

**India** is an attractive destination for conducting clinical trials. A young, highly educated work-force, a very large population concentrated in a few urban centers, prevalence of all major diseases, and importantly, use of English as the primary language make it easy to set up clinical sites in India.<sup>1,2</sup> Over the last couple of years, Indian regulatory and business processes have gone through several enhancements to harmonize with the rest of the world with the goal of making it easier for India to participate in global trials.<sup>3</sup> Outsourcing a clinical trial to India offers the promise of rapid completion and reduced cost to a sponsor from the US, Canada and Europe. It is widely projected that India might become a major destination for outsourced clinical trials in the next few years.

India is still relatively new to the scene; only about 1% of all clinical trials under a US Investigational New Drug application (IND) are currently being conducted in India.<sup>4</sup> Approximately 350 investigators have worked on clinical studies under US IND regulations. The total may be higher if all clinical trials conducted in India by indigenous and non-US companies were combined. However, the majority of clinical studies conducted in India are still in support of generic products. The core experience of both clinical research and regulatory professionals thus is in generic products.

Although ample information is available about the basics of conducting clinical trials in India, the practical aspects of the same might be surprising to the inexperienced. When going to a new place, one needs not only good textual information but also practical knowledge of how things operate. Seemingly minor details could have a great impact on the outcome of the project, not just in terms of time and money but also the quality and credibility of the data generated.<sup>5</sup> While there are a lot of similarities to the Western standards of clinical research, there are indeed some key differences. This article discusses practical issues to be aware of when planning a clinical trial in India.

#### Regulatory Approval of Clinical Trials

India's equivalent to the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) is the office of the Drugs Controller General (India) (DCGI). The DCGI is the federal official responsible for all pharmaceutical-related issues in India described in the *Drug and Cosmetics Rules, 2005 (DCR)*. Clinical

trials are regulated per Schedule Y of the DCR.<sup>1</sup> The DCGI is equivalent to the commissioner of FDA, and Schedule Y is equivalent to the IND regulations described in 21CFR§312. But that's where the similarity ends. Unlike FDA, the office of the DCGI is not subdivided into several centers and offices with authority to individually

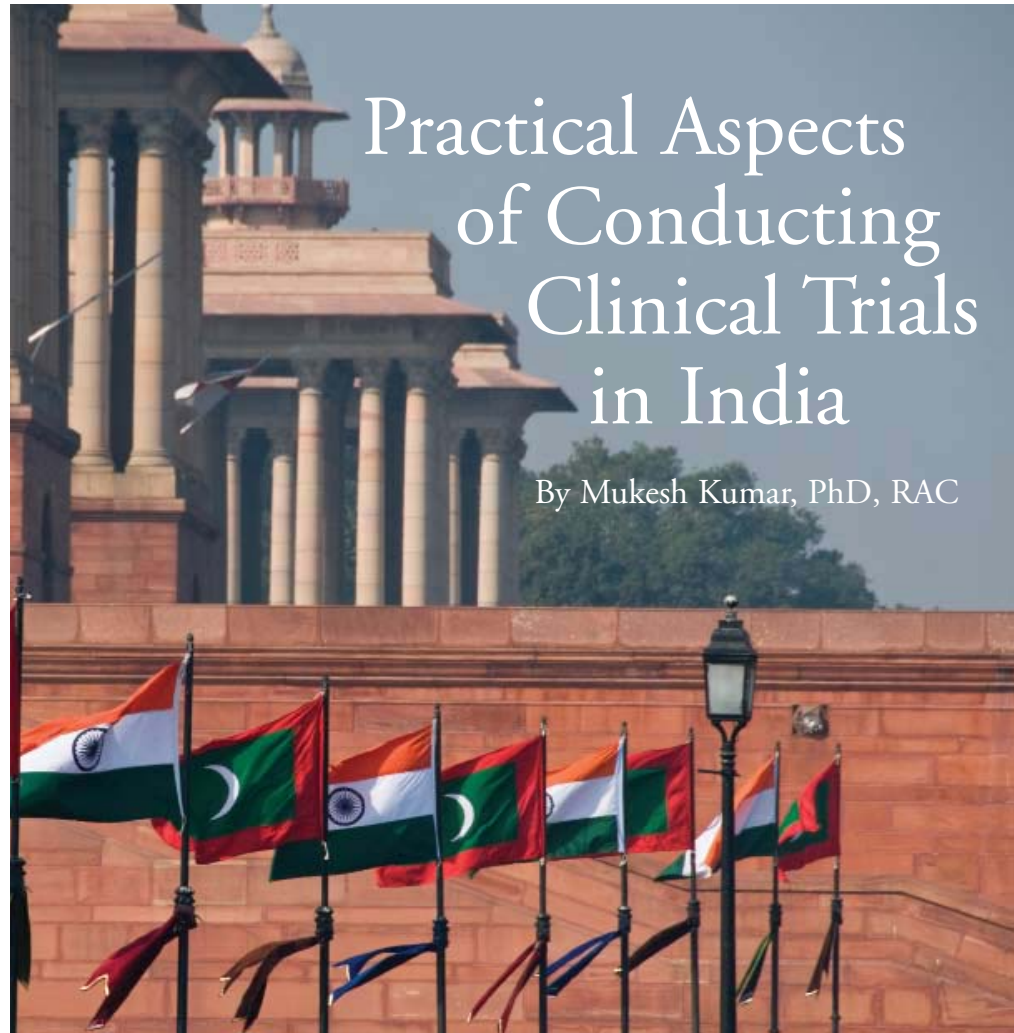
regulate different kinds of products. On the contrary, the DCGI himself signs off on all applications filed with his office. These include not just clinical trial applications but all applications for marketing approval of drugs and medical devices, for import and export of regulated products and for manufacturing. He also advises the legislature

