



Regulatory Reforms in India: Clinical and Marketing Opportunities

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ABSTRACT

The aim of this paper was to evaluate current regulatory guidelines for clinical research, drug development and the evolution and reforms in current and evolving practices in the United States, and Canada, with a detailed focus on India's regulatory reforms and growing market. The United States is the largest pharmaceutical market, and the epicenter of clinical trials and research. Canada is the world's second largest center of clinical trials and has pioneered many discoveries in diabetes care. India is gaining ground in clinical research with strengths in research, large drug manufacturing capabilities, world class hospital and medical facilities and infrastructure. The proficiencies of researchers in English, good clinical skills, a large population and prevalence of most disease types in India's are also reasons for its position in clinical research and a favorable destination. India's regulators have undertaken reforms of regulatory requirements to improve processes and ensure consistency with international standards. The over reliance by the Indian pharmaceutical industry on generics in sustainability and future growth of the industry may be dampened as the inevitable crowded space by international competitors and other manufacturers will likely cause ceding of some market share. Utilizing the immense talents in new drug development may provide new areas of economic opportunities. The promise for developing innovative and next generational products and marketing are immense. Continued investment in quality, discovery, achieving parity with international regulatory standards will expectedly fulfill great expectations and the inarguable tremendous potential India holds. The regulatory affairs and drug development discussion in India is further related to Type 2 Diabetes in India, as the incidence of Type 2 Diabetes is escalating exponentially worldwide and needs urgent therapeutic and management solutions.

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Introduction and Background

The aim of this paper was to assess clinical research, drug development and regulatory process of clinical trials and regulatory process and structures in current and evolving practices in the United States (US), Canada, and India. The goal is to also appraise the United States and international regulatory agencies, systems and regulations governing the research, development and commercialization of Type 2 Diabetes drugs in some part, however to largely focus on clinical trials and drug development opportunities and reforms in India. The United States is the largest pharmaceutical market, and the epicenter of clinical trials and research. Canada, has pioneered many discoveries in diabetes care. India has strengths in research, large drug manufacturing capabilities, and world class hospital and medical facilities and infrastructure (Sharma & Parekh, 2012; Lancet, 2014).

The commercial reasons and lower costs drivers in conducting clinical trials inevitably will shift some of the burden overseas, where the infrastructures, and competencies in India exist. Manavalan and Sinfield (2017) noted that the costs to undertake clinical trials in Brazil, Russia, India and China are significantly less than the US, and economics possibly accounted for the difference in trials conducted in 2017 (36% of US clinical trials versus 47% conducted in non-U.S. countries). India, with a population of 1.2 billion, is the second most populous country after China.

Gupta (2018) noted, that India has 1/5th of the global disease burden and must also contend with the patient management of many unmet medical needs. India represents 18% of the world's population and 20% of the global disease burden expressed as disability adjusted life years. The 1% expectation of involvement in clinical trials by the population by Regal (2018), is perhaps unrealistic and lofty. The importance for clinical research in India is nevertheless also driven by the enormity of the burden of both communicable and non-communicable diseases (Gogtay, Ravi, & Thatte, 2017).

Canada has an impressive record in contributing to the advancement of diabetes treatment and cure. From the pioneering efforts of the discovery of Insulin by Banting and Best in 1921, to the work of Drucker in Mount Sinai Hospital, Toronto, Canada's achievements in advancing drug development is noteworthy. Canada ranks second to the US in the number of clinical trial sites, and has instituted a Canadian clinical trial registry, and other regulatory improvements to address previously reported issues with approval timelines, however needs to improve transparency and other aspects of clinical research rigor (Shuchman, 2008). The United States is the largest pharmaceutical manufacturer and leads the world in clinical research, which makes its regulatory agency, the Food and Drug Administration (FDA) the gold standard regulatory authority. As clinical trials, or the manufacturing of products that will be marketed to U.S.

populations increase, the greater involvement in oversight by the FDA in several countries is evident.

The Type 2 Diabetes Epidemic

The impact of Type 2 diabetic epidemic reverberates around the world, arguably stems from an increasing sedentary lifestyle, food additives, obesity, genetic and other predisposing risk factors. The American Diabetes Association (2017) fast facts report indicated that 30.3 million Americans, representing 9.4% of the population have diabetes; that's 1 in 11 Americans have some form of diabetes. The FDA (2018), has reported that Type 2 diabetes represents about 90-95% diabetes cases in North America, compared to Type 1. In India, an estimated 60 million people have been diagnosed with type 2 diabetes mellitus (Davenport, 2018). There are 250 million people worldwide and 23.6 million in the US affected by diabetes (Harvey, Clark, Finkel, Rey, & Whalen, 2011).

A Synopsis of the Evolution and History of Type 2 Antidiabetic Drugs

A brief review in the development of some important research may serve to however highlight the drug approval process and offer pertinent perspectives on the evolution of Type 2 Diabetes pharmacologic treatments, to set the stage for a deeper analysis of the Indian marketplace. Metformin received approval in the United States only in the 1990s, however was first approved as an antihyperglycemic agent in 1959. Metformin belongs to the biguanide class, is the most used and prescribed antihyperglycemic agent in the world. Reducing hepatic glucose production is its principle mechanism of action and typically leads to a significant reduction in A1C levels (~1.5%).⁷ Reducing glucose via a mild increase in insulin-stimulated glucose uptake.⁷ is all achieved as well with its administration (White, 2014).

The success of the regulatory system in Canada is scientific research is apparent with the strides made in research. White (2014) lauded the contribution of Canada in the advancement of diabetes research. The discoveries by Dr. Drucker and sponsored by Diabetes Canada-funded research, has led to two new treatments for type 2 diabetes: 1) The GLP-1 analogues, which mimics the action of GLP-1 and include drugs like liraglutide (Victoza) and exenatide (Byetta), 2) The DPP4 inhibitors, which block DPP4 from removing GLP-1 from the body), and the include drugs sitagliptin (Januvia), vildagliptin, and saxagliptin (Diabetes, Canada).

