

**THE INTERACTION BETWEEN OPEN TRIAL DATA AND DRUG REGULATION IN
SELECTED DEVELOPING COUNTRIES**

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INTRODUCTION

A significant percentage of clinical trials of approved medicines are never published (see, e.g., Ross et al., 2009, 2012). Increasingly, there have been calls to make all clinical trial data part of the public record.¹ Drug regulatory agencies such as the U.S. Food and Drug Administration (FDA) receive extensive data related to such trials, and are now considering the implications of making more such evidence publicly available.

Originator drug companies have argued that making clinical trial evidence submitted to regulators publicly available will facilitate approval of competing products in other countries, and thus lead to competitive harm.² This paper reviews the laws of several key developing-country jurisdictions to further the ability of the Institute of Medicine (IOM) committee to evaluate this claim.

More extensive release of clinical trial data can facilitate the approval of competing/generic products in developing countries only if detailed data are in fact required by regulators in these jurisdictions. If regulators require detailed data, secrecy of clinical trial data may create barriers to entry for nonoriginators in two circumstances: (1) if a nonoriginator company is the first to seek to register a drug in a jurisdiction, meaning that no originator data have been submitted to a regulator for the nonoriginator to rely upon; and (2) if a nonoriginator company is second to register in a jurisdiction where data exclusivity law applies, and so cannot rely on originator data even though they have been submitted to a regulator.³ (Arguably, the first example raises few real competitive concerns, since an originator that does not seek to register in

¹ See, e.g., <http://www.alltrials.net/>.

² See, e.g., *AbbVie v. EMA*, Order of 25.4.2013—Case T-44/13 R (interim decision) para 61.

³ One reviewer suggested that release of clinical trial data could provide competitive intelligence, but (in the author's view correctly) this is of trivial importance in the developing world.

a jurisdiction presumably has little competitive concern there, and perhaps no legitimate interest in precluding others from entering.)

The IOM committee requested that this paper review the “laws on the books” in Brazil, China, and India, that speak to the level of clinical trial data required by regulators, and the data protection provided, in these countries.⁴ Unfortunately, these laws and regulations do not make clear exactly what clinical trial evidence is required. As described below, the information on how these laws are implemented that could be gathered in the time available—which comes from a very few but reliable, sources—supports the conclusion that neither India nor China requires detailed clinical data, and therefore, further release of such data would have little or no effect on practical exclusivity in these jurisdictions. It was not possible to confirm contemporary practice in Brazil, so conclusions with regard to practice in that country could not be drawn. Finally, laws and practices in these countries may, of course, change. But as described in the conclusion to this paper, revisions are possible in multiple directions, so it is not obvious what can be drawn from that fact.

THE INTERACTION BETWEEN OPEN DATA AND DRUG REGULATORY REQUIREMENTS

Drug regulatory schemes generally provide two paths for drug approval. For a new drug that has not previously been approved in a jurisdiction, clinical trials demonstrating its safety and efficacy must be conducted, and data or reports from these trials must be submitted to regulators. If a drug has already been registered once, however, a second-comer can typically follow an

⁴ See Appendix 1. The appendix is also a draft, and subject to revision. Note that it was not possible to identify all relevant regulations or guidance documents in English.

abbreviated process, providing evidence of bioequivalence to the original, and relying by reference on the safety and efficacy data provided by the first entrant.⁵ (Assume, for the moment, that no data exclusivity is in effect.)

As Appendix 1 shows, the statutes and regulations of the three countries considered here suggest that this standard scheme applies to small-molecule drugs in each country. The regulatory environment for biological drugs and biosimilars is more complex, but for present purposes similar. Setting aside the issue of data exclusivity, it appears that competitors may rely on the safety and efficacy data of originators, although in some cases, competitors may also be required to conduct small trials of their own. When competitors are second-comers and data exclusivity is not in effect, secrecy of clinical trial data provides no de facto barrier to entry.

However, there may be barriers to entry for nonoriginators in a different case, where the originator does not enter the jurisdiction to register its new drug, and a competitor seeks to be the first entrant. In this case, the competitor must meet the regulatory standards for new drugs, and will be prevented from entering if regulators require detailed data (for example, patient-level results, spreadsheets) that are not currently made publicly available.

Barriers to entry will exist in this case, however, only if regulators in the target countries in fact require that such detailed data be submitted to them. Statutory frameworks, conversations with those familiar with drug regulatory regimes in the identified countries, and a survey of the available literature suggest that, as noted above, neither India nor China requires detailed patient-level clinical trial data. Brazilian law also appears to be compatible with this account, though this could not be verified with local experts.

⁵ 1 Food and Drug Administration § 3:9 (3rd ed. 2013).

Appendix 1 provides detailed statutory and regulatory language under the “new chemical drugs” and “new biologics” columns for each country reviewed.

India

Under Indian law, the registration of a new drug or biologic “requires data from Phase I, II, and III clinical trials” (“including published review articles”), as well as “regulatory status in other countries.”⁶ In addition, any entity registering a drug for the first time in India must provide evidence of a local clinical trial showing safety and efficacy in an Indian population.⁷ India’s regulations suggest that detailed clinical data, such as subject selection criteria and statistical methods, are required for new drug applications, but also create a catch-all exception to this, providing that “the data required will depend upon the purpose of the new drug application.”⁸ Recent draft guidance, finally, suggests that India would permit new drugs to be registered on the basis of “entirely original data,” or “entirely data from the literature,” or both (CDSCO, 2011). Existing laws and regulations thus do not precisely describe the level of data required, and appear to provide some discretion to regulators.