about standards to be followed and revisions and amendments to the regulations.

Unlike in the US, where a sponsor can proceed with a clinical trial 30 days after submission of an IND application if FDA has not commented, in India, the sponsor or its agent in India must receive written approval from the

# Practical Aspects of Conducting Clinical Trials in India

By Mukesh Kumar, PhD, RAC



**Table 1. Requirements for Filing Applications for Global Clinical Trial**

1. Name of the applicant
2. Authorization letter from the sponsor
3. Name of the drug
4. Regulatory status of the drug in other countries (Names of countries where the drug is approved along with international package insert or where an IND application is filed)
5. Objective of the study
6. Phase of study
7. Names of the participating countries /investigator sites
8. Total number of patients to be enrolled globally
9. Number of investigator sites to be enrolled in India
10. Number of patients to be included in India
11. Regulatory/ IRB approvals from participating countries
12. Status of the study in other countries (number of patients enrolled, number of patients completing the study and number of patients discontinued)
13. Suspected Unexpected Serious Adverse Reaction (SUSAR) from other participating countries if any reported
14. Affidavit from the sponsor that the study has not been discontinued in any country, and in case of discontinuation the reasons for such a discontinuation and a statement that the applicant would further communicate to DCG (I) about future discontinuation
15. Data submitted
  - a) Chemical and pharmaceutical data
    1. Generic name and chemical name
    2. Dosage form
    3. Composition
  - b) Animal pharmacology data
  - c) Animal toxicology data
  - d) Clinical data
    1. Phase 1
    2. Phase 2
    3. Phase 3
    4. Phase 4
  - e) Rationale for selecting the proposed dose(s) and indication(s)
  - f) Documents submitted
    1. Form 44 and Treasury chalan
    2. Form 12 and Treasury chalan
    3. Details of biological specimens to be exported
    4. Protocol
    5. Informed Consent Documents (ICD)
    6. Case Report form
    7. Investigator's Brochure duly supported by an affidavit that the summarized information submitted is based on facts
    8. Undertakings by the investigators
    9. Ethics committee approvals (if already available)

DCGI to proceed with a clinical trial. The review of a clinical trial application could take up to six months, or even longer if the DCGI has queries about certain aspects of the study. In October 2006, the DCGI acknowledged that his office receives about 20 new applications for clinical trials every month. For global trials, a delay in getting DCGI approval could mean Indian sites lagging far behind sites in other countries for the same study. To avoid extensive delays in global clinical trials and to take advantage of reviews by regulatory agencies considered similarly stringent in approving those trials, the DCGI released a shorter route for approval of certain trials. Trials approved by regulatory agencies in nine regions of the World (US, UK, Switzerland, Australia, Canada, Germany, South Africa, Japan and Europe) are considered Category A trials and promised approval within two to four weeks of application, assuming a workload of about 20 studies per month.<sup>1,6</sup> All other applications, called Category B trials, originally projected to be approved within eight to 12 weeks of submission, actually take five to six months. All submissions made to the DCGI's office are paper-based.

