Thalidomide Tragedy Revisited

Are the lessons learnt from the Thalidomide Tragedy relevant in today's time? Finds out Ananya Sen in an interaction with Dr J Vijay Venkatraman, Managing Director & CEO, Oviya MedSafe Private Limited

The unforgettable disaster of the Thalidomide Tragedy of the 1960's is arguably one of the largest catastrophes recorded in the history of drug discovery. Fifty years after this calamity the global pharma scenario has undergone a radical transition today. The regulatory norms starting from manufacturing of the drugs, carrying out their clinical trials to approving them for their launch, the pharma industry has come a long way.

The need for stringent Pharmacovigilance study today can’t be overstated. Emphasising on the significance of Pharmacovigilance, Dr J Vijay Venkatraman, Managing Director & CEO, Oviya MedSafe Private Limited, a Pharmacovigilance Consulting & Services company calls it “an inseparable part of all phases of drug development”. He further adds saying that with the withdrawal of popular drugs from various markets across the globe making news in the media, the pharmaceutical industry and regulatory agencies have started waking up to the challenge.

Ever since the thalidomide tragedy occurred 50 years ago, the significance of pharmacovigilance has been felt throughout the world, particularly in the developed countries. With most of today’s drugs being developed and tested in well-regulated markets before being approved for marketing globally, a catastrophe of the magnitude and scale of the thalidomide tragedy is unlikely. India’s drug regulatory scenario is in the process of an overhaul and it is expected that we will have a stable and comprehensive pharmacovigilance system in the country in a few years from now. Since Indian regulators seldom face the situation wherein they have to make a decision on approving or rejecting new drugs which have not been hitherto approved in countries with mature pharmacovigilance systems, this is not a major problem at the moment. Added to these facts is that pharmacovigilance as a science has evolved a lot and almost all of the international and Indian innovator companies now have adequate internal control systems for ensuring that all precautions for patient safety are in place. However, all stakeholders of Indian pharmacovigilance need to gear up to cope with the fast-evolving global drug regulations.

Today when the industry is well equipped to conduct clinical trials both technically and on the regulatory front, the suspected unexpected adverse events definitely do not go unnoticed. But are they ever revealed to the world? To this Dr Vijay answers that for certain drugs, especially the recently approved ones, post-marketing surveillance studies are done across the world and these studies may unearth unusual outcomes occurring with the usage of the said drugs. He continues that, not all suspected adverse reactions are reported either to regulatory agencies or to the concerned pharmaceutical companies. Therefore, it may not be always possible to know even of significant harm caused by medications which are already available in the market, unless a huge population is exposed to the drug and reports of specific adverse events with the said drug emerge from various parts of the world. However, at this moment, India is yet to catch up with its global counterparts in these aspects.

According to the Schedule Y of the Drugs & Cosmetics Act, new drugs should be closely monitored for their clinical safety once they are marketed. Periodic Safety Update Reports (PSURs) containing all relevant new safety information from appropriate sources in relation to the patient exposure, summarising the market authorization status in different countries and any significant variations related to safety are necessitated to be submitted to the Central

Thalidomide was initially available in 1957 over the counter in Germany as an effective sedative which was exceptionally well tolerated and was not habit-forming. It was advertised to be “completely safe” for everyone, including mother and child, “even during pregnancy”. Discovering that thalidomide worked well to ease morning sickness, Australian obstetrician Dr. William McBride started recommending this off-label use of the drug to his pregnant patients, setting a worldwide trend. What followed this is familiar to all. The drug interfered with the babies’ normal development, causing many of them to be born with phocomelia, a congenital disorder involving malformation of the limbs. Hundreds of babies in Germany were reported to have been affected by thalidomide, ultimately compelling the manufacturers of the drug to finally stop distribution within Germany. At about this time, when the severe effects of this drug were discovered the then US President John F. Kennedy and the whole of America began praising FDA inspector Dr Frances Kelsey, who was earlier severely criticized and pressurized by pharmaceutical companies and FDA supervisors for not approving the drug in the United States. Kelsey found the data on the drug’s safety and effectiveness incomplete and insufficient.
Drugs Standard Control Organisation. The PSURs have to indicate whether changes should be made to product information in order to optimise the use of the product in India. New studies specifically planned or conducted to examine a safety issue should be described in the PSURs.

Commenting on post marketing surveillance that is mandated by Schedule Y under the D & C Act, Dr Vijay points out that PSURs are required to be submitted every six months for the first two years after approval of the drug is granted to the applicant. For subsequent two years – the PSURs need to be submitted annually. PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period. However, all cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant. If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

Apart from PSURs, there are some more post-marketing pharmacovigilance activities that have to be carried out in order to be on par with the global post-marketing drug safety regulations. Unfortunately, there aren’t any specific guidelines for post-marketing pharmacovigilance in India, as the Schedule Y focuses more on Clinical Trial Safety. “Not only framing stringent guidelines but implementing them with force is what is expected of our regulatory authorities in the near future”, asserts Dr Vijay.

While not all pharmaceutical companies are compliant with these regulations at the moment, the future seems to hold promise, as they have resulted in encouraging many Indian drug companies to launch their own pharmacovigilance systems or approach pharmacovigilance consultants and service-providers to set up and maintain the drug safety systems for their marketed products.

The system of reporting adverse events/ idiosyncratic reactions periodically in India today is changing. The Pharmacovigilance Programme of India (PvPI) which was initiated in July 2010 by the CDSCO, in collaboration with the Indian Pharmacopoeia Commission is a huge step forward in the right direction for collating Indian drug safety data. However, it is currently restricted to the approved medical college hospitals in India, public health programmes, and autonomous institutes like the Indian Council of Medical Research (ICMR).

Dr Vijay conveys that apart from PvPI, some Indian pharmaceutical companies also receive adverse events, process them and report them to the CDSCO. The CDSCO headed by the Drug Controller General of India (DCGI) mandates the submission of Periodic Safety Update Reports (PSURs) for new drugs but not all pharmaceutical companies are compliant. Pharmacologically, idiosyncratic reactions with drugs are also adverse events and the same protocol is to be followed for them too.

Thalidomide that was primarily available as a mild sedative was later being used to relieve morning sickness in pregnant women. How safe is off label use of drugs? Although off-label use is generally legal unless it violates specific ethical guidelines or safety regulations, nonetheless it carries health risks and differences in legal liability. “Since our pharmacovigilance system is still emerging, I personally feel, that regulating off-label prescriptions is something that can be done in the next step, as we are yet to fulfill the basic expectations that one would have of a pharmacovigilance system”, opines Dr Vijay.

“Generally, prescribing physicians decide to use a drug off-label in the best interests of their patients and based on their confidence levels of using particular drugs in selected patients with specific conditions, especially when an alternative approved therapy is unsuitable, unavailable, unaffordable or inaccessible. Hence, physicians usually take the liability for adverse outcomes of off-label use of drugs, if any”, he concludes.

In an era when the concept of teratogenigicity was not even well established, Dr Kelsey successfully prevented the entry of the drug in the American market. She could have easily approved the drug which was being used in over forty countries. But what prompted her for its denial to approval?

Kelsey felt, “There was something a little different about this one so it seemed better to be safe and sure.” The need to not only conduct pharmacovigilance and drug safety studies but also enforce strict regulatory norms has been greatly felt today. It is for this reason that these should not be seen as a road blocks to newer drug approvals, but as prerequisites before approving a drug to guarantee the safety of patients.