Drug Regulatory Agency Roles and Responsibilities

A critical analysis of the regulatory agencies of the USA, India and Canada may yield insight into potential lacunae and areas of needed improvement. In India, the government has oversight and involvement in clinical research, as the Indian Council of Medical Research (ICMR) is responsible for biomedical research policy and implementation, under the auspices of the Ministry of Health and Family Welfare and the Department of Health Research, Government of India. The involvement and frequent interference by the government and the judiciary of India often stalls drug development, however may be a necessity with the number of domestic and MNC drug companies. The independence of the regulatory system in Canada seems remarkable in this regard. Health Canada, one of the important governmental agencies, "in most cases" limits its regulatory role in clinical trials to the sale, distribution) and importation of non-approved drugs (Clinical Trial Regulations, 2017). The "Guidelines for Good Clinical Practice" is adopted by Health Canada that involve the participation of human subjects, for drug and device

studies, sets the standard conformance to international ethical and scientific quality, associated with the designing, conducting, recording and reporting trials.

Researchers in Canada have expressed frustration with the lack of centralized legislation for regulations for both principal investigators and sponsors, and the paucity of information on the provincial regulatory agencies in Canada (Alas, Godlovitch, Mohan, Jelinski, & Khan, 2017). A common lament, is that the regulatory oversight of clinical trials in Canada, the US and the UK is hampered by resource constraints (Shuchman, 2008), and is possibly true in other regions around the world as well.

The key regulatory authority in India, is under the purview and jurisdiction of the Central Drugs Standard Control Organization (CDSCO), which is headed by the Drugs Controller General of India (DCGI) and represents the apex National Regulatory Authority in India. The CDSCO may be considered the equivalent of the FDA in the United States, or Health Canada and the European Medicines Agency respectively. The CDSCO in India falls under the governance of the Ministry of Health and Family Welfare, the Government of India. The CDSCO is entrusted with safeguarding and ensuring quality in public health, and involved in assuring the safety, efficacy and quality of drugs, cosmetics and medical devices. From a clinical research regulatory affairs standpoint, oversight of clinical trial and manufacturing site inspection, and drugs approval is the responsibility of the Drugs Controller General of India (DCGI), representing the CDSCO (Gogtay et al., 2017).

The FDA in the United States is the regulatory agency which formulates clinical research policy and guidelines. The FDA offers extensive guidelines in the conduct of clinical research summarized in FDA Extracts and Guidelines (FDA, 2008). The FDA stance is that the guidelines and not rules, provides the flexibility required in clinical research. For example, the FDA (2008) in its draft guidelines specifies flexibility in the development of antidiabetic drugs, considering it is a relatively "novel" area. In an emerging and evolving field, the hope for more specific guidance hinges on the promise that with the passage of time, the future holds for greater experience accrual in clinical discovery and regulatory experience (FDA, 2008).

A Critical Review and Analysis of the Regulatory Environment in India

The complex legal regulatory environment demands an exacting price from regulators and developers in presenting guidance to clinical researchers and new drug development, while ensuring compliance and adherence respectively in the responsible conduct of clinical trials. Lakkis and Maha (2010) emphasized, that the lack of harmonization in US and international pharmaceutical regulatory in part, accounts for the high costs in the approval and marketing of new drugs. The convoluted and cumbersome, albeit necessary process in drug development, may delay public access to innovative and essential drugs, although one cannot disagree that it is wiser to err on the side of caution, in the interest of patient welfare and safety. The opportunities consequent to the globalization phenomenon, brings demand for generics, branded pharmaceuticals and medical devices from the emerging and new markets of Asia, Latin America, the Middle East, and Africa.

The constant quest for improvement in human health and longevity, has required progressive reforms in pharmaceutical regulations globally, ostensibly in the constant quest for greater standardization and international collaboration,

cooperation and harmonization in clinical research and drug development (Lakkis & Maha, 2010). The efforts in unifying and harmonizing different and constantly evolving regulatory systems worldwide, to a common and universal set of guidelines and practices is fraught with a multitude of challenges. Some progress has been made in ensuring greater inclination by member countries to demonstrably comply with the Trade-Related Intellectual Property Rights (TRIPS) agreement.

Most countries abide by the principles enshrined in 1994 Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). India is a member of the World Trade Organization (WTO) and TRIPS and reaped dividends globally in intellectual protection in many spheres, including IT. In the realm of pharmaceuticals, the TRIPS Agreement for India has possibly provided some protection for international companies, however possibly also constrained the activities of organizations who in the past reverse engineered and were adept in launching and marketing, with some impunity, extensions and derivatives of patented drugs.

The trade-off for countries benefitting from TRIPS however entails the required levels of reciprocity and harmonization of regulatory standards and patent laws on as much parity as possibly with countries which stand steadfast on their commitment to the preservation and protection of intellectual property and are often punitive and restrictive to violators. Berndt and Cockburn (2014) observed that several countries falling under the lower-income bracket has necessitated strengthening patent protection for local and foreign innovators in domestic markets, including the guarantees and protections for pharmaceuticals. These researchers have expressed the need to observe the commitment by Indian authorities to pharmaceutical patent protection, in the era of the post 2005 grace period expiration to the TRIPS Agreement, India passed a new patent law. India's track record in patent protection began in earnest in 2005 for new products. As a signatory to TRIPS, there have been very few new product launches from the Indian pharmaceutical companies after 2010 (Banerjee & Thakurta, 2015). The difficulties which confront pharmaceutical companies in the marketing of innovative drugs in emerging markets may not be entirely restricted to strong price controls, and generic competition (Lakkis & Maha, 2010)

US, Canadian, and Indian Clinical Research and Regulatory Affairs

The cost to bring one new drug to market, where countless molecules are sifted through, has escalated exponentially over the years. The road to bring a new drug costs through the process of commercialization costs on an average USD 1.78 billion and takes approximately 13.5 years from discovery to the market (Paul, Mytelka, Dunwiddie, Persinger, Munos, Lindborg SR, et al., 2010).

Clinical research in India has increased significantly, after a decline and lull in the early part of this decade. The regulatory bodies have focused on some simplification to the clinical research guidelines, which have served to enhance the regulatory process, and possibly spur greater clinical research activities. For example, the three levels of approval from committees of Subject Expert, to technical and apex bodies where warranted, is perhaps reflective of a focus in emphasizing the rigor, ingraining a systematic review process, while reducing bureaucracy and complexity. Yet, the lack of standardization plagues the clinical research world universally, as much as it does in India, notably on the basis by which clinical trial applications are reviewed (Gupta 2018)

Clinical trials in India continues to increase, as regulators strive to reform and change practices, ostensibly to elevate the opportunities for international and domestic drug development, and all that holds in terms of economics and revenue generation. The evolution in the change in clinical trials and regulatory affairs, involves regulators, sponsors and investigators. The Indian regulatory authorities seeking foremost patient benefit and safety, and reform is also intended to accelerate applications, approval, and reducing costs. Reform and change will entail improvement in ethical standards, patient recruitment and overall the efficiency and quality of the study. The reforms may lead to what Bopanna & Gupta (2009) have expressed, as a desire for quality research, with demonstrable compliance with international standards, which meets approval of sponsors, regulators and investigators on data quality and protection, through the continuum of clinical research studies.