However, the recent draft guidance suggests, and an expert on the Indian pharmaceutical sector has confirmed, that in India, standard practice is as follows. If a drug has been approved in the United States, the United Kingdom, Canada, the European Union, Japan, or Australia, approval in India is based largely on approval in these other countries (see CDSCO, 2011, p.

⁶ Drugs and Cosmetics Act of 1940 Rules, Form 44.

⁷ Schedule Y of Drugs and Cosmetics (IInd Amendment) Rules 2005, Art. 1(iv)(b).

⁸ Schedule Y of Drugs and Cosmetics (IInd Amendment) Rules 2005, Art. 1(iv)(c).

30).⁹ While applicants must provide summaries of the safety and efficacy data, these data are generally available, for example, through the summary basis of approval published by the U.S. FDA.¹⁰ It is thus common for Indian generic companies to seek and obtain approval for new chemical entities (NCEs) in India before (or entirely without) originator entry. For example, this has occurred with drugs including rasagiline mesylate, lenalidomide, and atomoxetine.¹¹

China

China has a complex regulatory structure, providing a different process for imported and nonimported drugs (see CFDA, undated, Article 12; Su, 2013. p. 20). As regards the degree of clinical data required, for both new biologics and small molecule drugs, and for imported as well as new drugs, the law only specifies that applicants provide “sufficient and reliable research data to prove the safety, efficacy and quality of the drug.”¹² In addition, all new drugs applicants must provide evidence of safety and efficacy specifically in Chinese patients, a requirement that may be met either by including a China trial site in a global clinical trial design, or via separate trials conducted in China (Su, 2013, p. 23). Imported drugs also must be approved in the producing country, or be specially reviewed by the Chinese agency (CFDA, undated, Article 36).

⁹ This information was provided via conversation and email exchange with Raghu Cidambi, in April 2014. Raghu Cidambi was formerly Advisor, Dr. Reddy’s Laboratories Ltd, Hyderabad, India. He worked in the areas of Corporate Strategy, Legal Affairs and IP. For additional confirmation of the practice, see PhRMA (2014, p. 28): “India conditions the approval of pharmaceutical products on the prior approval by a Regulatory Authority in another country rather than requiring submission of the entire dossier for review by its Regulatory Authority. An applicant in India needs only to prove that the drug has been approved and marketed in another country and submit confirmatory test and other data from clinical studies on a very few (in some cases as few as 16) Indian patients.”

¹⁰ Information from Raghu Cidambi, April 2014. If a drug has been registered by the FDA, detailed overviews of trial results and protocols are already made publicly available on the Drugs@FDA website. See <http://www.accessdata.fda.gov/Scripts/cder/drugsatfda/index.cfm>.

¹¹ Information from Raghu Cidambi, April 2014.

¹² Regulations for Implementation of the Drug Administration Law of the People’s Republic of China, Art. 13 (2005).

Conversations with an expert on the pharmaceutical sector in China confirmed that Chinese practice with respect to the level of clinical trial data required is much like practice in India.¹³ If a drug has been approved by the U.S. FDA, a nonoriginator may gain approval of the drug by submitting evidence drawn entirely from publicly available sources, such as the FDA summary report described above.¹⁴ The requirement to prove safety and efficacy in Chinese patients of course must also be met, requiring a competitor company to conduct local trials itself if an originator does not seek entry and submit such data.

One member of the IOM committee raised the concern that a competitor might be advantaged by the interaction between wider access to clinical trial data and the protracted nature of the approval process for imported drugs in China. When a foreign company follows the import drug regulatory route, it must produce and submit local clinical trial data, with final approval after submission of those data reportedly taking 12-15 months (Su, 2013, p. 21). Local registrants follow a different review process, raising the possibility that if local registrants gain quick access to originator-produced local clinical trial data (e.g., through release by the U.S. FDA), local companies might obtain approval during this year-long lag period. It is unclear how likely this is to occur in practice, because it turns on how rapidly the local registration could be concluded after the local trial data had been submitted—about which no evidence could be found.

Consequences would, in any case, likely be modest. Local clinical trials are small—perhaps 100 people—and of limited scope, so are relatively inexpensive (Su, 2013). The financial gain from

¹³ This was confirmed in conversation and correspondence with a China expert who did not wish to be identified by name, in April 2014. This expert has more than 10 years of research experience in the field of life sciences; served as in-house intellectual property (IP) counsel for a pharmaceutical multinational corporation (MNC); and worked as an IP attorney for many years, focusing on IP and regulatory matters for the pharmaceutical and life science industry.

¹⁴ See also PhRMA (2014, p. 42): “China’s regulatory procedures permit non-originator, or follow-on, applicants to rely on a foreign regulatory agency’s approval of the originator product in another market during the RDP term in China. This [allows] the follow-on manufacturer...to rely on the full clinical data submitted by an innovator to a foreign regulatory agency.”

secrecy of data regarding these local trials thus is likely very small, limited to the cost of the trials themselves (for were gains higher than costs, local companies could simply conduct their own trials to seek earlier entry). Multinational corporations (MNCs) also have the option of avoiding the importer track if sufficiently concerned about the speed of entry into the market (Su, 2013).

