**Therapeutic Drug Monitoring in India : A SWOT analysis**

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**Introduction**

Therapeutic drug monitoring evolved in the 1960s focusing primarily on the correlation of adverse events with drug concentration ([1](#_ENREF_1)). The term was coined in mid 1970s and intended to build therapeutic ranges or therapeutic windows for some of the commonly used drugs at that time including phenytoin, digoxin, lithium, theophylline etc([2-4](#_ENREF_2)) ([5](#_ENREF_5)). It was initially intended to minimize drug related adverse events, which were clearly correlated to the increased concentration of the drug in the body. The indications gradually broadened into assessing efficacy of drugs, monitoring patient compliance, drug interactions, determining interindividual variability in drug response or to tailor therapeutic regimen ([6](#_ENREF_6), [7](#_ENREF_7)). Over the last several decades, TDM has widened its scope to encompass several emerging strategies such as target concentration interventions for antimicrobial drugs, personalized immunosuppression in organ transplantation and biomarker based precision pharmacotherapy in oncology ([8](#_ENREF_8)). Hence TDM became ‘Therapeutic Drug Management’ rather than only monitoring.

Practice of TDM is not extensive in India despite it being one of the fastest growing major economy in the world ([9](#_ENREF_9)). India is the seventh largest country by area, second largest by population, fifth largest by nominal GDP, third largest by purchasing power parity (PPP)([10](#_ENREF_10)). Providing healthcare to the citizens of this vast country is not only herculean but also enormously challenging. However, in the last decade, it has been a destination for medical tourism as state-of-the-art healthcare facilities are offered at an affordable cost at some of the centres compared to that of the developed nations ([11](#_ENREF_11)). Despite the impact of TDM in clinical science and it’s wider application in other parts of the world, TDM has failed to receive the attention it deserves in India. This review intends to bring out a strength-weakness-opportunity and threats (SWOT) analysis for TDM in India so that appropriate strategies for fostering TDM including introducing technologies suitable for developing countries, provide cost effective methods, logistics for remote areas like the point of care alternatives.

**TDM framework in India**

TDM in India is carried out largely in teaching hospitals and medical research centres. It exists in two types of sectors - public sector tertiary care teaching hospitals and private sector owned health care institutions ([1](#_ENREF_1)). There are several other diagnostic clinical biochemistry laboratories conducting the drug assays to support the health care systems. However, these essentially do not qualify as TDM service, due to the lack of back and forth communication between the clinician and the laboratory, that is integral to TDM. There is neither an inquiry regarding the appropriateness of the collected sample nor suggestion for dose modifications though the analytical stringency is largely adequate. The interpretation of the drug assay results in the light of the available information and patient’s clinical condition primarily rests on the treating physicians, leaving the TDM feedback loop incomplete ([12](#_ENREF_12)).TDM is a multi-disciplinary activity with a global aim to optimize therapy in well-defined therapeutic areas which are of importance in academic research organizations and hospitals in India. However, the academic organizations. are not able to meet the requirements of high infrastructural and operational cost, and hence, there has been an exponential growth in the commercial clinical chemistry laboratories performing drug assay in the country as the academic organizations were not able to meet the requirement. The TDM market in India has been estimated to be at 85 million USD in 2021 (compared to the global market of 1.4 billion) and expected to grow up. to 119 million (and up to 2.0 billion for the global market) in the next five years. This is a market based projection taking into consideration both the commercial establishments and academic centres. This business forecast includes the growth in different segments such as products (consumables and equipment), technology (immunoassay, chromatography etc), class of drug (immunosuppressant drugs (ISD), antiepileptic drugs (AED), antibiotics, antiarrhythmic drugs etc.) and the end-user (hospitals, research centres. and private laboratories) ([13](#_ENREF_13), [14](#_ENREF_14)). Figure 1 depicts the SWOT analysis that we have performed to summarize the current scenario of TDM and also propose an action plan to strengthen it in future in the country.

**Evolution of TDM in India**

India has demonstrated its strength by keeping abreast with the world with regard to the development of TDM and clinical pharmacology as a discipline. Many clinical pharmacology departments were set up in India since the late 1970s and 1980s. TDM was started in the late 1980s in some of these centres parallel to the growth of TDM supporting tailored use of older antiepileptic drugs (AED) globally. Many of these centres have offered TDM service over the years at a very reasonable cost([15](#_ENREF_15)). Seth G S Medical College and King Edward Memorial (KEM) Hospital in Mumbai were the pioneers of TDM services in the country (1988). The other centres that followed in due course of time were Christian Medical College (CMC), Vellore (1991); Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh (1996) etc. Currently a few more academic centres are also engaged in providing TDM services, notable amongst them are the Topiwala National Medical College and BYL Nair hospital Mumbai, PD Hinduja National Hospital and Medical Research Centre, Mumbai, Tata Memorial Centre, Mumbai and Jawaharlal Institute of Postgraduate Medical Education & Research (JIPMER) Puducherry, though this list is non-exhaustive. The success of this endeavour is evident from the contributions to the scientific literature from these centres, quoted later in this paper.

**Strengths**

The strength of TDM is to identify the population who may respond differently to a given drug. India fits into this quite well because of its unique ethnic and genetic diversity. In addition, significant prevalence of nutritional deficiencies, and tropical infectious diseases due to parasitic infestations such as malaria, kala-azar, filaria, amoebiasis and wide spread presence of tuberculosis and HIV, expected to alter the clinical response profile to drugs due to altered pharmacokinetics and dynamics. Therefore, it has been recognised that the therapeutic window for many drugs may be different in this part of the world compared to the others ([16](#_ENREF_16), [17](#_ENREF_17)). A few sporadic incidence suggest that available drugs in the market may be not of standard quality or spurious in nature. Moreover, there may be complex pharmacokinetic interactions resulting from wide spread use of alternative system of medicines (Ayurveda, Unani, Siddha and others) with modern medicines add another level of complexity([12](#_ENREF_12)). These justifications rationalize a wider practice of TDM in India.