Regulatory Reform in India

On the current reforms assessment, it may be valuable to examine the changes and amendments in India over the last few years. The Central Drugs Standard Control Organization (CDSCO) for instance has more explicitly defined the scope and purview and the interpretation of clinical trials, within the broader context of global clinical trials (GCT). The amendment also defines certain terms such as global clinical trials (GCT), IND, and new chemical entity (NCE). Suvarnapathaki (2015) noted, that the clarity has extended to a) include compensation rules and the time frame and reporting by the investigator on guidelines for a serious adverse event (SAE) reporting timelines in the event it is not reported within 24 hours of occurrence, b) explanations on the provision for import, manufacture, and CT with devices and cosmetics c) penalties proposed for various offences like conduct of CT without permission from licensing authority and Expert Committee (EC), violation of conditions of clinical trial permission, not providing compensation, d) "assessment of risk versus benefit to patients," "innovation vis-à-vis existing therapeutic option," and "unmet medical need in the country" and e) draft standards for accreditation of EC and sites.

In another streamlining effort, the introduction of a system of formal pre-submission meetings of applicants with CDSCO officers, to illuminate regulatory pathway, and facilitate expediency in application, approvals, with the ingraining a greater transparency, accountability, predictability, and speedy disposal of cases (Suvarnapathaki, 2015). The Ministry of Health and Family Welfare in India, entrusting accreditation with a specific bureau in the Quality Council of India, is also indicative of placing emphasis on uniformity and quality.

Davis (2010) proposed utilizing, selecting judiciously and leveraging the liaison potential and expertise of internal, or external and consultant regulatory scientists in developing and sustaining the relationship of pharmaceutical companies with regulatory agencies. It is advantageous for successful drug development in any geography to heighten the opportunities and possibilities for success. Engagement in early access programs, (EAPs) can offer the knowledge and exposure to investigational drugs in routine and for life-threatening diseases. The involvement of key opinion leaders (KOL), patients, advocacy groups and regulators, with the data captured from the implementation of EAPs, can advance insight and knowledge in global commercialization (Early access programs, 2016).

The lack of specific guidance by regulatory authorities, for sponsors, researchers and applicants in India was hitherto, a significant gap. The relative absence of clarity in enunciated requirements at the stages of preclinical, toxicological, clinical, stages may have led to willful and inadvertent lapses in clinical research and drug development in the past. The CDSCO's efforts to reform clinical research, while providing explicit directions for applicants and reviewers in reducing bureaucracy and complexities, may be evident in the issuance of a Good Clinical Practices inspection checklist and Handbook. The involvement of different agencies by the CDSCO and the Indian Council of Medical Research (ICMR) and the constituted Expert Group, may be a ground-breaking initiative, specific and customized to Indian clinical research settings, yet denoting reference to FDA standards. The success of these reforms through the guidelines will likely hinge on how these are diligently enacted and implemented in clinical trials. Undoubtedly clarity and explicitness will need to overcome the ambiguities of the past, and could serve to present a clear regulatory, administrative, and scientific review pathway of processes for applicant and reviewers of new drugs/clinical trials in India.

The guidelines pertain to General, Legal and Administrative aspects, Organization and Personnel, Conduct of Trial, Sponsor, Investigational Product, Ethics Committee, Pathology Laboratory, Quality Assurance, Record Keeping, and Data Handling, with the amendments, will enable analysis of risk vis-a-vis benefit in new and existing therapies, as well as assessment of unmet medical need, to the ethical conduct of research (Bhave, 2018), however has also created some controversy in the ethical aspects of patient safety and India-specific concerns. In furtherance of the goals of international harmonization a handbook grounded in expert opinion has been released in January 2017 by CDSCO in collaboration with Indian Council of Medical Research (ICMR). The handbook may be an important step in the right direction as guidance for applicants and reviewers. The handbook may serve to expedite and ingrain rigorous clinical trials and research, while also potentially facilitating an increase in efficiency and quality of review and highlights regulatory, administrative, and scientific review processes that should be followed by applicant and reviewers if new drugs/clinical trials (Bhave, 2017).

The Amended Drug Approval Process in India

In the wake of litigation, frequent delays and a slow approval process, the regulatory authorities desirous of expediting research without compromising standards and quality have been amended, to foster expeditiousness, standardization, and patient safety. Lahiry, Sinha, Choudhury, Mukherjee, and Chatterjee (2018) noted that the implementation of a "three-tier" means that final approval of a drug by the Drug Controller General of India (DCGI) hinges on the recent amended process, entailing a sequential and expedited review process of a) initial review by a technical committee, b) apex committee, thereafter c) by a subject expert committee (SEC). The amended process will draw down and expedite the 6–7 months for protocol approvals by the DCGI subject to meeting the referenced three step process (Lahiry, Sinha, Choudhury, Mukherjee, & Chatterjee, 2018).

The economics of drug development research is often linked to the entities that benefit and profit the most. The organizations often reap the rewards and financial gains from painstaking research. The pharmaceutical industry often the primary sponsor of clinical trials and studies, encapsulated in

Phase I-IV studies must demonstrate written and unstated ethical, legislative, regulatory norms and mandates. The double standards by MNC's in marketing fixed combinations of metformin, with very little rationality and supportive clinical research data may need greater ethical conduct and awareness to dispel concerns. The charge has been India's vulnerable and poor segments of the population are at risk of exploitation and experiment. The two sides of proponents and opponents to clinical trials are those with some antipathy to western companies, versus the "make in India" sentiment. A middle ground could be high quality academic research.

