
32	Portugal	Western Europe	342	0.5	25.3
33	Switzerland	Western Europe	309	0.4	-7.6
34	Norway	Western Europe	290	0.4	-14.7
35	*Slovakia*	*Eastern Europe*	*246*	*0.3*	*27.7*
36	*Turkey*	*Middle East*	*243*	*0.3*	*30.9*
37	*Bulgaria*	*Eastern Europe*	*215*	*0.3*	*12.7*
38	*Chile*	*Latin America*	*179*	*0.2*	*10.6*
39	*Philippines*	*Asia*	*178*	*0.2*	*30.9*
40	*Puerto Rico*	*Latin America*	*167*	*0.2*	*3.6*
41	*Malaysia*	*Asia*	*161*	*0.2*	*32.1*
42	*Lithuania*	*Eastern Europe*	*146*	*0.2*	*30.2*
43	New Zealand	Oceania	138	0.2	5.9
44	*Thailand*	*Asia*	*133*	*0.2*	*26.4*
45	Ireland	Western Europe	126	0.2	5.0
46	*Peru*	*Latin America*	*125*	*0.2*	*32.5*
47	*Colombia*	*Latin America*	*119*	*0.2*	*28.1*

Tabulation of the contribution in BCTs of the top 50 countries based on the number of clinical sites actively recruiting on April 12th 2007. Countries in traditional regions (North America; Western Europe; and Oceania) are labeled in blue (regular font), while countries in emerging regions (Eastern Europe; Latin America; Asia, Middle East; and Africa) are labeled in green (italics font). Global shares of currently recruiting clinical sites of each country and their average relative annual growth rates (ARAGRs) in shares (2002 through 2006) are also shown. Thecountry-specific trial capacity corresponds with the average number of clinical sites per trial that each country contributed in large trials (> than 20 clinical sites).

Table 2

Ranking of 2002-2006 Average Annual Growth Rates (AAGR) in Number of BCT Sites

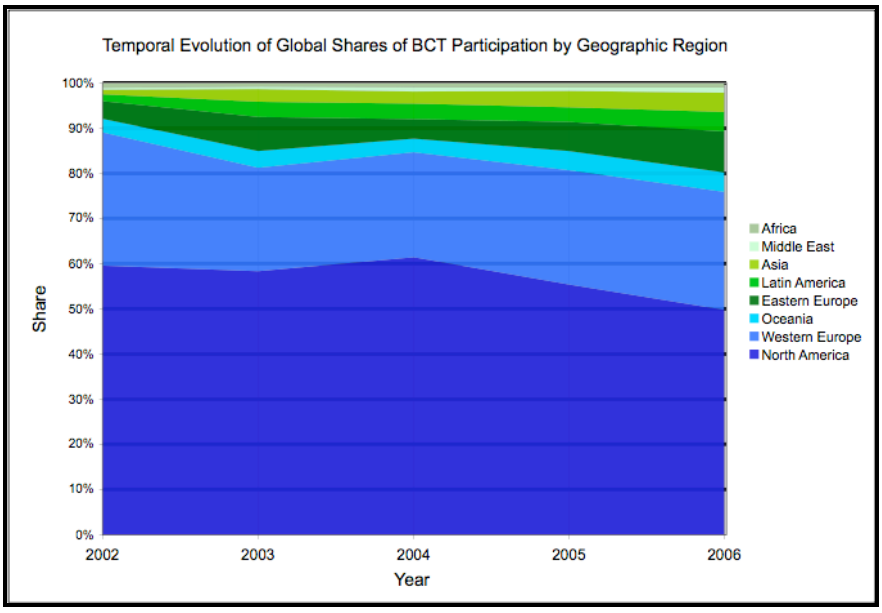
Ranking	Country	Region	AAGR (%)	Number of Sites	Share of Sites (%)
1	China	Asia	47.0	533	0.7