Brazil

In the Brazilian case, for new chemical drugs, a “report” of clinical trials is required, as well as evidence of registration in the country of origin.¹⁵ For new biological drugs, the situation is still less clear: Brazil requires “clinical trial documents,” but specifies only that “protocols” of such trials are required if this is the first registration in the world for the biologic.¹⁶ Further research is needed to confirm how these laws and regulations are implemented in Brazil.

Conclusion

In both India and China (with practice in Brazil unconfirmed), competitors (or generics) can today register new products even if an originator has not preceded them. Secrecy of clinical trial data thus does not now provide effective barriers to entry for competitors in these jurisdictions. The release of more such data should thus have no practical effect in these jurisdictions. In theory, competitors could still face a barrier to entry if a drug had not been approved elsewhere in the world, or at least not approved in jurisdictions such the United States

¹⁵ RDC No. 136 of 2003, Art. II (2)(c), 3(d).

¹⁶ RDC No. 315 of 2005, Art. 13, 38.

that are well respected and that make reports on the basis for their decisions public. However, if the larger question before the IOM committee is the effect of the release of clinical trial data from an agency such as the FDA for postapproval drugs, then by stipulation, the drug in question would have been approved by that agency. Finally, it is worth noting that where an originator has decided not to enter a jurisdiction, it is not obvious that the entry of a competitor creates genuine competitive harm in any case. If an originator is not selling a drug in a jurisdiction, it presumably has little competitive interest in that market, and perhaps no legitimate interest in preventing entry by others.

THE IMPACT OF DATA EXCLUSIVITY

In a country with data exclusivity rules, competitors may not register a drug with reliance on the originator's safety and efficacy data until the exclusivity period has expired. Although some originator companies and governments argue that Trade-Related Aspects of Intellectual Property Rights (TRIPS) Article 39.3 requires a "data exclusivity" approach, no established authority—for example, a World Trade Organization (WTO) dispute settlement decision—confirms this, and many countries take the view that TRIPS requires only "data protection" (Clift, 2007, p. 432). Under a data protection model, a country protects data submitted to a regulator from unfair commercial use and disclosure (for example, by not releasing the data absent public justification), but allows regulators to reference such data in their decision making (Clift, 2007, p. 432).

Appendix 1 reviews the relevant statutory provisions with respect to data exclusivity/protection law. Some details are difficult to draw from the statutes, however, so a

brief discussion of each jurisdiction will be helpful. India has taken the data protection approach (see Reddy and Sandhu, 2007).¹⁷ The Indian government has also many times reiterated its commitment to a data protection model, and rejected a move to data exclusivity (see Gopalakrishnan and Kadavan, 2013; The Economic Times, 2011).¹⁸

The picture in Brazil is more complex. Brazilian law provides that “a crime of unfair competition is perpetrated by anyone who:...divulges, exploits, or utilizes, without authorization, results of tests or other undisclosed data whose preparation involves considerable effort and that were submitted to government agencies as a condition for obtaining approval to commercialize products.”¹⁹ Different interpretations of the law have been offered, with some arguing that it provides data exclusivity and others data protection. The broad interpretation of data exclusivity was undermined by the passage 6 years later of Brazilian Law No. 10.603, which provides data exclusivity only for veterinary and agricultural products (Andanda, 2013). Although the original version of the 2002 act also provided for data exclusivity with respect to human pharmaceuticals, the Brazilian National Congress expressly rejected this category and omitted it from the final version of the act (Andanda, 2013). Thus, the predominant interpretation appears to be that Brazilian law does not recognize data exclusivity for human pharmaceuticals (Andanda, 2013). Pharmaceutical companies have, however, challenged this interpretation in court, creating some confusion about the state of the law (for a discussion, see Andanda [2013] and Center for Strategic Studies and Debates [2013, p. 160]). A new report from the Brazilian Centre for Strategic Studies and Debates of the Brazilian Chamber of Deputies (a federal legislative body)

¹⁷ Drug and Cosmetics Act of 1940, Art. 53; Official Secrets Act of 1923, Section 6.

¹⁸ During negotiations with the European Union in which data exclusivity was a major topic, the Indian government reiterated its opposition to data exclusivity and commitment to a “data protection” model.

¹⁹ See Art. 195 XIV.

proposes that as part of a patent reform bill, a new provision be added to make clear that Brazil provides only data protection (Center for Strategic Studies and Debates, 2013, pp. 161-162).

China, in contrast, provides 6 years of data exclusivity. Chinese law provides that:

Within six years from the date a drug manufacturer or seller obtains the approval documents for producing or marketing a drug containing new chemical entities, if any other applicant uses the data mentioned in the preceding paragraph to apply for approval for production or marketing of the drug in question without permission of the original applicant who has obtained the approval, no approval may be given to any other applicant by the drug regulatory department except that the data submitted are acquired *independently* (emphasis added).²⁰

China has apparently interpreted its data exclusivity law very narrowly. For example, Chinese agencies in practice have allegedly interpreted “new chemical entities” to include “only pharmaceutical products that are new to the world—in other words, products that make their international debut in China” (PhRMA, 2014, p. 42).

