India, Once Again the Jewel in the Clinical Trial Crown

India is the seventh largest country in the world by total area, with the second highest population at 1.2 billion, and is bordered by the countries of Bangladesh, Bhutan, Burma, China, Nepal, and Pakistan. India has the largest postal network in the world, with over 1.5 million post offices, and the name 'India' is derived from the River Indus, the valleys around which were the home to the early settlers. According to the census of India of 2001, India has 122 major languages and 1599 other languages, of which 30 are spoken by more than a million native speakers. Generally Hindi and English are used for administrative, government and business purposes.

The Healthcare Environment

Healthcare issues and diseases include tuberculosis, malaria, HIV, vascular diseases, cancers, and diabetes. Childhood mortality is high and the WHO estimated total diarrhoeal deaths in India among children aged 0-6 years to be 158,209 in 2013. Infant mortality stood at 39 per 1000 live births as of 2013. Clearly there are significant challenges to be faced. India is home to more than 17 per cent of the world's population and around one fifth of the global burden of disease. According to the 2012 WHO report, non-communicable diseases (NCDs) are responsible for two- thirds of the total morbidity burden and 53 % per cent of total deaths in India. Due to financial constraints, the sick and the suffering poor have restricted access to healthcare.

Government expenditure on health and provision of state-funded facilities has fallen over the years, standing at approximately 4.7 % of GDP. This has led to a rise in the private healthcare sector, which successfully services the higher levels of society. Most healthcare in India is conducted through private health provision, with expenses paid direct by patients and their families, rather than through any system of insurance. Public healthcare is free for those below the poverty line, but there is just one hospital bed per thousand persons. The total number of registered doctors in the country was 936,488 as of December 31, 2014. Average life expectancy is 68.45 years, which is 167th on the global league tables.

Private insurance is available in India, as are various government-sponsored health insurance schemes. According to the World Bank, about 25 % of India's population had some form of health insurance in 2010. A 2014 Indian government study found this to be an over-estimate, and claimed that only about 17 % of India's population was insured. Insurance generally does not cover consultations or medication. Over 35 % of poor Indian households have incurred catastrophic health expenditure (CHE) which can be defined as health expenditure that threatens a household's capacity to maintain a basic standard of living.

Clinical Trial Infrastructure

The Indian government invested significantly in the early 2000s in order to encourage foreign investment and clinical trials. The money was used to create systems and to recruit and train personnel to process applications, conduct ethics reviews, etc.; this proved a serious draw for pharmaceutical companies. Global share of CTs in India grew from 0.9 per cent in 2008 to 5 per cent in 2013.

Issues were reported between 2011 and 2013, culminating in the Supreme Court of India requiring information from the Health Ministry concerning etiquette and ethical conduct for clinical trials. The government responded to the issues by enacting a series of amendments to the clinical trial regulations under the Drugs and Cosmetics Rules (Third Amendment) in February 2013. The objective was to improve patient safety, reporting timeliness of serious adverse events including deaths during clinical trials, and the payment of compensation to patients. These amendments led to many multinational companies choosing to withdraw their clinical studies from India, and a suspension across all clinical areas and phases.

Resolution was reached following the formation of subject expert committees (SEC), and additional safeguards for each therapeutic area and studies have resumed. The responsibility of reporting serious adverse events has been moved by the licensing authority from the sponsor to the investigator and must happen within 14 days. There are currently 440 open clinical trials in India as per Clinicaltrial.gov, a major upturn over the last two years.

The Import Process

It takes about 180 days to get clinical trials approved in India. Reviewing and approval timelines for all types of applications must occur in consultation with the SEC. Only institutional ethics committees can review and grant approval for the conduct of clinical studies at any site.

The Drugs Controller General of India (DCGI) issues an approval letter to conduct a clinical trial, to an accredited principal investigator of the trial and the ethics committee of the institute. This is needed for clearance together with an import license which the consignee needs to apply for after getting a no objection certificate from the DCGI. The permit usually takes 12-14 weeks and requires the importer of record to complete extensive amounts of documentation. Customs also require an IEC number (import export code number) and an invoice for clearance, which generally takes 24-48 hours.

The invoice must be original, on shipper's official letterhead, and should clearly state:

- Importer of record if different from consignee
- Reference to protocol or study ID
- The name of the drug must match the "Name of the Drugs" on the import licence
- The 'mg' or 'ml' of the drug unit (capsule or vial) must match the stated unit amount on the import licence
- Customs must be able to easily tally the exact amount of drugs that the invoice represents in order to debit the correct amount from the tally section of the licence
- Value must be provided at a unit (per tablet, capsule) level in addition to the total
- Value of the shipment, which is a definite number and not a value for customs
- Incoterms
- Manufacturing date, expiry date and batch number. These must be identical on invoice, packing list and product label
- A value evidence certificate (VEC) for customs is required, stating that the invoice value is true & correct. This should be on company letterhead of the shipper, in duplicate.

Facilities En Route and Logistic Needs

Major ports like Delhi, Mumbai, Bangalore & Hyderabad have temperature control facilities at the airports for storage during customs clearance. The second Saturday of each month is a customs holiday; if a shipment is due to arrive on Sunday then pre-clearance documents need to be received by midday Saturday (midday Friday for every second Saturday of the month). Caution should be taken around monsoon season to avoid spoilage of goods if the warehouses are full. Shrink wrapping should always be used to reduce water ingress. Simple pack outs are recommended in case customs decide to remove and count each component in a shipment. Temperature monitors should always be declared on the invoice.

The Future for India in the Global Landscape

So India has returned to the fold of clinical trial countries which, with the additional safeguards in place can only be a positive step for all concerned – sponsors, patients and CROs alike. Looking forwards, given the ability of Indian pharmaceutical companies to routinely re-engineer processes for manufacturing generic drugs to make medication available at much lower costs (which is a result of Indian patent law which only protects formulation rather than composition of a drug), it would be foolhardy to exclude them. Biosimilars and generic drugs are big business in India and they typically become available very quickly once patent protections expire. This will be the way forward for this exciting sub-continent, which once again is taking its place in the global pharmaceutical marketplace.

Sue Lee has worked for World Courier for 25 years. During this time she has experienced a variety of customer service and operational functions, including the setting up of numerous, multi national, clinical sites for the transportation of biological samples in her capacity as Head of the Major Clinical Trial Unit. Sue has orchestrated the shipping thousands of shipments with very specific temperature requirements to a host of challenging locations, and each presenting their own obstacles and dilemmas. More recently in her role as Regional Quality Manager, Sue has been auditing and developing procedures and systems for regulatory compliance, package and vehicle testing, as well as temperature control and mapping. Currently, Sue's role includes delivering pertinent, technical information and updates on latest industry developments via technical presentations, articles and white papers, workshops, association and discussion group involvement and direct links with other industry professionals. This also includes direct involvement delivering and maintaining World Courier's online presence.
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