2	Estonia	Eastern Europe	34.6	83	0.1
3	Russia	Eastern Europe	33.0	1084	1.5
4	Peru	Latin America	32.5	125	0.2
5	Malaysia	Asia	32.1	161	0.2
6	Ukraine	Eastern Europe	31.0	440	0.6
7	Turkey	Middle East	30.9	243	0.3
8	Philippines	Asia	30.9	178	0.2
9	Lithuania	Eastern Europe	30.2	146	0.2
10	Colombia	Latin America	28.1	119	0.2
11	Slovakia	Eastern Europe	27.7	246	0.3
12	Argentina	Latin America	26.9	757	1.0
13	Hong Kong	Asia	26.5	111	0.1
14	Thailand	Asia	26.4	133	0.2
15	Portugal	Western Europe	25.3	342	0.5
16	Israel	Middle East	25.2	399	0.5
17	Czech Republic	Eastern Europe	24.6	799	1.1
18	Hungary	Eastern Europe	22.2	622	0.8
19	Mexico	Latin America	22.1	683	0.9
20	India	Asia	19.6	757	1.0
21	Romania	Eastern Europe	19.4	354	0.5
22	Greece	Eastern Europe	19.1	413	0.6
23	South Korea	Asia	17.9	466	0.6
24	Poland	Eastern Europe	17.2	1176	1.6
25	Brazil	Latin America	16.0	754	1.0
26	Spain	Western Europe	14.9	2076	2.8
27	Taiwan	Asia	13.9	420	0.6
28	Bulgaria	Eastern Europe	12.7	215	0.3
29	Germany	Western Europe	11.7	4214	5.7
30	Chile	Latin America	10.6	179	0.2
31	Japan	Oceania	10.3	2002	2.7
32	Austria	Western Europe	9.6	540	0.7
33	Denmark	Western Europe	9.2	492	0.7
34	Australia	Oceania	8.1	1131	1.5
35	Italy	Western Europe	8.1	2039	2.7
36	Singapore	Asia	7.1	86	0.1
37	New Zealand	Oceania	5.9	138	0.2
38	South Africa	Africa	5.5	553	0.7
39	Ireland	Western Europe	5.0	126	0.2
40	Puerto Rico	Latin America	3.6	167	0.2
41	Finland	Western Europe	2.3	370	0.5
42	Netherlands	Western Europe	2.1	1394	1.9
43	France	Western Europe	-4.0	3226	4.3
44	United States	North America	-6.5	36281	48.7
45	Switzerland	Western Europe	-7.6	309	0.4
46	Sweden	Western Europe	-8.6	739	1.0
47	Belgium	Western Europe	-9.4	986	1.3