Since implementation of the above shorter pathway in November 2006, there have been a few major changes in the office of the DCGI. A new DCGI came into office; the office was relocated to a new building; and, due to the availability of the shorter pathway, the number of applications for Category A clinical trials shot up. It is usually surprising to most sponsors with experience working with FDA and EMEA to realize that the DCGI is an individual with limited support staff (most prominently, his deputies) who personally reviews and signs off on all applications. This does lead to delays in getting approval from the DCGI's office. The Category A applications are usually approved within six to eight weeks of submission unless there are queries, which is still a remarkable accomplishment in view of the above constraints.

Another major caveat is that, unlike FDA and EMEA, there is no formal process for pre-IND meetings with the regulatory reviewers. Meetings can be requested, but due to the extremely heavy workload, they are granted on a case-by-case basis. This increases the anxiety of a non-Indian sponsor since there is no way to know if its application has been filed satisfactorily. Also, once the application is submitted, it is hard to track its progress within the DCGI's office: by all accounts, it could take up to three weeks for the application to move through the internal records system to the final reviewer.

All indications are that the office is very aware of the issues and working hard to resolve them. The next year or two should be interesting for those tracking Indian regulatory processes.

A major problem facing a foreign sponsor going into India is the extreme shortage of regulatory experts. Unlike FDA and EMEA, DCGI does not release guidance documents providing the current interpretation of the regulations. Since the regulations described in DCR and specifically in the Schedule Y are meant to be general, their interpretation is highly subjective and based upon the experience of the regulatory consultants. It is not uncommon to have several experts come to varying conclusions about the same regulation, leading to a lot of confusion for the sponsor. Each query from regulatory reviewers could delay the approval by months. Ideally, a sponsor needs to perform due diligence at the beginning of the process and, once initiated, should stick with one set of advisors to avoid confusion and delays. A sponsor should identify the core experience of a given consultant and its relevance to the study.

Table 1 lists the key elements of a Category A application. Each application must include a cover letter describing the key elements of the study, the suggested category (A or B) and a rationale for the recommendation. Category A applications should be easy to understand and information relevant for review by the DCGI should be readily identifiable. This can be achieved by providing all the elements described in Table 1; arranging them in chronological order; providing a table of contents; and writing in plain English. As with FDA submissions, a sponsor's goal should be to make it as easy as possible for the regulatory reviewer to understand the proposed study and the available supporting information. Normally, Category A applications can be considered abbreviated INDs since a sponsor does not need to repeat all the information filed in the regulatory applications in other countries, such as the US IND, and can focus on issues relevant to the conduct of the trial in India.

#### Approval by Independent Ethics Committee (IEC)

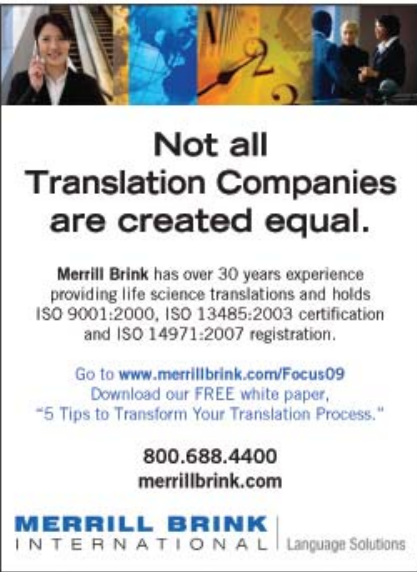
An IEC in India is similar to an Institutional Review Board (IRB) in the US. All sites need to have IEC approval, in addition to the DCGI's approval, before enrolling any subject. Just as in the US, IEC reviews can be done in parallel with the DCGI's review. There are very few central IECs in India. There is no regulation or guidance for or against a central IEC; however, most sites

in India are more comfortable using local IECs. Although all IEC submissions are made in English, the sponsor is required to include certified translations of the documents given to the subjects. India has 14 official languages and depending upon the site location, as many as six different translations might be needed. For a multi-site clinical trial in India, this number might rise to eight or 10 translations. Due diligence must be done to ensure the quality of translation, as minor errors are normal.

