



# Biologics Regulation in India

India is restructuring its regulation of biopharmaceuticals to help the country's industry compete internationally

**D**uring the past decade, India has been actively reforming its key industrial sectors to compete at world-class levels. These reforms have been motivated by its expanding global trade and a self-image that has moved beyond that of a developing country. As with other industrializing countries undergoing rapid shifts, India clearly recognizes the need to restructure its regulatory system so that its biopharmaceutical industry can compete in international markets.

India's regulatory situation is described in detail by Uri Reichmann, Bharat Kurana, and Steven Ferguson in the publication, *Advances in Biopharmaceutical Technology in India*, a joint study by BioPlan Associates, Inc., and the Society for Industrial Microbiology. According to the authors, a new regulatory structure in India is being formed, "to centralize drug approvals and tighten the still somewhat lax manufacturing practices that have led to a proliferation of poor ethical practices and substandard drugs."<sup>1</sup>

## THE CURRENT REGULATORY SYSTEM

India's federal regulatory structure has been plagued by some of the classic problems of developing countries, including red tape and corruption. Expanding bureaucracies have been particularly hard on biologics manufacturers in India, who must seek approval from multiple state, district, and federal agencies for routine activities such as the importation of recombinant molecules and cell cultures for research purposes.<sup>2</sup>

In India, state authorities are responsible for licensing a drug maker's research and manufacturing

facilities. But the federal Central Drugs Standard Control Organization (CDSCO) and the drugs controller general of India (DCGI), have been responsible for approvals of preclinical and clinical trials, new drug applications, and the importation of drugs from abroad. For biologics, additional approvals have been required by other offices and agencies, including the Genetic Engineering Approval Council (GEAC); Recombinant DNA Advisory Committee (RDAC); Review Committee on Genetic Manipulation (RCGM); Institutional Biosafety Committees (IBSC); State Biosafety Coordination Committees (SBCC); and the District Level Committees (DLC).

Arguably, a worse problem has been the general lack of state-level regulation in certain areas. India's state drug regulatory authorities (DRAs) often lack the staff to police their respective domains. These staffing problems, combined with their relatively limited technical experience in regulatory issues, makes for a difficult situation. The DRAs have been susceptible to influence by local political authorities, and in some cases have been able to do little to prevent illegal drug manufacturing and marketing activities. Manufacturers that set up operation in states where regulatory oversight and enforcement are weakest can then market their drugs in the rest of the country. One senior federal regulator in India lamented, "There are hardly any regulations or control over the mistakes or offences committed by the State DRA Officers who permit even [the] manufacture [of] banned or new [i.e., unapproved] drugs."<sup>3</sup>

India's relatively lax regulatory environment potentially affects every country that imports its drugs. Products made in India accounted for 20% of US FDA generic applications in 2006, up from only 7% in 2001.



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between the FDA and Indian companies seldom make it to the media, in 2006 Ranbaxy Laboratories and Wockhardt, two of the largest Indian drug makers, were sent warning letters by the FDA over documentation and quality-control issues.<sup>4</sup>

## STREAMLINING APPROVALS

India has recently begun to tackle its red tape to accelerate drug development. To encourage would-be makers of biogenerics, for example, India's regulators have begun to issue guidelines on biosimilars and the requirements for obtaining approvals.<sup>5</sup> In 2005, India's legislature enacted an amendment to the prevailing Drugs Control Act, clarifying

its rules on clinical trials. Previously, for example, Phase 3 trials in India of a drug intended for market in the country, were allowed to proceed only if all prior studies had been completed in Western countries. This rule was relaxed to encourage the development of new drugs in India. Now, in contrast, only Indian companies are permitted to conduct first-in-human studies and involve substantial effort to gain approval.

India has also taken pains to streamline its clinical trials approval process. Ethics committee and DCGI reviews of applications now generally occur in parallel and take no more than 14 weeks.<sup>6</sup> Occasionally, trial sponsors speed up this process further by submitting a draft application to the DCGI to get the clock ticking, and then file more complete data weeks later.<sup>7</sup>

The long-term goal is to encourage the industry by reducing turnaround times for all regulatory approvals. Recent recommendations for what is called the *R-pharma*

industry

included the following targets:<sup>8</sup>

- approval of preclinical animal studies 45 days
- approval of a human clinical trials protocol 45 days
- examination of clinical trials and response 90 days
- DCGI and GEAC decision (simultaneous) 45 days

Of course, fast approvals don't always make for good enforcement. In 2004, C. M. Gulhati, then the editor of India's Monthly Index of Medical Specialties, cited an example in which, a voluminous protocol on trastuzumab [a biologic, a.k.a. Herceptin], sponsored by Roche, was approved within five working days. "It is humanly not possible to read and analyse the bulky documents in such a short period," Gulhati said.<sup>9</sup>

## TIGHTER MANUFACTURING RULES

In the manufacturing area, though, the country has been tightening the rules and enforcement. A new regulation

"Schedule M" of the Drug and Cosmetics Act, now specifies the good manufacturing practice (GMP) requirements for factory premises and materials. These requirements were modeled after US FDA regulations, to improve regulatory coordination between Indian and US regulators. The change has not met with universal approval, however. Small-scale manufacturers in particular argue that although the new requirements will improve quality, the changes should have been phased in gradually. It took the FDA nearly 15 years to implement similar programs in the US, they argue.