The pressures of revenue generation are perhaps less in 'investigator-initiated studies' (IISs), Academicians, conducting research generated from personally led funding efforts from pharmaceutical companies and other sources in 'Investigator initiated studies' (IISs), must however unfailingly focus on achieving regulatory compliance (Paul et al., 2010). The onus for the ethical, regulatory compliance and rigorous conduct of drug development and clinical trials rests on all, including the pharmaceutical industry, when it sponsors, funds and oversees clinical research through CRO's, academic institutions, other entities.

The Factors in Favor of India as a Clinical Research Destination

The available pool of world class clinical research talent and the no dearth of patients and research subjects is reason for India potentially carving a place in the world of clinical research as an excellent destination. Clinical research in the US problem by contrast is plagued by difficulties, including the enrollment of Asian and other ethnic minorities. Minorities is largely referred to African Americans, while immigrants from Asia are a significant and growing demographic, nevertheless are often reticent in enrolling in research studies stemming from linguistic, cultural and other barriers (Wong et al., 2015). Researchers possibly fail to understand important sociocultural factors, and that determine minority participation in trials, and communicate strategies that suitably appeal in recruitment. Participant specific barriers in respect of participating in clinical trials include naivety of the informed consent process, trepidation and distrust, limitations in understanding English, while socioeconomic, and cultural factors, lack of health insurance and survival in earn a living "often take precedence over altruistic participation in research studies" (Wong et al., 2015).

India is a preferred destination for most of the leading global companies for carrying out clinical trials. The frustrations in previous years from the chaotic regulatory environment, with legal challenges, inordinate delays, inadequate enforcement, and has given way to a sense of optimism. Lahiry et al. (2018) for instance credit several reasons for greater expectation in India living up to its expected potential to contribute to global clinical drug development. The researchers have cited the paradigm shift in regulatory amendments and a disposition favoring greater ethical conduct, accountability and enforcement to regulatory compliance, improved research rigor and focus on patient safety in clinical research. The transformation and the evolution in this context is spearheaded by the Indian Council of Medical Research (ICMR) and the Central Drugs Standard Control Organization (CDSCO), Directorate General of Health Services, Government of India, obviously strive to achieve standardization and keeping pace with global regulatory guidelines.

Sharma and Parekh (2012) highlighted the advantage of India's "strategic location, skilled manpower, low cost, good medical infrastructure and English-speaking population" accounting for the increase in clinical trials from 1300 in 2009, to more than 1900 by 2013". The regulatory bodies therefore recognized the need to frame guidelines and regulatory approval processes on par with international standards. The international locations can often offer access to a larger number of patients, with quicker enrollment, and in general a shorter trial timeline from start to finish. India's favorability is also the quick and easy access and enrollment of significant numbers of trial participants from India's crowded clinics (Regal, 2018).

Constraints and Factors Impeding India's CR Favorability

Several researchers including Torjesen (2015), Davenport (2018) McGettigan, Roderick, Mahajan, Kadam, & Pollock (2015) have reported the lack of published and unpublished clinical trial data for the five top-selling FDCs metformin combinations, marketed without safety and efficacy data from appropriately designed and conducted clinical trials. The latter have called for these FDC's to be banned and phased out. The five top-selling metformin FDCs, in India holding 80% market share from among the over 500 brands in 2011-2012, for type II diabetes mellitus in India were 1) glimepiride/metformin 2) glimepiride/pioglitazone/metformin 3) glipizide/metformin 4) glibenclamide/metformin, and 5) gliclazide/metformin. The researchers cited, have noted that three of the five leading metformin FDC's were sold and marketed prior to receiving any approval, although also lacked meeting WHO guidelines for FDC's, there was only one poorly conducted study from India's drug regulator. The five metformin FDC's despite the lack of data, were subsequently approved.

The clinical research industry in India is perhaps sullied by recent reports and studies, notably the lack of thorough and robust safety, efficacy, and rationality of clinical trial data for the leading five diabetes drug metformin fixed-dose combinations (FDC) in India, for adults with type II diabetes mellitus. As the market leader metformin FDC's are marketed by multinationals in India only and not in the US, it perhaps advances the duplicitous standards argument of drug manufacturers in emerging markets for the commercial gain with irrational combinations. Davenport (2018) has reported in *Medscape*, that "very few metformin FDCs are approved for use in the United States and other western countries" which may reinforce the double standards. From the outcry on drug approvals, and consequent to the media, parliamentary and judicial actions, and clinical researcher concerns worldwide, diabetes drugs require scrutiny of Indian and MNC origins. India is a low middle-income country, clinicians and regulatory authorities first look to meet the needs and empowerment of the population, with low cost interventions, so that diabetes can be managed (Health & Medicine Week, 2017).

The transparency of other regulatory bodies like the FDA is indeed noteworthy as in contrast, Evans, Roderick, and Pollock (2018) noted that India's Central Drug Standards Control Organization (CDSCO) does not provide full disclosure on the standards and parameters it uses to assess and approve drugs and FDCs. McGettigan et al. (2015) also cited the need for greater transparency in information used on approval decisions, which must be "made available by the CDSCO for public scrutiny". There are possibly many ways of how bureaucracies have functioned in India, with the age

of informed patients and speedy communication, accountability in greater measure will be demanded by all stakeholders.

India's Potential in Clinical Research and New Drug Development

The naysayers may dispute the potential India holds for clinical research and drug development, largely because of the recent issues of withdrawal in approval for marketing of many drug combinations, which will be discussed. India yet offers many advantages for companies interested in conducting clinical trials if the regulatory guidelines are streamlined and closely aligned with international standards of the North America, and Europe. The country has a vast population of patients with common communicable diseases that affect poor countries, but it also has increasing numbers of patients who have the so-called "diseases of affluence" or lifestyle, that are common in wealthy countries and contribute to the coffers of drug companies. For example, more than 20 million Indian people have type 2 diabetes, many have never received drug treatment for their conditions, and large numbers open for enrollments, may come from populations that would considered vulnerable in view of poverty and other factors.

The many attributes of India as a clinical research destination and a future greater contributor to new drug development lies in its well-developed drug industry, many modern hospitals, fluency in English and medically competent physicians and researchers (Lancet, 2014). The Lancet report of a large pool of western-trained, English-speaking doctors available for clinical research may however not be entirely accurate, as these physicians invariably reside overseas after training. The fluency and language competencies of Indian clinical researchers has received wide acknowledgement as the factors which favor clinical research in India. Sharma (2017) also discussed the increase in CR, and medical writing over the last couple of decades and observed a paucity of skills in domain expertise, technical writing skills, high attrition rates, and paucity of standardized training programs as well as quality assessment tools. While Sharma presents the notion that that the shortcomings may account for the reason for under exploitation of Indian medical writing industry of the global medical writing business market, it may also suggest the potential for improvement in clinical research, where medical writing skills are paramount in all facets of reporting and documentary submissions. The FDA approved manufacturing plans is also the highest outside of the United States (Manavalan & Sinfield, 2017), which is another good reason.