Most important for our purposes, according to the Pharmaceutical Researchers and Manufacturers of America (PhRMA), China permits “non-originator, or follow-on, applicants to rely on a foreign regulatory agency’s approval of the originator product in another market during the [data exclusivity] term in China. This...permit[s] it to rely on the full clinical data submitted by an innovator to a foreign regulatory agency...while having to submit only a small amount of China-specific supplemental data to CFDA” (PhRMA, 2014, pp. 41-42).

²⁰ Implementation of Drug Administration Law of the People’s Republic of China, Ch. 5, Art. 35.

Even where data exclusivity is in place, as this suggests, the key question remains whether regulatory bodies in developing countries in fact require detailed clinical trial data. In China, which does not require such detailed data, broader release of clinical trial data by an entity such as the FDA should not affect data exclusivity. This is because nonoriginators can today apparently rely upon publicly available data to enter, under China's interpretation of its data exclusivity provision, presumably on the grounds that the nonoriginator has an "independent" source for these data—namely, the summary basis of approval or perhaps simple fact of approval in other jurisdictions.

Finally, it bears noting that laws in these jurisdictions may change. For example, China is under pressure to change its data exclusivity laws, and could decide to require competitors to submit full data even when a drug has been approved elsewhere. But by the same token, China could forbid the submission of "downloaded" data (as opposed to data generated through new, nonoriginator clinical trials) for these purposes. In other words, national law could be changed in ways that would create, or avoid, interaction with practices of open release for FDA-submitted data. Therefore, it is not clear what conclusions can be drawn from the possibility of revisions to the laws identified here.

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APPENDIX 1. Clinical Data Requirements in Brazil, India, and China [DRAFT]

This chart collects the statutory and regulatory provisions relevant to the clinical trial data requirements for new and follow-on drug registration in India, Brazil, and China. (It does not cover other requirements, such as requirements for preclinical toxicity information, pharmacokinetics, good manufacturing practices [GMP], and quality control.) Official translations are used where available, and noted where unavailable.

Brazil: Clinical Data Requirements

New Chemical Drugs	New Biologics	Follow-Ons
<ul style="list-style-type: none"> • Governed by Law No. 6,360 of 1976; RDC No. 136 of 2003 (official translations) <p><u>Law No. 6,360 of 1976</u></p> <ul style="list-style-type: none"> • Registration of chemical drugs requires: “That the product, by means of scientific verification and analysis, be recognized as safe and effective for the intended use and possess the necessary, activity, quality, purity and innocuity;” (Art. 16.II) • “In cases of new products, that extensive information be provided on their composition and use, so that their nature be assessed and their necessary degree of safety and efficacy be determined;” (Art. 16.III) • “Registration of drugs, medicines and pharmaceutical inputs of foreign provenance shall depend, in addition to on the conditions, requirements and procedures provided for in this Law and in its regulation, on the verification that such products are already registered in their countries of origin” (Art. 18) <p><u>RDC No. 136 of 2003</u></p> <ul style="list-style-type: none"> • New drugs must provide: “Report of clinical trials to prove therapeutic efficacy in compliance with specific legislation. Data shall be accompanied by bibliographic references whenever available. Information 	<ul style="list-style-type: none"> • Governed by RDC No. 315 of 2005 (official translation) <p><u>RDC No. 315</u></p> <ul style="list-style-type: none"> • Imported new biological must be registered and authorized for use in the manufacturing country (Arts. 8.2, 9.1) • “All therapeutic activities...shall be proven by clinical trial documents, which must be compiled in the dossier for product registration.” (Art.13) • If this is the <u>first registration in the world</u>, must also submit “all protocols of phase-1, phase-2, and phase-III clinical trials. “ (Art. 38). • Required documents for registration include: “Phase-I Clinical Trials; Phase-II Clinical Trials; Phase-III Clinical Trials; Phase-IV Clinical Trials—Post-marketing, if existent “ (Ch. III Art.2.12.2) 	<p><u>Generics</u></p> <ul style="list-style-type: none"> • Governed by Law No. 9,787 of 1999; RDC No. 135 of 2003 (official translation); RDC No. 136 of 2003 (official translation); RDC No. 16 of 2007 (not available in English) • RDC No. 16 replaced RDC No. 135, but only RDC No. 135 is available in English (official translation) <p><u>Law No. 9,787 of 1999</u></p> <ul style="list-style-type: none"> • Generic definition: “drug product similar to a reference or innovative product, expected to be interchangeable with the latter, usually produced after the expiration or waiver of patent protection or of other exclusiveness rights, its effectiveness, safety and quality being proven....” (Art. 3 (XXI)) • Appears that the reference drug must first be registered in Brazil. <ul style="list-style-type: none"> ○ Reference drug definition: “innovative product registered at the federal agency in charge of the sanitary surveillance and marketed in the country, for which effectiveness, safety and quality have been scientifically proven to the competent federal agency, upon its registration.” (Art. 3 (XXII)). ○ “Federal agency” refers to the Brazilian federal agency: “The federal agency in charge of sanitary surveillance shall regulate, within ninety days: <ul style="list-style-type: none"> ▪ I - the criteria and conditions for the registration and quality control of generic drugs;