The IEC review could take two to six weeks, depending upon the meeting schedule and workload. Indian IECs are as diligent as their counterparts in other parts of the world in reviewing a study from the human subject protection perspective. Investigators almost always expect the sponsor or its agent to address any issues raised by their IECs directly. All IEC approvals are conditional upon DCGI approval.

#### Clinical Operations

India follows ICH E6 guidance for clinical trials. The Indian Council of Medical Research (ICMR) released an Indian version of GCPs to address India-specific issues for conducting clinical operations.



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**Table 2.** Investigational Drug Label Requirements

- Study code (Name and assigned number of the clinical study)
- Active ingredients and formulation
- Batch number/lot number
- Expiry date/retest Date
- Dosage
- Directions for use
- Storage conditions
- Randomization code/method of assigning the subject
- Sponsor name and address
- Manufactured by
- "FOR CLINICAL TRIAL USE ONLY"

Sponsors should be aware of some key practical issues when going into India.

#### Site Qualification and Selection

Sites need to be qualified regarding not only the expertise of the investigators and site personnel, but also the subject pools available and even their geographic locations. As stated above, India has only a few hundred investigators with experience in global trials. There are extensive training resources available and much excitement among potential investigators for clinical trials, so this number should increase in the next few years. A primary sponsor concern is an investigator's ability to recruit subjects to the study at an acceptable rate. Similarly, investigators are concerned about sponsor awareness of India-specific patient issues. The site qualification process is where the two parties try to assure each other that their concerns are addressed appropriately.

Most Indian clinics do not maintain electronic patient databases and are very reluctant to provide data about the desired subject population. A site qualification visit by the sponsor's representative is almost always needed to interview the personnel, review training files and site capabilities, and try to understand the available patient pools by visiting the clinic. The protocol is discussed and any concerns are addressed. This is good time to raise any site limitations and ensure compliance with criteria required to participate in the study. Most investigators are able to assess whether they can participate in a proposed study right at the site qualification visit. A site is selected only if the sponsor's representative is satisfied it meets the previously established basic criteria.

#### Central Laboratories

India has some excellent clinical laboratories with internationally accepted quality certifications that could be used as central laboratory for a given clinical study. Since shipping biological samples out of India requires extensive permits and appropriate justification, a foreign sponsor is best served by using a central laboratory located in India. Most accredited laboratories are located in major metropolitan areas, well connected by all modes of transport. However, a limiting factor could be the amount of time required to ship samples to the laboratory from different parts of the country. Shipping samples is usually not a problem for sites in major urban centers, but for those in smaller cities and town, it could be a critical issue. Also, depending upon a site's geographic location, the ambient temperature can vary extensively, requiring special sample handling that leads to increased cost. Most central laboratories identify vendors for shipping based upon their long-term contracts.

Once the sample arrives at the laboratory and is processed, there are typically no quality issues. Data from Indian clinical sites have been used successfully in support of marketing submissions to FDA and many other agencies. Of course, there is no substitute for a sponsor's due diligence.

#### Drug Shipment

The import license called the Test-License or T-License is applied for at the same time as the clinical trial approval and is issued by the office of the DCGI. Indian labeling requirements are provided in **Table 2**. A sponsor needs to be aware that the drug label must meet requirements for clearance by Indian customs. For multi-country studies, investigational drugs might require relabeling prior to shipping to India. However, Indian labeling requirements are very similar to those in other regions of the world and hence can be met easily.

For practical purposes, a sponsor is best served by shipping the investigational drugs in bulk to a local warehouse in India managed by the sponsor's agents and subsequently divided and shipped to individual sites. As opposed to shipping to individual sites directly from abroad, this approach avoids repeated custom clearance and reduces time to get the drug to the sites. Similar to case for biological samples, temperature control and drug handling issues need to be addressed with the couriers in advance. Most sites have pharmacists to handle all medicinal and investigational products. Once the product reaches the site, storage and handling per the protocol are not problematic.