Informed Consent in Clinical Trials in India

The doctrine of informed consent must be examined, as it provides the foundational basis for all clinical research and represents the right of every individual to have control and say over personal choices in medical treatment. To exercise this right, the patient or clinical research subject, must receive adequate and unambiguous information to make an informed decision, in consenting, refusing treatment, or in enrolling in a study (Thornton, 2000). With regulatory reforms in India, and the rights, now almost universally codified in statute, it is incumbent upon physicians and researchers to provide relevant disclosures on all about the risks associated in all clinical research studies involving human subjects. The process of creating awareness by clinical investigators by providing the appropriate depth in the level of knowledge and insight to human participants and volunteers represents the fundamentals of informed consent.

Informed Consent Challenges

The goal of clinical research, is to aid discovery in drug development however is mired in many difficulties, even with the best interests in mind of researchers and study participants. The process of informed consent entails patient autonomy to participate in trial with full awareness, knowledge, and ability to make an informed decision. However, the copious amounts of bureaucratic process, regulations, documentation and oversight, represents complex and burdensome details and protocols for participants and investigators, and the short timeliness do not alleviate the situation as well. Clinical researchers and investigators cannot however plead ignorance in respect of the informed consent process in the era of complexity in clinical research. Laws and amendments must be fully cognizant of, and complied with, to the letter and spirit.

The intense scrutiny and copious FDA, and Indian, other regulatory compliance mandates may seemingly limit discovery and business growth; however, the informed consent process cannot be disregarded due to voluminous reporting, or comprehensive processes. Knowledge from clinical research benefits humankind where vigilance is required to ensure the choices made by patients, physicians, administrators, and policy makers and others in the clinical research enterprise are compliant with the informed consent process. The inculcation of good recruitment practices and standards during initial study start up is essential. Observance to regulatory compliance must not be construed as obstacles and impediments, rather denote the oversight and planning which may help in observance with compliance, and informed consent reflects the voluntary and personal choices participants may make in participating in a clinical research study or consider declining. When patents, investors, decades of research, and most importantly, patients' lives are at stake, a one-size-fits-all approach simply will not work (Goldman, 2004), and this can be said of the informed consent as well. Research subjects must be furnished with extraordinary detail, so that they can comprehend the risks and benefits and make an informed decision in willfully partaking in a study, or in deciding to abstain.

The FDA and Indian guidelines is a good starting point to examine the elements of Informed Consent, since all research must display conformance to ethical. Critically, research studies falling under the purviews of the requirements of the FDA regulations, the informed consent documents should meet the requirements of 21 CFR 50.20 and contain the information required by each of the eight basic elements of 21 CFR 50.25(a), and each of the six elements of 21 CFR 50.25(b) that is appropriate to the study (FDA, 2018). IRBs however are the final arbiters to determine the adequacy of the information in the informed consent document and that the enrollment is free from unethical missteps.

While many IRBs have developed uniformity in documents, the customization to local cultures, languages and dialects remains a challenge. Nevertheless, the standardization serves to provide an acceptable source of reference, that will facilitate adherence and compliance with confidentiality, compensation, recording of queries to questions, and to record voluntary participation. Each investigator should comply with the local IRB requirements before submitting a study for initial review (FDA, 2018). On the surface, it appears that the different regulatory agencies are working seamlessly to advance the cause for research. On looking at the complexities involved, there seems to be a

different story of fragmentation and a lack of cohesion. A common thread of lament regarding failure to achieve harmonization, with reasons including: complacency, a maze of bureaucracy, excessive paperwork, comprise some of the major reasons which run against the grain of streamlining the responsible conduct of research (Mastroianni, 2008), with informed consent signifying an import step in the conduct of a clinical trial.

Unique Barriers to Informed Consent in India

A facilitator of informed consent, is comprehensive information offered to study participants to make informed decisions. Bolcato, Zanotti, Fratucello, and Venturini (2014) noted, that there is a responsibility in enrolling subjects in a clinical trial, for subjects to be thoroughly informed about the nature of the study, and every possible benefit and risk, so that a voluntary decision to participate is consciously made. The inadequacy of information is a barrier. The authors cite the great emphasis the Ethics Committee (EC) of the Verona University Hospital assigns to ensure the adequacy and completeness of the written information to the subjects, presenting statistics on over 101 the changes the institution saw necessary in recent IC (Informed Consent) processes. Descriptions of major differences between the interventions studied and commonly practiced usual care, as well as potential risks associated with these differences, are essential elements of adequate informed consent (Cortés-Puch, Wesley, Carome, Danner, & Wolfe, 2016). The willful, or inadvertent failure to provide adequate and comprehensive information on risks and benefits to study participants, represent the major barriers to informed consent, as the facilitators and barriers that would fall under these good practices and lapses

Clinical trials are in increasingly global and geographically dispersed, for good reasons of economics, a more readily available and suitable pool of research participants, however that only exacerbates the ethical complexities, and increases the potential for informed consent breeches and lapses. The focus of this component of the paper is on clinical research studies, with an Indian perspective. The justification, is that this is a country of over 1.2 billion people, and an ever-increasing number of clinical trials are conducted there. A country also with the highest number of pharmaceutical companies in the world. Every clinical trial must be customized to the operating environment, for clinical trials will vary by country and geography. Awareness of ethical, social, cultural and other factors are critical.

The emphasis universally is on the ethical conduct of clinical research studies, providing complete information and ensuring voluntary participation. The efforts on harmonization of ethical tenets of informed consent, and with all the good intentions, the lapses and breeches nonetheless prevail. The dilemma seems more prevalent in developing countries, where "when intentional lapses in conduct of trial hamper the ability of socially and economically disadvantaged communities in developing countries to make free and informed decision (Agrawal, Joshi, & Shah, 2014). To counter willful, negligent or other forms of ethical impropriety, regulators in the US have made compulsory the audio-video (AV) recording of informed consent, to supplements the mandatory written consent from participating subjects. The documentation and recording must be safeguarded and securely stored, to adhere to the principles of confidentiality.