<p>shall be submitted in the following order: phase I, II and II clinical studies. ANVISA may review the data of phase III clinical studies to check whether the difference found in the results of the groups that received different” (Art. II (2)(c)).</p> <ul style="list-style-type: none"> • To import new drugs must “submit a registration receipt emitted by the sanitary authority of a country that hosts the company and the respective package insert text.” (Art. II (3)(d)). • <u>Exceptions</u>: “In case of pharmaceutical forms, concentrations, routes of administration or indications for use that are new in the country for synthetic or semi-synthetic active ingredients by companies that do not possess the initial registration of that/those active ingredient(s),” the applicant need provide the following: <ul style="list-style-type: none"> ○ “The results of the Phase III studies for companies that discover a new therapeutic indication in the country for an active ingredient registered by another company, in the same concentration and pharmaceutical form.” ○ “Phase II and III studies for companies that discover a new concentration and/or pharmaceutical form, and/or administration route in the country for the same therapeutic indication for a pharmaceutical ingredient registered by another company. These studies shall be considered unnecessary and substituted by 		<ul style="list-style-type: none"> ▪ II - the criteria for bioavailability tests of pharmaceutical products in general; ▪ III - the criteria for the assessment of therapeutic equivalence, through bioequivalence tests of generic drugs, in order to characterize their interchangeability.” (Art. 2) <p><u>RDC No. 136 of 2003</u></p> <ul style="list-style-type: none"> • Apparently do not have to submit clinical trial data unless: <ul style="list-style-type: none"> ○ The registration is for a new therapeutic indication (Phase III study required) ○ The registration is for a new concentration, pharmaceutical form, and/or administrative route (Art. II (2)(f)) • (See New Chemical Drugs column for exact text) <p><u>RDC No. 16 of 2007 (not available in English)</u></p> <ul style="list-style-type: none"> • Bioequivalence: Must show that active ingredient is chemically identical to a branded-approved drug, document bioavailability, pharmaceutical equivalence with the branded product, and compliance with sound manufacturing provisions required by Anvisa.ⁱ <p><u>Biosimilars</u></p> <ul style="list-style-type: none"> • Governed by RDC No. 55 of 2010 (not available in English) • Appears that reference biologic does not have to be registered in Brazil – simply has to be registered in another country with a well-established regulatory frameworkⁱⁱ
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<p>relative bioavailability tests whenever they fall within the already approved therapeutic range” (Art. II (2)(f))</p>		<ul style="list-style-type: none"> • Two potential registration processes: (1) comparability pathway; and (2) individual development pathwayⁱⁱⁱ <ul style="list-style-type: none"> ○ Eligibility depends on how well documented the reference biologic is^{iv} ○ Comparability pathway: don’t need to submit clinical studies where the manufacturer can demonstrate bioequivalence (similar physiochemical characteristics)^v ○ Individual development pathway: The applicant needs to provide complete data regarding quality issues, but unlike for new therapeutics, is only required to present comparative data for Phase III clinical trials.^{vi} • Regulations are confusing: would appear to be regulated by RDC No. 315 of 2005 as well, but in practice they are not: <ul style="list-style-type: none"> ○ RDC 315 purports to regulate “Biological Drugs” —e.g. those biological drugs “containing a molecule with known biological activity, already registered in Brazil...” (Art. 18.1) ○ “In case of a Biological Drug, the registration requester may present Comparable Clinical trials (showing non-inferiority) as demonstration of therapeutic activity and safety” (Art. 12.1-2) ○ Since these guidelines failed to define what is required of Comparable Clinical trials, Brazilian regulators adopted RDC No. 55^{vii}
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China: Clinical Data Requirements

Import Drugs	New Drugs/Biologics	Follow-Ons
<ul style="list-style-type: none"> • Governed by several statutes/regulations: • (1) “Drug Administration Law of the People’s Republic of China of 2001”; (2) “Regulations for Implementation of the Drug Administration Law of the People’s Republic of China”; (3) “Provisions for Drug Registration”; (4) “The Procedure For Import Drug CFDA (sfda) Registration” (official translations) <p><u>Drug Administration Law of the People’s Republic of China of 2001</u></p> <ul style="list-style-type: none"> • “Evaluation of drugs to be imported shall be organized by the drug regulatory department under the State Council. A drug may be imported only upon approval granted after the fact that it conforms to the quality specifications and is safe and effective is affirmed through examination, and an import drug license shall be issued.” (Art. 39). <p><u>Regulations for Implementation of the Drug Administration Law of the People’s Republic of China (2002)</u></p> <ul style="list-style-type: none"> • Law distinguishes between import drugs (apparently those “produced by 	<p>Governed by three statutes/regulations: (1) “Drug Administration Law of the People’s Republic of China”; (2) “Regulations for Implementation of the Drug Administration Law of the People’s Republic of China”; (3) “Provisions for Drug Registration” (official translations)</p> <p><u>Drug Administration Law of the People’s Republic of China</u></p> <ul style="list-style-type: none"> • “Measures for verifying the qualifications of clinical study institutions for drugs shall be formulated jointly by the drug regulatory department and the administrative department for health under the State Council.” (Art. 29). • “When a new drug has gone through clinical trials and passed the evaluation, a New Drug Certificate shall be issued upon approval by the drug regulatory department under the State Council.” (Art. 29). • “The State exercises special control over the circulation of preventive biological products. Specific measures shall be formulated by the State Council.” (Art. 104). <p><u>Provisions for Drug Registration</u></p>	<p><u>Generics</u></p> <ul style="list-style-type: none"> • Governed by “Provisions for Drug Registration” (official translation) • Distinguishes between import drugs and generic drugs (Art. 12) • Generic Drug Definition: “Application for generic drugs refers to registration application for producing the drugs having existing national drug standard which is approved to be marketed by the State Food and Drug Administration” (Art. 12). • “To apply for the registration of a generic drug, the applicant shall fill the Application Form for Drug Registration, submit relevant dossiers and apply for production site inspection to the drug regulatory department of the province, autonomous region, or municipality directly under the Central Government where the applicant is located.” (Art. 75) • On face of the law it is unclear when clinical data might be required: “Clinical trials shall be conducted in accordance with the requirements in the Annex of the Provisions” (We have been unable to locate the Annex in English.) • Secondary Sources: Only need bioequivalence data^{ix} <p><u>Biosimilars</u></p> <ul style="list-style-type: none"> • Governed by “Provisions for Drug Registration: Registration Categories and