Table 3

Rankings of BCT Density As of April 12, 2007 per million 2005 Population

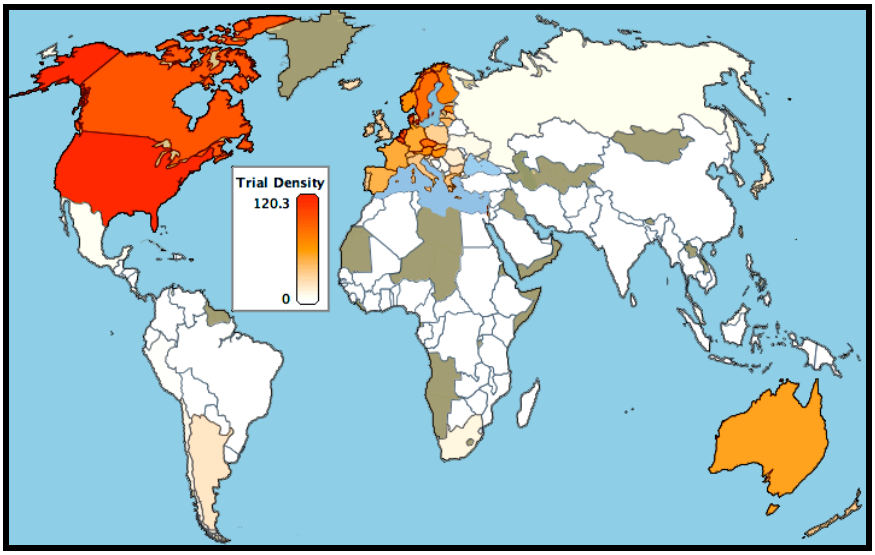
Ranking	Countries	Region	Density	Number of Sites	Share of Sites (%)	AAGR (%)
1	United States	North America	120	36281	48.7	-6.5
2	Belgium	Western Europe	95	986	1.3	-9.4
3	Canada	North America	92	3032	4.1	-12.0
4	Denmark	Western Europe	90	492	0.7	9.2
5	Netherlands	Western Europe	85	1394	1.9	2.1
6	Sweden	Western Europe	81	739	1.0	-8.6
7	*Czech Republic*	*Eastern Europe*	*78*	*799*	*1.1*	*24.6*
8	Finland	Western Europe	70	370	0.5	2.3
9	Austria	Western Europe	65	540	0.7	9.6
10	*Estonia*	*Eastern Europe*	*63*	*83*	*0.1*	*34.6*
11	*Hungary*	*Eastern Europe*	*63*	*622*	*0.8*	*22.2*
12	Norway	Western Europe	62	290	0.4	-14.7
13	*Israel*	*Middle East*	*56*	*399*	*0.5*	*25.2*
14	Australia	Oceania	54	1131	1.5	8.1
15	Germany	Western Europe	51	4214	5.7	11.7
16	France	Western Europe	50	3226	4.3	-4.0
17	Spain	Western Europe	46	2076	2.8	14.9
18	*Slovakia*	*Eastern Europe*	*45*	*246*	*0.3*	*27.7*
19	*Lithuania*	*Eastern Europe*	*43*	*146*	*0.2*	*30.2*
20	*Puerto Rico*	*Latin America*	*42*	*167*	*0.2*	*3.6*
21	Switzerland	Western Europe	41	309	0.4	-7.6
22	*Greece*	*Eastern Europe*	*37*	*413*	*0.6*	*19.1*
23	Italy	Western Europe	35	2039	2.7	8.1
24	New Zealand	Oceania	33	138	0.2	5.9
25	Portugal	Western Europe	32	342	0.5	25.3
26	*Poland*	*Eastern Europe*	*31*	*1176*	*1.6*	*17.2*
27	Ireland	Western Europe	30	126	0.2	5.0
28	*Bulgaria*	*Eastern Europe*	*29*	*215*	*0.3*	*12.7*
29	United Kingdom	Western Europe	29	1753	2.4	-9.9
30	*Singapore*	*Asia*	*19*	*86*	*0.1*	*7.1*
31	*Argentina*	*Latin America*	*19*	*757*	*1.0*	*26.9*
32	*Taiwan*	*Asia*	*18*	*420*	*0.6*	*13.9*
33	*Romania*	*Eastern Europe*	*16*	*354*	*0.5*	*19.4*
34	*Hong Kong*	*Asia*	*16*	*111*	*0.1*	*26.5*
35	Japan	Oceania	16	2002	2.7	10.3
36	*South Africa*	*Africa*	*12*	*553*	*0.7*	*5.5*
37	*Chile*	*Latin America*	*11*	*179*	*0.2*	*10.6*
38	*South Korea*	*Asia*	*10*	*466*	*0.6*	*17.9*
39	*Ukraine*	*Eastern Europe*	*9*	*440*	*0.6*	*31.0*
40	*Russia*	*Eastern Europe*	*8*	*1084*	*1.5*	*33.0*
41	*Mexico*	*Latin America*	*6*	*683*	*0.9*	*22.1*
42	*Malaysia*	*Asia*	*6*	*161*	*0.2*	*32.1*
43	*Peru*	*Latin America*	*4*	*125*	*0.2*	*32.5*
44	*Brazil*	*Latin America*	*4*	*754*	*1.0*	*16.0*
45	*Turkey*	*Middle East*	*3*	*243*	*0.3*	*30.9*
46	*Colombia*	*Latin America*	*3*	*119*	*0.2*	*28.1*
47	*Thailand*	*Asia*	*2*	*133*	*0.2*	*26.4*

Figure 1



The years designate the year in which the BCT site began recruiting patients. The vertical axis is the share of BCT sites by region.

Figure 2



Density of actively recruiting clinical sites of BCT trials per country inhabitant (in millions - based on 2005 population censuses). The darker orange denotes a higher density of trials, while white means close to zero number of recruiting sites per million residents. The countries labeled in gray had no actively recruiting BCT sites as of April 12th 2007.