Citing the track record and recent instances of ethical failings, researchers have drawn attention to numerous instances globally, and in India, where humans have been subjected to undue risks and abuse and recommend increased oversight and regulations for their safety (Agrawal et al., 2014). The conviction seen in transition and regulatory reforms emphasize voluntary participation and conformity to ethical principles in patient recruitment for a clinical trial. Patient consent must be obtained in a fair and just manner, however undesirable lapses in the conduct of clinical trials have not entirely disappeared. Intentional ethical mishaps in the conduct of trials often seem to stem from exploitation of socially and economically disadvantaged individuals and communities in developing countries. The dangers in developing countries is that failure to enact ethical recruitment of participants will stymie the speed of drug development as well as the goal of affordable medicines, which is an important goal in India (Agrawal et al., 2014). Video recording may be a step to prevent failings in ethical conduct, as ingraining best practices in the continuum of a research study, should aid patients in making well-considered and informed decisions, by evaluating the pros and cons.

Multiculturalism is another potential barrier in India, arising from logistical, linguistic, cultural and other challenges. The difficulties in efforts at harmonization notwithstanding, national and international guidelines, codes and regulations do serve to guide the ethical conduct of research involving human participants in India. The problem is compounded when applying ethical principles in obtaining informed consent in a multicultural society, as in India. Kulkarni, (2014), expressed the challenge eloquently: "While, on the one hand, they are not to violate universally applicable ethical standards, the local culture of research participants must also be considered", citing a strong role of Ethics Committees (ECs, over 850 registered in India) for researchers to document the informed consent process and all the relevant information in the protocol before initiation of the study, including waivers. In a multi-centric study, it takes Regional Ethics Committees (RECs) to examine the informed consent (Kulkarni, 2014), which may be the solution to overcome the potential exploitation and the barriers due to cultural and other factors.

The important issues and challenges of Informed Consent include participant-related factors and entails comprehension and even translation of instructions and information to the regional languages in India for the understanding of participants, where there are many vulnerable participants. The vigilance of ethical enrollment must include care in the storage period of biological samples, obtaining audio-visual and online informed consent, providing post-trial access and benefits to the participants, and monitoring the process of informed consent in studies, and where applicable, all pertinent documentation for a waiver of informed consent. Awareness of these challenges appears a step in the right direction to forging a path to drug development and affordable health for all in India.

The Informed Consent Road Ahead

Is informed consent going to be redundant in the future, will be anybody's guess. Genetic mapping, molecular genetics and developments in biomedical research and healthcare can in the future cause a revisiting of the concept of informed consent, as we know it, and possibly challenge existing perceptions and imperatives in informed consent. The informed consent concept hinges on informed decision-making based on a careful evaluation of risks and benefits,

and forms as well, the underlying principles for the protection of study participants, safeguarding their privacy, and the responsible conduct of research. However, advances in genetics and biomedical research as well as new forms of decision-making in healthcare may well require a rethinking of this traditional idea (Kegley, 2004) with suitable adaptation.

Adequate information is the cornerstone of informed consent, which may not reflect future trends. To promote a thought in this direction, are recent advances in genetic science and medicine, and particularly the development of population genetics databases. It may be not long before the notion of informed consent, as we know it, is laid to rest as new forms of consent emerge, with patients not in the forefront of direct risk. Kegley, (2004) vociferously made the crystal ball prediction: "Old rules often cannot fit new situations, and the changing needs, knowledge and globalization in biomedical and genetic research may demand a new ethical and legal framework for consent".

Clinical and Marketing: Strategic Considerations

In India, clinical research studies are often pharmaceutical company sponsored. A greater number of academic research studies will however arguably be less encumbered with vested interests, profitability and other factors which often constrain advancement of research, in favor of the goals of only profitability. Academic studies, or 'Investigator initiated studies' (IISs), usually have funds raised from various sources including possibly the pharmaceutical industry. The personal efforts of this individual include "roles of investigator and 'sponsor' and thus directly becomes responsible for ensuring regulatory compliance" (Gogtay et al., 2017).

Rewards in Marketing and Expansion into Western Countries

The potentially rewarding economics for drug companies from India, China, Korea, and other Asian countries, makes it quite appealing to garner regulatory approval in markets of the United States, European Union, and Canada. The marketing opportunities are there, albeit there are investments required in improvements in quality, research rigor, and in science and discovery. The financial returns for new drug development and successful clinical research capabilities for international players may be promising, in the wake of what some experts consider a diminishing pipeline of many pharmaceutical companies, many drugs nearing patent expiration, and inevitable and near expiration of biologics. The opportunities may however present learning opportunities by manufacturers and CRO's in BRIC and other countries US and western approval to enhance regulatory standards and amelioration of existing practices by researchers to follow and comply with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines to achieve regulatory success in the US.

The recommendations of Huml, Iliach, Kamali, and Rulewski, (2017) for regulatory approval of marketing of biosimilars by Asian companies in Western markets, may serve Indian regulatory authorities, manufacturers, and CRO's, in the conduct of studies to meet US and international standards. In this context, the pertinent imperatives and recommendations suggested by these researchers and inferred herewith, include a) demonstrable understanding of regulatory expectations b) ensuring manufacturing process compliance with FDA and meeting GMP requirements, c) rigorous adherence to expected standards in all phases of

clinical research d) appropriate sample size, and duration of studies e) ethical recruitment strategies.

The recommendations of Huml et al. (2017) for companies interested in developing and marketing biosimilars are on point. The actions to reach world standards would necessitate systematically assessing in-house capabilities, consult and engage experts steeped in Western regulatory requirements early in the product development, thereby from a gap and deficit analysis, develop practices and strategy to streamline overall development. Similar assessments by regulators may be of value to authorities who are engaged in the transformation of the regulatory system. The advice is that all development programs should be fully vetted with Western regulators prior to initiation of clinical trials (Huml, Iliach, Kamali, & Rulewski, 2017). These researchers recommend that collaborative synergies will aid in advancing research, sharing and cutting costs in partnerships with Western companies for product development from US and EU origins.