<p>a foreign manufacturer” Art. 36) versus new drugs (drugs that have not been marketed previously in China – Art. 83):</p> <ul style="list-style-type: none"> • “Any drug applied to be imported shall be the one obtained marketing authorization in the country or region of manufacturing. A drug without such an authorization may be approved of its importation in accordance with the provisions in the Drug Administration Law and in the Regulations, provided that its safety, efficacy and clinical needs have been confirmed by the drug regulatory department under the State Council.” (Art. 36) • Apparently for all new drugs, “The applicant shall provide sufficient and reliable research data to prove the safety, efficacy and quality of the drug, and be liable for the authenticity of all the dossiers submitted.” (Art. 13) • (No more detailed information in regulation on clinical trial data) <p><u>Provisions for Drug Registration (SFDA Order No. 28) (2007)</u></p> <ul style="list-style-type: none"> • Also distinguishes between import drugs and new drugs. • “New drugs” are those that have not been marketed previously in China. (Art. 12). “Import drugs” are those “manufactured abroad to be marketed” 	<ul style="list-style-type: none"> • Biologics = New Drugs: “The application for biological products shall be submitted as the process of new drug application” (Art. 12) 	<p>Application Information Items Requirements of Biological Products” (no official translation; summary given by Navote).</p> <ul style="list-style-type: none"> • Regulations do not distinguish between biologics and biosimilars—biologics registration includes “[a] product that is marketed already overseas but not yet marketed domestic [sic].”^x • As a result, biologics and biosimilars follow the same registration process, and presumably also rely on bioequivalence and (in certain cases) on clinical trials of the second-entrant.
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<p>in China (Art. 12).</p> <ul style="list-style-type: none"> • Under the provision for “Import Drugs,” states: “A drug being applied for importation shall have already obtained the drug marketing authorization in the producing country or region where the overseas pharmaceutical manufacturer is located; those not yet obtained marketing authorization in the producing country or region, however confirmed with safety, efficacy and clinical needs by the State Food and Drug Administration may be approved for importation.” (Art. 84) • “To apply for import drug registration, the applicant shall fill the Application Form for Drug Registration, submit relevant dossiers and samples, provide relevant approval documents, and submit the application to the State Food and Drug Administration” (Art. 85) • Also for import drugs: “Where the regulations are conformed to, a Clinical Trial Approval shall be issued; where the regulations are not conformed to, a Disapproval Notice shall be issued with reasons” (Art. 92). • “After a clinical trial application is approved, the applicant shall conduct the trial in accordance with the requirements in Chapter III of the 		
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<p>Provisions and the other relevant requirements” (Art. 93).</p> <ul style="list-style-type: none"> Chapter III does not define the requirements of a local clinical trial as part of an import drug application. Secondary sources indicate that the clinical trial would replicate a Phase III clinical trial, but would be conducted in China and on a small number of local patients (circa 100-200)^{viii} 		
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India: Clinical Data Requirements

Chemical Drugs	Biologics	Follow-Ons
<ul style="list-style-type: none"> Governed by the Drugs and Cosmetics Act, 1940 Draft Guidance for Industry, which do not have statutory force, but largely represents current practice of approval: <ul style="list-style-type: none"> On Fixed Dose Combinations, August 20, 2010 On Approval of Clinical Trials & New Drugs, July 2011 Guidance for Industry on Preparation of Technical Document For Import / Manufacture and Marketing Approval Drugs For Human Use <p><u>Drugs and Cosmetics Act of 1940, Rules</u></p> <ul style="list-style-type: none"> Importers are required “to submit data as given in Appendix I to Schedule Y...and submit the report of such clinical trials in the format given in appendix II to the said Schedule.” (Art. 122-A) According to the relevant registration Form (Form 	<ul style="list-style-type: none"> Governed by Schedule Y and Appendix 1 of Schedule Y Regulations do not specifically mention biologics, but secondary literature says biologics follow the same procedure as chemical drugs^{xi} 	<p><u>Generic Drugs</u></p> <ul style="list-style-type: none"> Governed by Appendix 1-A to Schedule Y Drugs only qualify if the reference drug “is already approved in the country” Requires “Bioavailability / Bioequivalence and comparative dissolution studies for oral dosage forms” <p><u>Biosimilars</u></p> <ul style="list-style-type: none"> Governed by Guidelines on Similar Biologics (Sept. 2012)^{xii} Reference biologic does not have to be registered in India— “In case the reference biologic is not authorized in India, it should have been licensed and marketed for at least 4 years with significant safety and efficacy data.” (§5). “Although the extent of testing of the similar