Table 4: Log Cumulative 2002-2005 BCT Sites Equation (Heteroskedasticity-consistent Standard Errors in Parentheses)

Explanatory Variable	Base Model	Model II	Model III
LGDP	**1.176****	**1.163****	**0.875*****
	(0.485)	**(0.465)**	**(0.465)**
LPOP	-0.298	-0.257	-0.051
	(0.472)	(0.452)	(0.421)
LCOSTPP	**-0.750***	**-0.811***	**-0.766***
	(0.261)	**(0.259)**	**(0.229)**
LRCT	-0.118	-0.141	-0.031
	(0.125)	(0.131)	(0.144)
HCI	**2.716***	**2.674***	**2.668***
	(0.787)	**(0.780)**	**(0.736)**
EREADY	0.027	0.031	**0.031*****
	(0.020)	(0.021)	**(0.018)**
ΔIPR	0.072		
	(0.307)		
ΔRX		0.359	
		(0.243)	
ΔBIOMED			**1.100****
			(0.543)
Constant	**-16.747***	**-16.986***	**-14.010***
	(4.710)	**(4.610)**	**(4.749)**
R-squared	0.816	0.820	0.845
No. Observations	46	46	46

Note: Statistically significant estimates in boldface. *. **, and *** denote statistical significance at p-values of <0.01, 0.05 and 0.10, respectively.

Table 5

Parameter Estimates in AAGR Equation
(Heteroskedasticity-Robust Standard Errors in Parentheses)

Explanatory Variable	Base Case	Model II	Model III
LCOSTPP	0.016	-0.052	-0.073
	(0.111)	(0.108)	(0.105)
LGDPPOP	**-0.370****	**-0.357***	**-0.397***
	(0.157)	**(0.116)**	**(0.119)**
LRCT	**-0.041****	**-0.072***	**-0.060***
	(0.018)	**(0.026)**	**((0.019)**
HCI	0.090	0.318	0.314
	(0.291)	(0.283)	(0.273)
EREADY	0.006	0.006	**0.007*****
	(0.004)	(.004)	**(0.004)**
IPR2000	0.013		
	(0.081)		
RX2000		**0.235****	
		(0.107)	
BIOMED2000			**0.358****
			(0.147)
CONSTANT	**3.429***	**3.233***	**3.401***
	(1.132)	**(0.827)**	**(0.842)**
R-squared	0.583	0.659	0.677
No. Observations	46	46	46

Note: Statistically significant estimates in boldface. *, **, and *** denote statistical significance at p-values < 0.01, 0.05 and 0.10, respectively.

FOOTNOTES

[1] For historical perspectives, see Lerner [2002a,b] and Scherer [2005].
[2] See, for example, Acemoglu, Johnson and Robinson [2001], Gerschenkron [1962], Griliches [1984] and Olson [1982].
[3] The literature on this is extensive, and encompasses various levels of aggregation. For recent discussions and references, see Bottazzi and Peri [2003], Branstetter, Fisman and Foley [2006], Chen and Puttitanum [2005], Eaton and Kortum [1996, 1999], Evenson [1990], Jaffe and Trajtenberg [2002], Javorcik [2004], Keller [2004], Lee and Mansfield [1996], Nelson and Phelps [1966], and McCalman [2001].
[4] Jaffe and Lerner [2004], p. 76.
[5] DiMasi, Hansen and Grabowski [2003, p. 166] report that based on their survey of biopharmaceutical expenditures, the ratio of preclinical to total R&D averaged about 30%.
[6] Thiers, Berndt and Sinskey [2007].
[7] There is, however, considerable variability across drugs and therapeutic classes. This figure is reproduced from Berndt, Gottschalk and Strobeck [2005], which in turn is constructed in part from data cited by Mathiew, M. P., ed. (2003/2004), 'Development Pipeline Attrition' and 'Attrition Rates (Probability of Success) Used by 29 Companies for Planning Purposes in 1998,' PAREXEL 2002/2003 Pharmaceutical R&D Statistical Sourcebook, Waltham, MA, p. 184, based on studies at the Tufts Center for the Study of Drug Development, Hambrecht & Quist estimates.
[8] See Rehnquist [2001] and Milne [2003].
[9] See Owen-Smith et al. [2002], and Stern and Loffler [2006].
[10] For discussions of the medicinal regulatory approval process at the EMEA, in the UK, and Japan, see U. S. Government Accounting Office [1996] and Vilas-Boas and Tharp [1997].
[11] See, for example, Berndt, Bui, Reiley and Urban [1995, 1997] and the references cited therein.
[12] Azoulay [2004].
[13] See McCray [2000], and U.S. Food and Drug Administration [2002,2005].
[14] ICMJE [2004].
[15] Data on the response of various types of clinical investigators to the September 13, 2005 registration deadline are provided in Zarin, Tse and Ide [2006]. A number of other trial registries exist or are in the development process, and vary in terms of details provided regarding the trial protocol and results; to the best of our knowledge, these