The drug policy in India has typically and historically been predicated on arguably socialist and nationalistic leanings, hence there is merit in the justification for affordability, generics, support of domestic manufacturing of generic drugs. In the past, multinationals have experienced limited patent protection for pharmaceuticals. The Intellectual property rights, patent protection and violations are causes for consternation for international companies operating in Asia. India possibly treads a delicate line in keeping in tow with international treaty obligations to provide patent protection for new drugs. Disputes over intellectual property continue to cause friction with major trading partners (Berndt & Cockburn, 2014).

In any analysis of the quality of clinical trials in India, the saga of dual PPAR alpha/gamma agonist Saroglitazar will likely show that the system needs to overcome several deficient areas in outlining requirements for duration and length of trials, sample size, and clinical safety reports and outcomes before granting approval. Saroglitaza launched in India by Zydus, Cadila perhaps presents a snapshot of indigenous drug development in India. The questions and acrimonious debate which ensued, included the charges of the inadequate safety and efficacy data in gaining approvals and the substantiated denials by the manufacturers and others (Mudur, 2015). In sharp contrast, Chatterjee, Majumder, and Ray (2015) reported that although overall Saroglitazar was well tolerated and there was no serious adverse event reported, the short 14 weeks' duration and small number of patients, which precluded making a definitive assessment of the drug. The point may well be, that opportunities exist for regulators to define all the parameters for a rigorous study with adequate samples sizes, appropriate research designs and protocol and patient safety assurance from extensive trial data before large scale marketing.

The arguments of accusations for and against the patriotic tinged views on drug approval and commercialization is also indicative that there is a dire need keep patriotic fervor, nationalistic ideals and views aloof in scientific research. The frequent interference of the courts and judicial system, although relevant, can possibly be prevented, if the regulatory authorities are vested with greater authority to be the final arbiters of quality of data, the length of trials and the validity of the data, and ethical standards compliance assessments. The explicit guidelines, standardization and harmonization with international standards by regulatory authorities in India may be the true barometer to aspire for in

reaching the sustained maturity levels of rigorous and ethical standards as the only true benchmarks that will gain the acceptance of the international medical community.

Marketing and Collaborative Opportunities

India has a vital role to play in the global supply of drugs with its developed pharmaceutical industry and could contribute as an important strategic partner in alleviating drug shortages in US and globally. The US Food and Drug Administration (FDA) expresses a drug shortage as the inadequate situation reflecting the unavailability of all clinically interchangeable versions of an FDA-regulated drug to meet current or anticipated patient need and demand (CDER, 2014).

The cause of the problem: From personal knowledge and experience in the pharmaceutical industry, and as also cited by the US Food and Drug Administration (FDA, 2018), the problems most encountered in drug shortages include delays associated with manufacturing, in terms of quality and discontinuations. However other reasons may also include a surge in demand, for instance in an epidemic, during a disaster, or failing to forecast for uncharacteristic virulence or higher demand situations. In terms of failed forecasting models, retailers running out of common hay fever and allergic rhinitis remedies is sometimes uncommon for failing to anticipate expected demand, manufacturers lacking contingency plans to manage sudden surges in demand are also contributory reasons.

Kantarjian (2014) presented exhaustive reasons and noted, that shortages are often attributed to the unavailability of raw materials, problems in the supply chain, production, contamination of materials, aging production plants, limited inventories of generic drugs, limited profit margins, over FDA regulation and long timelines to approve new sources of generics, and others. In the realm of generic chemotherapy drug shortages, the large purchases of group purchasing organizations (GPOs) has seen a potential major root cause of (Kantarjian, 2014). Economics and small profit margins for generic, as opposed to branded products are also responsible, as manufacturers for profits discourage generic companies from competing for a share of the US generic chemotherapy market. The over reliance on a small number of manufacturers creates shortages, noticeable predominantly in older drugs, generic and injectable medications. Mazer-Amirshahi and Fox (2018) noted, that in the United States only three companies: Baxter International, B. Braun Medical, and ICU Medical produce saline. The researchers lamented drug manufacturers lacking the provisions to address redundancy and business contingency plans for disaster, perhaps disregarding the onerous responsibilities in essential or lifesaving the medication they are producing. Collaborative partnerships with quality pharmaceutical manufacturers worldwide with the setting up a just-in-time delivery headed by an international body such as the WHO, to address emergency drug shortage worldwide, areas may be a marketing opportunity as well as contribution to human welfare. Indian company's can expand business and philanthropic networks with such ideals and expand opportunities abroad, including the United States.

The Extent of the Problem: The FDA acknowledges the prevalence and problem in shortages of drugs and biologics. Shortages "pose a significant public health threat, delaying, and in some cases even denying, critically needed care for patients" (FDA, 2013). The economic and healthcare burden in the US, is quite discernible from FDA statistics in

preventing between 200, to more than 280 drug shortages in 2011 and 2012 respectively (FDA, 2013).

From the extensive information and literature reviewed, the findings indicated that the drug shortage problem in the US was severe in the first half period of this decade, also corroborated by FDA commissioner Gottlieb (2018). While the FDA and manufacturers have displayed better coordination to mitigate these risks, the problem persists. The extent of the problem is far reaching. In the United States, severe shortages of prescription and many lifesaving drugs threaten public health and patient safety. The recent example of the critical effects the existing shortage of saline solution, was further exacerbated in consequence and presented significant challenges when Hurricane Maria devastated Puerto Rico (Mazer-Amirshahi, & Fox, 2018).

Some consequences of drug shortages: Aside from the estimated costs to hospitals of over \$416 million a year, long-term OD shortages pose serious health consequences, including “deterioration of health and death” (Jarosławski, Azaiez, Korchagina, & Toumi, 2017). From the list of significant in the domain of sterile injectables (73%) cancer drugs, anesthetic used for surgery, emergency medicine, and electrolytes (Schmittling, 2016)), the consequences to increasing patient survivability are seriously constrained.

Cost of drug shortages: The cost of drug shortages may be incalculable in respect of the serious costs to public health issue may be evident from data collected. The new drug shortages in the US increased exponentially from 70 in 2006 to a high of 267 in 2011, exceeding the 450 mark in 2012, and costs hospitals over \$416 million a year (Jarosławski et al., 2017). The FDA tracked shortages from January 1, 2010 to August 26, 2011 of 127 drugs and determined that 118 (93%) fell in the category of “medically-necessary” to treat or prevent a serious disease or medical condition where there are almost no substitutes (Schmittling, 2016). Manufacturers worldwide have the moral and ethical responsibility to prevent shortages and protect human life. The expectations of US, Indian, Canadian and drug firms worldwide therefore must display the conduct of globally responsible corporate citizens, with a genuine desire to serve humanity, and beyond mere compliance with statutory/legislative, civic, corporate and socially responsibility and expectations. Philosophically, if the one good turn deserves another is to be believed, Indian drug firms can expect financial returns and new opportunities commensurate with global commitment to human welfare and health.