<p>44), permission to market a new drug requires data from Phase I, II, and III clinical trials (“including published review articles”) as well as “regulatory status in other countries.”</p> <ul style="list-style-type: none"> • “Application for permission to import or manufacture new drugs for sale” requires “human Clinical Pharmacology Data as prescribed in items 5, 6, and 7 of Appendix I” is required • “[F]or new drug substances discovered in countries other than India, Phase I data as required under items 1, 2, 3, 4, 5 (data from other countries) and 9 of Appendix I should be submitted along with the application.” (Art. 1(iv)(b)) • “After submission of Phase I data generated outside India to the Licensing Authority, permission may be granted to repeat Phase I trials and/or to conduct Phase II trials and subsequently Phase III trials concurrently with other global trials for that drug. Phase III trials are required to be conducted in India before permission to market the drug in India is granted;” (Art. 1(iv)(b)) • “[T]he data required will depend upon the purpose of the new drug application.” (Art. 1(iv)(c)) • Also must include “regulatory status in other countries as prescribed in item 9.2 of Appendix I.” <p><u>Appendix I</u> (“Data to Be Submitted With the Application . . . to Import . . . New Drugs”)</p> <ul style="list-style-type: none"> • Items 1-4 do not involve clinical data • As per above, the following data is required: • “5. Human / Clinical pharmacology (Phase I) <ul style="list-style-type: none"> ○ 5.1. Summary ○ 5.2. Specific Pharmacological effects 		<p>biologic is likely to be less than that required for the reference biologic, it is essential that the testing of the similar biologic be sufficient to ensure that the product meets acceptable levels of safety, efficacy and quality to ensure public health.” (§6).</p> <ul style="list-style-type: none"> • “Generally, a reduction in data requirements is possible for preclinical and / or clinical components of the development program by demonstration of comparability of product (similarity to authorized reference biologic) and the consistency in production process, which may vary depending on the characteristics of the already authorized reference biologic.” (§6). • Reduction of data requires on the following conditions: <ul style="list-style-type: none"> ○ “Similarity with respect to quality has been proven to reference biologic ○ Similarity with respect to preclinical assessment has been proven to reference biologic ○ Clinical safety and efficacy is proven in one indication ○ Mechanism of action is same for other clinical indications ○ Involved receptor(s) are same for other clinical indications” (§6).
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<ul style="list-style-type: none"> ○ 5.3. General Pharmacological effects ○ 5.4. Pharmacokinetics, absorption, distribution, metabolism, excretion ○ 5.5. Pharmacodynamics/early measurement of drug activity” ● 6. Therapeutic exploratory trials (Phase II) <ul style="list-style-type: none"> ○ 6.1. Summary ○ 6.2. Study report(s) as given in Appendix II ● 7. Therapeutic confirmatory trials (Phase III) <ul style="list-style-type: none"> ○ 7.1. Summary ○ 7.2. Individual study reports with listing of sites and Investigators.” ● “9. Regulatory status in other countries <ul style="list-style-type: none"> ○ 9.1. Countries where the drug is <ul style="list-style-type: none"> ▪ a. Marketed ▪ b. Approved ▪ c. Approved as IND ▪ d. Withdrawn, if any, with reasons ○ 9.2. Restrictions on use, if any, in countries where marketed/approved ○ 9.3. Free sale certificate or certificate of analysis, as appropriate.” ● “All items may not be applicable to all drugs. For explanation, refer text of Schedule Y.” <p><u>Appendix II:</u> (“Structure, Content, and Format for Clinical Study Reports”)</p> <ul style="list-style-type: none"> ● This section details specific information that must be submitted, including detailed elements such as “overall trial design,” “Subject selection criteria,” “statistical methods,” etc. ● Also requires “Investigator’s report that he/she has read the report and that the report accurately 		
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describes the conduct and results of the study.”

- It is unclear when this requirement is applied – see above bolded text, which suggest discretion to require more or less data depending on situation.

DRAFT Guidance on Approval of Clinical Trials & New Drugs (2011)

- 8.2 New Chemical Entity approved & marketed in other countries not approved in India.

For such New Drugs to be approved for marketing, data required to be submitted will be similar as per Appendix I of Schedule Y which is similar to data required for any new chemical entity (NCE).

Generally, the new drugs which are approved in one or more countries like USA, UK, Canada, European Union, Japan, and Australia will be considered for approval of manufacture/import & marketing of the drug in the country....