other registries do not provide detailed information on trial site location. See, for example, CenterWatch Clinical Trials Listing Service™ , accessible online at http://www.centerwatch.com/letter031105.html, last accessed 21 May 2006; the World Health Organization's International Clinical Trials Registry Platform, accessible online at http://www.who.int/ictrp/data_set/en/index1.html, last accessed 20 May 2006; and the American Medical Informatics Association's Global Trial Bank, accessible online at http://www.amia.org/gtb/. A number of registries exist for specific medical conditions, such as oncology and multiple sclerosis.

[16] See, for example, Rockhold and Krall [2006], Sim et al. [2006] and Vince [2006].

[17] See, for example, Andersen, Kragstrup and Sondergaard [2006], Corrigan and Glass [2005], and Glass [2004,2005]. Classic studies of factors affecting the diffusion of medical innovations are by Coleman, Katz and Menzel [1966] and Rogers [2003].

[18] The framework in this section is very similar to that in United Nations Conference on Trade and Development [2005, chapter V], which describes how the transnational investment and the internationalization of R&D depends on pull factors (market size), push factors (skill shortage and rising costs in industrialized countries), policy factors (IPR, tertiary education, market orientation) and enabling factors (PC and internet access, international harmonization).

[19] These data can be accessed from the clinicaltrials.gov website, which provides data element definitions. Available online at http://prsinfo.clinicaltrials.gov/definitions.html, last accessed June 6, 2006.

[20] We are grateful to Professor Park for making this data available to us; he can be reached at <wgp@american.edu>

[21] The PIRACY index can be accessed online at www.bsa.org/globalstudy.

[22] Kahn [2003], p. 1.

[23] We are grateful to Mr. Ed Seguine, Chief Executive Officer of Fast-Track Systems Inc., for making this proprietary data available to us.

[24] In two cases, India and China, we constructed an estimate of cost per patient.

[25] World Health Statistics 2006, World Health Organization. Data range from 1997 to 2004. Available online at http://www.who.int/whosis/whostat2006.pdf

[26] From OECD Health Data 2006. Data from 2003-2004. Available online at www.irdes.fr/ecosante/OCDE/240020.html.

[27] There are some differences in the composition of the 2003 and 2006 connectivity indexes, particularly involving broadband and WiFi. For discussion, see the methodology and category score appendices in Economist Intelligence Unit [2003,2006].

[28] Data from the World Development Indicators Database, 1 July 2006 and April 2004.

[29] Data from World Health Statistics 2006, World Health Organization. Available on-line at: http://www.who.int/whosis/whostat2006.pdf.

[30] Data from World Health Statistics 2006, World Health Organization. Available on-line at: http://www.who.int/whosis/whostat2006.pdf.

[31] Data from World Health Statistics 2006, World Health Organization. Available on-line at: http://www.who.int/whosis/whostat2006.pdf.

[32] For further discussion, see Gwartney, Lawson and Block [1995]. More recent information is in Gwartney and Lawson [2005], available online at http://www.cato.org/pubs/efw/index.html. …..

[33] Johnson and Shochy [1995]. More recent information is available from the Heriate Foundation website.

[34] Lanjouw [2005], p. 10. For related discussions on the effects of parallel trade on pharmaceutical pricing, see Ganslandt and Maskus [2004] and Kyle [2006].

[35] Currently we are missing some data from four countries: China (excluding Hong Kong), Croatia, Estonia and Puerto Rico.

[36] These regression results are based on 2002-2005 data; we are currently updating data through 2006.

[37] Since our measure of costs per patient is an average over all therapeutic areas and trial phases, and therefore reflects possible heterogeneity among countries in its composition, we examined an alternative specification in which countries were placed into one of three categories: costs per patient less than $3000, costs per patient between $3000 and $4999, and costs per patient of $5000 or greater. The resulting estimates revealed consistent findings in that countries in the medium cost category had a greater number of cumulative BCT sites than those in the highest cost category, while those in the least cost group had an even larger positive effect; these parameter estimates were positive and statistically significant.