Recommendations for FDA to help prevent drug shortages: It is incumbent upon the FDA and manufacturers to work closely with agencies and retailers distributors to “prevent or reduce the impact of shortages”. The FDA machinery in this regard includes a drug shortage database, email, discontinuation notification, and other alerts/information for professionals and other stakeholders. The FDA can provide information that is seamless and instantly accessible with options for alternatives provided by the FDA. Such methods will entail enhancement of the existing IT interface with supply chain integration and infrastructure of the FDA, manufacturers, providers, and others concerned. Developing improved forecasting models for classes of drugs that are most needed in disasters, acts of God, unexpected virulence and other scenarios can be factored into planning for shortages. In the developing of these models, the Juries of executive opinion can include experts from the industry, clinicians, and others.

Another strategic recommendation would be for the FDA, to develop a national registry of patients who are receiving drugs in short supply and provide actions to deliver from identified sources options to meet these needs – akin to a ‘strategic reserve’ to safeguard national interests in an energy crisis. For instance, countries such as India, Canada, and Europe have well developed pharmaceutical industries to partners in Just-in-Time initiatives. A contingency plan will be specific to meet patient needs regardless of economic, geographic and other factors. The principal aim of a contingency plan should be to aid those in dire need, and facing the impact of shortages, in the form of adverse events, worsening conditions, exacerbation of symptoms, accelerated disease progression and who face the negative consequence of using less effective or less safe alternatives. As much as it is about coordination, the supply chain, astute management is critical. Ventola (2011) eloquently summarized the solution as the need for comprehensive management strategy that “includes clear policies and procedures for information gathering, decision-making, collaboration, and timely communication should be established to effectively handle drug shortages”.

Recent Type 2 Diabetes New Drug Development in India

Underway in India, is a Phase 2a clinical trial in India by SIRT, a biopharmaceutical company to evaluate its SRT501 product candidate in patients with Type 2 Diabetes with inadequate control of glucose levels by current first-line therapy of metformin (Business Wire (2017).

Cultural and Traditional and Novel Studies: Diet and exercise are the buzzwords in the management and treatment of Type II Diabetes and touted in prevention. A study in India involving integrative system of medicines of Ayurveda, acupuncture, metaphysical energy-healing therapies, with limited use of relatively safer allopathic drugs, as the aim is to evaluate 'treatment outcome' without adverse side effects (Clinical Trials Week, 2017). The trends of integrating the traditional Indian forms of medicine Ayurveda, acupuncture, and Yoga goal in the treatment and sustainable management of diabetes, is excellent and provides the opportunity to scientifically document the results of the integration of these ancient forms in terms of modern clinical research outcomes.

Conducting a clinical trial on mobile apps and digital therapeutics, an Indian innovation, can possibly be a new tool in the management of blood sugar levels and improving overall quality of life of patients with diabetes (First *Global Data Point*, 2017). In another study, Isalkar (2017) reported that a low-calorie food intake can reverse diabetes, typically denoted by glucose levels above 126mg/dl (fasting) and that of 200mg/dl post-meal. A low-calorie diet (LCD) of about 1,000 kcal/day was found to help reverse diabetes in newly diagnosed patients.

A study to evaluate and compare safety and efficacy of glimepiride and sitagliptin in combination with metformin in patients with type 2 diabetes mellitus (T2DM). The results indicated that in T2DM patients, glimepiride/metformin combination exhibited significant reduction in glycemic parameters as compared to sitagliptin/metformin combination (Diabetes Week, 2017). A study sponsored by the Endocrine and Diabetes Foundation, India, indicate, that in the standard treatment for type 2 diabetes, empagliflozin (an SGLT-2 inhibitor) reduces liver fat and improves ALT levels in type 2 diabetes and nonalcoholic fatty liver disease (NAFLD) patients with (*Diabetes Week* 2018).

Conclusion

The reforms and changes by Indian and US regulatory systems and its connotations to clinical research, drug development and marketing have been discussed in respect of opportunities and improvement imperatives. The opinions of pharmaceutical and drug development experts indicate the immense potential of India in clinical research and drug development on the world stage. The optimism of Parekh and Shewale. (2012) and those of several others is that Asia is gaining importance for clinical research, with India a favorable destination because the proficient English pool of educated and young researchers, with a large population and prevalence of most disease types, it is easy to see why. The thrust and determination by regulators in India to reform and ensure consistency with international standards, is reason for international interest and apprehension. The constantly shifting and evolving guidelines, among other factors are also causing consideration for other geographic options. One recommendation for India being an attractive CR and drug development destination, is to accelerate timelines and manage complexity (Parekh & Shewale, 2012).

The views presented in this discourse on the evolution of the Indian clinical research, drug/medical device industry are positive with strides made in present day regulatory reforms and some of the major accomplishments detailed. On the flip side, Banerjee and Thakurta (2015) have also stated the limitations and areas for future improvement stem from the deficiencies in a) skilled manpower b) limited finances c) current technology infrastructure and d) access to new technologies, and e) importantly the lack in focus and ability in development discovery of biologics, the direction in which the future evolution seems headed.

India has a strong generic manufacturing capability, which is used advantageously to market within the country. The low manufacturing costs relative to developed countries facilitate the export of generic and branded drugs to several international countries and individual buyers in advanced economies and developing nations. The new drug development expertise, especially in biologics, however lags considerably in contrast to the tremendous capabilities in generic manufacturing, attributed to technical abilities in small molecule synthesis. Banerjee and Thakurta (2015) have expressed reservations on the over reliance by the Indian pharmaceutical industry on generics in sustainability and future growth of the industry as the inevitable crowded space by international competitors and other manufacturers, will cause it to cede market share in the future. While the promise for marketing and developing innovative and next generational products is immense, investment in quality, discovery, and in achieving parity with international regulatory standards will need to be shored up to fulfill great expectations and the inarguable tremendous potential.

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