For such new drugs, Phase III studies need to be carried out locally primarily to generate evidence of efficacy and safety of the drug in Indian patients when used as recommended in the prescribing information. Prior to conduct of Phase III studies in Indian subjects, Licensing Authority may require pharmacokinetic studies to be undertaken to verify that the data generated in Indian population is in conformity with the data already generated abroad. As per the provisions given in the Drugs & Cosmetics Rules requirement of submitting results of local clinical trials may not be necessary, if the drug is of such a

nature that the licensing authority may in public interest decide to grant such permissions on the basis of data available from other countries.		
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ⁱ Paulo Arvate, et al., “Generic-Branded Drug Competition and the Price for Pharmaceuticals in Procurement Auctions” (July 22, 2013).

ⁱⁱ Jun Wang and Shein-Chung Chow, “On the Regulatory Approval Pathway of Biosimilar Products,” 5 *Pharmaceuticals* 353, 364 (2012).

ⁱⁱⁱ “Regulatory Pathways Are Opening Up Globally For Biosimilars,” IPQ (August 7, 2012).

^{iv} *Id.*

^v Thomas Kirchlechner, “Biosimilar Regulatory Overview,” Sandoz Pharmaceuticals, 17 (June 25, 2013).

^{vi} Otto Licks, “Generics and Biosimilars in Brazil: Elements on the Industrial Policy of the Brazilian Government,” updated November 1, 2011.

^{vii} “The Procedure For Import Drug CFDA (sfda) Registration,” SFDA (last visited March 26, 2014), *available at* <http://www.sfdachina.com/info/80-1.htm>

^{viii} Ling Su, “Drug Development Models in China and the Impact on Multinational Pharmaceutical Companies,” Sidley Austin LLP, 20 (September 2013).

^{ix} Shaoyu Chen, “The Regulatory Approval Process for New Drugs & Devices in China,” Covington & Burling LLP (not date given).

^x “Provisions for Drug Registration: Registration Categories and Application Information Items Requirements of Biological Products,” Novote, Part I.

^{xi} Rajashree Sharma, “Guidelines on Similar Biologics- a milestone for India,” PharmaBiz.com (Oct. 4, 2012).

^{xii} “Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India,” Government of India (Sept. 2012).

Brazil – Data Protection

Law 9.279 on Industrial Property; Title V, Crimes Against Industrial Property; Chapter VI, Protection Against Unfair Competition

“A crime of unfair competition is perpetrated by anyone who: . . . divulges, exploits, or utilizes, without authorization, results of tests or other undisclosed data whose preparation involves considerable effort and that were submitted to government agencies as a condition for obtaining approval to commercialize products.” (Art. 195 XIV)

**NOTE: two Brazilian laws governing data protection do not have English translations. First, Decree 1.355 of 1994 is a Portuguese translation of Article 39.3 of TRIPS. Second, Law No. 10.603 of 2002 provides data exclusivity to veterinary and agricultural products for ten years. The law does not mention human pharmaceuticals.

Pamela Andanda, *Managing intellectual property rights over clinical trial data to promote access and benefit sharing in public health*, 44 INTERNATIONAL REVIEW OF INTELLECTUAL PROPERTY AND COMPETITION LAW 2, 5 (2013).

China – Data Exclusivity

Regulations for Implementation of the Drug Administration Law

“The State protects undisclosed data of drug study and others which are independently acquired and submitted by drug manufacturers or sellers to obtain production or marketing approval of the drugs in question which contain new chemical entities. No one may make unfair commercial use of the said data. Within six years from the date a drug manufacturer or seller obtains the approval documents for producing or marketing a drug containing new chemical entities, if any other applicant uses the data mentioned in the preceding paragraph to apply for approval for production or marketing of the drug in question without permission of the original applicant who has obtained the approval, no approval may be given to any other applicant by the drug regulatory department except that the data submitted are acquired independently. No drug regulatory department may disclose the data set forth in the first paragraph of this Article except (1) for the need of public interests; or (2) where steps are taken to ensure that the data are protected against unfair commercial use.” (Art. 35)

Provisions for Drug Registration

“In accordance with the provisions in Article 35 of the Regulations for Implementation of the Drug Administration Law, where a manufacturer or distributor submits undisclosed drug experimental and other data which are independently acquired in order to obtain approval for production or marketing of the drug in question which contains any new chemical entity, the State Food and Drug Administration shall, within six years from the approval date of the drug, reject any application made by any other applicants by using the undisclosed data of the drug in question without permission of the original applicant who has obtained the drug approval, unless the data submitted are independently acquired by the applicants other than the original one.” (Art. 20)

India – Data Protection

Drug and Cosmetics Act of 1940

“Except for the purposes of official business or when required by a Court of Law, an Inspector shall not, without the sanction in writing of his official superior, disclose to any person any information acquired by him in the course of his official duties.” (Art. 53).

Common Law, Law of Torts, and the Indian Contract Act, 1872.

“The protection to undisclosed information or trade secrets against unfair competition is provided through the provisions of Common law, Law of Torts and the Indian Contract Act, 1872. “

-- Swatnat Reddy, *Report on Steps to Be Taken By the Government Of India in the Context of Data Protection Provision of Article 39.3 of Trips Agreement*, INTER-MINISTERIAL CONSULTATIVE COMMITTEE, iv (May 31, 2007).

Official Secrets Act of 1923

Prohibits disclosure by “any person having in his possession or control any...sketch, plan, model, article, note, document, or information...which has been entrusted in confidence to him by any person holding office under Government, or which he has obtained or to which he has had access owing to his position....” (Section 6).

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