Partnering for Clinical Development: The OSDD Mandate

SARALA BALACHANDRAN

Open Source Drug Discovery (CSIR-OSDD) is at present building a platform to take drug candidates into clinical trials. And as far as it is permitted by the regulatory agency, the data will be shared on an open portal.

If we look into the matrix of drug discovery and development, clinical trial can be viewed as a step in the later stages. But as far as testing the drug entity in humans is concerned, this is the first step. Up until now drug entity has been evaluated in the lab on rodents and mammals, its toxicity and stability and other parameters have been determined and it has been deemed worthy of being tested in humans.

To reach this stage in itself is a big step, as this particular candidate for clinical trials has already cleared several hurdles and emerged successful as compared to numerous other hopeful analogs. But the acid test begins now when finally it has to prove its worth in humans, where it has to undergo the various phases of clinical trials (phase I to phase III). Only after successful completion of these trials, the permission to market can be obtained.

Even then the perils are not over. After being marketed, if it is found wanting in a phase IV trial, the life of the drug can be cut short.

Usually the drug discovery process is a long one and on an average takes about 8-12 years. Before it reaches clinical trial, it has already undergone an array of tests to determine its activity against a particular target, potency in functional assay, selectivity and toxicity assays have been carried out, and a good therapeutic index has been observed. This entity must possess drug-like properties, should be stable and amenable to be synthesized and formulated on a large scale under good manufacturing conditions (GMP).

In brief, here is a picture of what phase I to phase III entails:

- In phase I the drug is tested generally in about 20-60 healthy volunteers (except in cancer where it goes to the patients) to look at its safety parameters at various doses. Once the safety parameters have been found to be satisfactory in humans it can now be taken up for phase II.
- In phase II the drug goes to the patients and its efficacy is determined for the intended use. Generally the number of patients in this stage is about 100-400. If the end points are successfully demonstrated, then it can be tested on a wider population of patients in phase III.
- In phase III, the number of patients will be about 600-3000 depending on the kind of study which looks for confirmation of efficacy.

Open Source Drug Discovery (CSIR-OSDD) is at present building a platform to take drug candidates into clinical trials. The first clinical trial to be taken up will be the one for tuberculosis (TB). Information regarding the cause and cure for this disease in earlier times was very limited. As Siddhartha Mukherjee in the Emperor of Maladies says, "Tuberculosis

The process of developing a drug from initial discovery to launch is estimated to be 10-15 years on an average. This is dependent on the therapeutic area and the line of treatment. One drug emerging from about 250 compounds in the preclinical stage is fortuitous.
coagulated out the Latin tuber, referring to the swollen lumps of glands that looked like small vegetables. Lymphatic tuberculosis, TB of the lymph glands was called scrofula, from the Latin word ‘piglet’, evoking the rather morbid image of a chain of swollen glands arranged in a line like a group of suckling pigs.”

In the nineteenth century, TB was known as consumption and by way of cure the patients were just advised to take rest in sanatoriums. A glimpse of this can be seen in Alice Munro’s story entitled Amundsen. To quote from her work: “I know, I know. You have read the Magic mountain... things have moved on a bit from that...”.

At present, things are better and we do have some drugs for TB. For drug-sensitive tuberculosis (DS-TB) the current regimen consists of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol and for drug-resistant tuberculosis (DR-TB) the regimen is usually Kanamycin, Levofloxacin, Pyrazinamide, Ethionamide, Ethambutol and Cycloserine.

Many of these drugs were discovered several decades ago. Among the newer ones are: Delamanid (OPC67683) from Otsuka pharmaceutical, Bedaquiline (TMC207) from Janssen Pharmaceutical, which recently has been given clearance by USFDA to be used for drug resistant TB and is available for MDR patients as Sirturo. We have some drugs like SQ109 (Sequella), Sutezolid (Pfizer), AZD-5847 (Astra Zeneca) in the pipeline. But that is not enough. If you look at the side effects and duration of treatment which is two years in case of drug resistant (DR) patients, non-compliance is a big issue.

To address this issue head on, what is required is a completely new regimen containing less number of drugs with less side effects and shorter duration of treatment.

PA-824 is one drug of real interest as this is being developed by Global Alliance for Tuberculosis (GATB, TB Alliance) as a combination regimen. This has already undergone several phase I clinical trials, for early bactericidal activity (EBA) in man. A combination of PA-824, Moxifloxacin and Pyrazinamide (PaMZ) has also undergone studies in mainly drug sensitive (DS) patients in a phase II trial in South Africa. It still has to be extensively tested in multi drug resistant (MDR) patients, which is what OSDD intends to do in India. For this, approval has been obtained from DCGI and this will be soon taken up. The partnering hospital is going to be the National Institute of Tuberculosis and Respiratory Diseases (NITRD, erstwhile LRS hospital) in New Delhi.

Generally every trial for new drug entities is carried out in a traditional manner, wherein a novel drug candidate is added to the existing regimen i.e. Standard of Care (SOC) to see if it is performing any better. In the current trial that we plan to undertake the first arm will be the combination regimen of PaMZ, in the second arm PA-824 will be given to trial subjects along with the SOC and the third arm will be the control arm having SOC which will be the standard drugs for MDR patients.

CSIR-OSDD being a non-profit, autonomous body under the government of India, the trials that have been planned are in public hospitals. The aim is to keep the cost down and bring in an element of affordability.

The idea is to conduct the trials in an open manner and as much as it is allowed by the law of the land, it will be made open to public. Please look into www.osdd.net for information.

While some things cannot be compromised like revealing the identity of the patient etc., other parameters of ethical and scientific interest will be made available in an open manner. Any new drug that comes out of this effort, will be provided to pharmaceutical companies to be manufactured (as generic medicines) with a view to control the cost during development. Whereas any new drug which gets developed outside the country will take its own time to reach Indian patients.

In the end, while gauging the current scenario of clinical trials wherein there is mistrust in some sections of the society and it is being advocated that companies are not sharing data and are hiding some to serve their interest, the open philosophy of conducting trials seems to be the best way forward. In OSDD, as far as it is permitted by the regulatory agency, the data will be shared on an open portal.

In the case of infectious diseases, the cost of conducting trials and development is much more as compared to the return on investments. The pharmaceutical companies will not be in a position to bring a new drug into the market. In our country where infectious diseases play a major role in the health of the nation, it is the duty of public and governmental institutions to take up such endeavours in order to bring about affordability in treatment of infectious diseases.

Dr Sarala Balachandran is a Scientist in the OSDD Unit, Council of Scientific and Industrial Research, Anusandhan Bhawan, 2 Rafi Marg, New Delhi-110001; Email: sbalachandran@csir.res.in