#### Investigator's Meetings and Other Training

A sponsor is responsible for ensuring that all study personnel are appropriately trained. The first protocol-specific training for site personnel is during the site initiation visit by the clinical monitors. At the initiation, site personnel are trained in protocol-specific processes as well as general processes including Good Clinical Practices and informed consent. India does not have a regulation similar to the US *Health Insurance Portability and Accountability Act (HIPAA)*, but if the study is in support of a US IND or New Drug Application, site personnel need to be trained in US confidentiality and privacy issues. The site initiation training is critical and cannot be replaced by any other form of training. This is the only way a sponsor can document that all personnel at all sites meet the same standards for a given study.

Investigator's meetings (IMs), on the other hand, serve not only as training venues but also as discussion and information-sharing platforms. The sponsor and all investigators meet to discuss general issues affecting the entire trial. The best time for conducting an IM is after at least a few sites have begun recruiting subjects. This enables active sites to share their experiences with the sponsor and other sites regarding project execution. No matter how well planned and thought out a trial is, there are always issues that arise once a few subjects are recruited. These could be subjects' concerns, issues regarding execution of study processes, investigator concerns that were not so obvious earlier or sponsor concerns based upon early data. A common mistake is to conduct an IM before the trial has been initiated at any site. In that case, the IM serves only as a training platform, and loses one of its major benefits. A second IM may be needed later in the trial, thus adding to the cost of the study.

There is another not-so-obvious advantage of an IM. If site qualification and initiation could be considered the brain of a study, the IM provides the heart. It could and should be used as a morale-building and motivational tool for study participants. Outsourcing a study to India is not just to save money and time but also to bring vital therapies to the market faster. Sponsors need to emphasize the importance of this goal, especially to investigators in order to enhance their pride in participating. An IM also can be used by the sponsor as a public relations exercise to build credibility and demonstrate the importance of the study to its own business, enhancing its brand.

**Table 3.** Recruitment Strategies for India\*

- Site qualification
  - Number of subjects/month
    - Based on earlier studies
    - Referrals
    - Recruitment camps
  - Feasibility analysis
- Back-up sites
- Subject retention strategies
- Advertisement
  - Media
  - Public speaking
  - Patient advocacy groups
- Incentive programs
  - Finders fees
  - Bonuses
  - Subject reward programs
- Getting an agreement for recruitment strategy
  - Regular meetings and follow-up
  - Additional training

\*All the above strategies may need preapproval by IEC/DCGI before implementation

#### Recruitment Strategies

Improved subject recruitment is the primary reason for outsourcing clinical trials to India and other similar regions. In the US, about 80% of trials are delayed due to poor enrollment, and more than 75% of the general public state that they have little or no knowledge of the clinical research enterprise.<sup>7</sup> There are some key advantages in going to India to conduct a clinical trial. Of the more than 1.1 billion people in India, about 30% live in a few major urban centers. The literacy and general awareness levels of this population segment are above average. But a good recruitment campaign is still the key to meeting the study goals for India.

Many things can be done to increase and sustain recruitment of subjects to a study. **Table 3** lists some of the more common recruitment strategy elements. Most, if not all, need IEC approval and might even need DCGI approval before implementation. All would need investigator agreement. An important component of a good recruitment plan is a deep understanding of logistics and the ability to adapt to changing scenarios.

#### Safety Monitoring and Safety Reports

India follows processes for monitoring of adverse events among study participants that are very similar to those of the US and Europe. The same safety monitoring plans and reporting formats

used in the US or other regions can be used in India, and since all communications are in English, no translations are needed. Indian regulators accept all forms of safety reports including MedWatch (FDA Form 3500A) and those of the Council for International Organizations of Medical Sciences (CIOMS).

However, a local medical monitor is required to help sites make urgent safety decisions. This local medical monitor can, in turn, communicate with the sponsor's medical monitor to make major safety decisions. It could be hard for a non-native to understand Indian accented English and vice versa; the local medical monitor, generally a physician, could help avoid any issues that might arise from poor understanding on either side. In India, additional measures for safeguarding subjects might be needed, such as providing additional diagnostic support or medication that is not described in the protocol and is generally covered under medical insurance in the US and other countries. Since more than 95% of Indians do not carry any form of medical insurance, a sponsor should be prepared to cover more than the usual safety incidents. That said, the cost of healthcare in India is much lower than in the US and Europe, and hence, might not represent a huge expense.