## RATIONALIZING THE BUREAUCRACY

In the wake of drug-trial scandals in the early 2000s,

the Indian government acknowledged the need for tighter regulatory standards. Regulatory officials announced stricter enforcement to international good clinical practice (GCP) and World Health Organization protocols. The DCGI also announced that it would begin regular inspections of ongoing trials.<sup>10</sup>

More importantly, two major regulatory initiatives have been taken. The first is the creation of the National Biotechnology Regulatory Authority (NBRA), under the Department of Biotechnology (DBT), as part of India's long-term biotech sector development strategy. The creation of the NBRA is expected to be confirmed by the legislature this year and become fully operational by 2010.<sup>11,12</sup> According to the DBT's latest development strategy, the NBRA will be an "independent, autonomous, and professionally led body to provide a single window mechanism for the biosafety clearance of genetically modified products and processes." In other words, the NBRA will replace many of the other bureaucracies with which biologics makers in India now must interact for biosafety issues. The NBRA reportedly will also include a training center for its biotech regulators, to build and maintain their professional competence.<sup>13,14</sup>

The second major initiative, for which enabling legislation is expected in 2008, will affect the entire Indian pharmaceutical industry. This is the replacement of most state, district, and central drug regulatory agencies with a single, central, FDA-style agency, the Central Drug Authority (CDA). Over a five-year transition period, this new agency will take on nearly all facility-inspection, manufacturing-license, and data-evaluation

functions concerning drugs in India.

The CDA is expected to have separate, semi-autonomous departments for regulation, enforcement, legal, and consumer affairs; biotechnology products; pharmacovigilance and drugs safety; medical devices and diagnostics; imports; quality control; and traditional Indian medicines. It will set up offices throughout India and will be paid for by inspection, registration, and license fees. Its enforcement powers will be strengthened by a new law increasing the criminal penalties for illegal clinical trials.<sup>15-17</sup>

India has recognized the importance of these issues for some time, but it has taken the country several years to go from the talk stage to the implementation of solutions. Meanwhile, its sales of pharmaceutical products to the West have been growing and the risk of a major setback because of regulatory or quality problems has been rising. As India puts its own house in order, India has coordinated some of its regulatory functions with Western organizations. The US Pharmacopoeia established an office in Hyderabad in 2007 and has already been paid by at least one Indian drug maker, Dr. Reddy's Laboratories, to inspect its facilities.<sup>18</sup> A representative of the Indian pharmaceutical lobby also recently has expressed openness to an expansion of the FDA's oversight of Indian manufacturing.<sup>19</sup> As India expands its global drug and biologics production, US and Europe, as the world's largest drug importers, will likely expand their regulatory support in the development of the country's regulatory systems. ♦

## REFERENCES:

1. Reichmann, U. et al. "Biopharmaceutical Research Collaborations between India and the West: A Guide to Prospective Partnerships in," *Advances in Biopharmaceutical Technology in India*, E. Langer, ed (Bioplan

- Associates: Rockville, MD, 2007).
2. Wong, J. et al. "Harnessing the Power of India," *BCG Focus*, May 2006, accessed 26 Dec 2007
3. Subbi Reddy, K. "How Drugs Regulatory System in India Should Be?" *Pharmabiz* (27 Aug 2003)
4. Kaufman, M. "FDA Scrutiny Scant In India, China as Drugs Pour Into U.S.," *Washington Post* (17 June 2007)
5. Kumar, A. "Biogeneric Manufacturing in India," in *Advances in Biopharmaceutical Technology in India* (Bioplan: Rockville, MD), ed. E. Langer.
6. Goodall, S. et al. "The Promise of the East: India and China as R&D Options," *Bioentrepreneur* (25 Jul 2006)
7. Varawalla, N., "Poised for Growth: The Indian CRO Industry," *Contract Services Europe*, 1 April 2005
8. "Notification Regarding Adoption of the Recommendations of the Task Force on R-Pharma Under the Chairmanship of Dr. R. A. Mashelkar, DG-CSIR, with effect from 1.4.2006,"
9. Gulhati, C. *Ibid.*
10. Basu, I. *Ibid.*
11. "Indian Government to Set Up Biotech Regulator," accessed 26 Dec 2007
12. Dept Plant/Molecular Biology, University of Delhi, "India's National Biotechnology Regulatory Authority Functional in Two Years"
13. "National Biotechnology Development Strategy" (NBDS), Department of Biotechnology, Nov 2007
14. Department of Plant and Molecular Biology, *Ibid.*
15. Narendranath, K. "Central Drug Authority to Have Sweeping Powers," *Financial Express*, 28 June 2006.
16. Reichmann et al. *Ibid.*
17. Hiddleston, S. "New Body to Streamline Drug Licensing, Imports," *The Hindu* (7 Sep 2007)
18. USP-India, "Quarterly Update" (Oct 2007)
19. Kaufman. *Ibid.*