### Security, Politics and Business Issues

In November 2008, Mumbai, India, was the scene of a horrific terrorist attack. That attack led to the closure of all major types of transport to and from the city for almost two days. Some international meetings were cancelled and others rescheduled. India is the world's largest and most diverse democracy. Citizens in different part of the country not only speak different languages (14 official languages) but are very diverse in their cultural, religious, social and political beliefs. Although Indians as a whole are very peaceful people, unfortunately, there are several radical groups that occasionally conduct acts of terrorism and anarchy, leading to disruption of life. It is a reality that all Indians have learned to live with. To a non-Indian, the resilience of the Indian populace comes as a surprise. Just three days after the terrorist attack in Mumbai, people were back at work as usual. There were no long-term disruptions of business and travel.

Any sponsor thinking about India needs to understand and be prepared for such random events. To date, these events have not affected the quality of work and the speed of project execution for clinical trials, and there is no reason to

assume that this will change. However, sponsors should establish a disaster recovery plan for their Indian operations. These plans should take into account all possible disruptions to work due to acts of man and nature. All key study personnel should be trained on this plan and there should be provisions for drills and audits to make sure than no one is caught by surprise.

India also has a very vibrant and vocal political environment that could affect a business. Last year, an Indian industrial giant, Tata Automobiles, had to move its manufacturing plant from one location to another due to political opposition to its presence at the former location. This resulted in significant delays in project execution and losses in revenue. Similarly, deaths of infants participating in a clinical trial sponsored by a major global pharmaceutical corporation led to political and bureaucratic pressures to restrict all clinical trials. Later, those concerns were shown to be unfounded but the damage by the media had already been done and could possibly affect subject recruitment for all trials. All clinical trials could face similar political pressures in case of safety events. Sponsors should be prepared for addressing all incidents before they become issues.

The current economic turmoil has affected all parts of the globe; over the last six months of 2008, the US dollar lost 15-20% of its value. In December 2008, one US dollar was equivalent to about 50 Indian rupees compared to 44 in October. Fluctuations of this type could lead to a significant change in financial plans, both positively and negatively, depending upon where the sponsor is based. Last year, India eliminated the service tax on the clinical trial industry leading to a savings of about 10% for sponsors. The current economic environment could change that situation. There also might be some changes in the US tax structure.

### Conclusion

India is at the top of the list of any biomedical product developer in the US, Canada and Europe as a site for outsourcing development steps. Over the last few years, there have been numerous presentations and publications touting India's superiority over other locations for conducting clinical trials. However, India is still a relatively small player in the clinical trial field. Clinical trial outsourcing is a very competitive business.<sup>8</sup> Practically every country in the world is vying for a piece of this pie. India is occasionally compared to China, to which it offers some obvious

advantages; however, other emerging regions of the world give both India and China stiff competition. Sponsors need to take all the above factors into account before committing to clinical trial locations, but once committed, the sponsor needs to give the sites ample opportunity to show the fruits of their labor. Unrealistic expectations, incomplete plans, lack of due diligence and short-sighted strategies are the prime reasons for failure of a clinical project in India.

India is not just vying to be a source of service but also of innovation. Of late, some of the major investments attracted by India have been in the fields of discovery and early-stage development. With more indigenous sponsors of clinical development, India could progress rapidly into a reliable, smart and long-term partner in clinical product development.

### References

1. Kumar M and Kher S. "Regulatory Considerations for Conducting Clinical Trials in India." *Regulatory Affairs Focus*, 12(3):26-31, 2007
2. Kumar M. "Agencies Involved in Approving Clinical Trials in India." *Regulatory Affairs Focus*, 12(8):34-39, 2007

3. Kumar M and Mehra M. "Regulatory Harmonization Efforts in India: Keeping In Step with the Globe." *Regulatory Affairs Focus*, 13(6):28-33, 2008 [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
4. Kumar M and Tate K. "Designing a Global Product Development Strategy." *Regulatory Affairs Focus*, 13(6):16-21, 2008
5. [www.cdco.nic.in/Global\\_Clinical\\_Trials.htm](http://www.cdco.nic.in/Global_Clinical_Trials.htm)
6. <http://philadelphia.bizjournals.com/philadelphia/stories/2008/12/08/story1.html>
7. Kumar M. "Considering Outsourcing: Risk and Benefits for FDA-Regulated Firms." *Regulatory Affairs Focus*, 13(10):22-26, 2008

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