Moreover, with a population of more than 1.3 billion, the magnitude in terms of numbers is enormous. Rising burden of chronic diseases such as diabetes mellitus, chronic renal failures needing transplantations, cancers and infectious diseases will further increase the need for TDM with improvement in the healthcare standards and rising investments in the healthcare infrastructure. The growing elderly population shall also require these services as the use of antidepressant, antiepileptic and antipsychotic drug use will increase. The therapeutic areas of relevance for TDM in India are many. We enumerate here the major classes of drugs.

**Antiepileptic drugs**

Phenytoin, phenobarbitone and carbamazepine have been the classical agents for TDM since its inception worldwide. Even in India, TDM started with these drugs and has been proven to be immensely useful for the older antiepileptic drugs (AEDs) in patients ([17-20](#_ENREF_17)). Even in the resource constrained setting like ours, TDM of older AEDs have proven to be pharmacoeconomically rewarding providing an increased likelihood of remission with better control of the seizure and reduced adverse events ([15](#_ENREF_15)). Several important effect modifiers unique to the Indian setting such as role of protein-energy malnutrition ([12](#_ENREF_12)) [11] and iron deficiency anaemia ([21](#_ENREF_21)) have been characterized. Similarly several clinically important pharmacokinetic interactions with complementary alternative medications ([22](#_ENREF_22), [23](#_ENREF_23)) leading to therapeutic failures have also been brought out.

The newer AEDs have better adverse effect profile and lesser drug interactions with comparable efficacy, obviated the need for TDM and therefore, have replaced the older AEDs in the developed countries ([24-27](#_ENREF_24)). However, the newer agents are significantly more expensive than the older AEDs and hence the older AEDs continue to be in use in India ([28-30](#_ENREF_28)). A similar trend can be seen in urban centres and tertiary care settings in India ([30](#_ENREF_30)), yet due to their lower cost, the older AEDs are prescribed in the semiurban and rural areas ([31](#_ENREF_31), [32](#_ENREF_32)). The older AEDs continue to be available in the public distribution system and commonly prescribed as the first line treatment when the choice has to be made between ‘no-treatment (due to lack of affordability)’ versus older AEDs rather than ‘newer AED’ versus ‘older AED’([30](#_ENREF_30)). Many centres in India continue to provide TDM for these drugs and as reported by *Rane et. al.* and *Gogtey et. al.*, TDM is still being managed for the old AED therapy in a cost-effective manner in India ([11](#_ENREF_11)) ([12](#_ENREF_12)), with emerging experience with the newer AEDs in our population ([33](#_ENREF_33), [34](#_ENREF_34)).

**Immunosuppressive drugs**

This class of immunosuppressive drugs (ISD) have become the prototype for precision pharmacotherapy candidates as they fulfils all prerequisite criteria for TDM. Currently, the ISD top the list of TDM requisitions at most of the centres worldwide and therefore, this segment drives the market around TDM ([35](#_ENREF_35)). Change in the trend to this pattern of TDM is observable after the introduction of the ISDs in the late 1980s and early 1990s and the surge in their use in the therapeutic management of organ transplantation. In India, a similar pattern TDM requisitions is observed as in the developed countries. Majority of the ISD assay are performed in commercial clinical chemistry laboratories in India as only a few academic TDM centres are providing the services for ISD at present. Renal transplantation is the most common solid organ transplantation performed. India is positioned second largest in the world, next to the USA in terms of number of renal transplantations performed ([36-38](#_ENREF_36)). According to a 2016 estimate made, 7500 renal transplants were performed in 250 centres in India([36](#_ENREF_36)). The need for transplantation will rise in the near future with increasing incidence of end stage renal disease and the consequent strengthening of the diseased donor transplantation program in the country ([39-41](#_ENREF_39)). The use of immunosuppressive agents for autoimmune disorders has also increased several folds over the past decade. These factors have strengthened the presence of TDM in India, and ISDs are likely to dominate the list of drugs requiring TDM.

**Anticancer drugs**

Cytotoxic anticancer drugs used for myeloablation in haematopoietic stem cell transplantation like high dose methotrexate and busulfan have decades of evidence favouring TDM with well-defined targets([42](#_ENREF_42)). There has been strong recommendation for 5-Flurouracil TDM by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology ([1](#_ENREF_1)) and dose optimization is being practised at several centres along with *DPYD* genotyping ([43](#_ENREF_43)). Despite a robust evidence in favour of dose individualization of anticancer drugs based on TDM for the prevention of chemotherapy induced toxicity or optimization of efficacy, the practice of TDM is rare in Indian settings. Only a few centres are performing TDM for methotrexate for guiding the leucovorin dose . In the last decade, practice of precision medicine in oncology has been extensively popular in other parts of the world and not only intravenously administered anticancer drugs but many targeted oral anticancer drugs have been found to be aligned to a target blood concentration window for optimal therapeutic response and treatment failures have been well described([44](#_ENREF_44)). Tyrosine kinase inhibitors, which are extensively used in Indian settings as many generic brands are available, are rarely monitored even though we have sufficient evidence([44](#_ENREF_44), [45](#_ENREF_45)). Epidemiological investigations suggest a four-fold increase in the incidence of cancer in India in the last five decades like many other parts of the world([46](#_ENREF_46)). With improved oncology diagnostic and treatment standards, TDM must catch up. Moreover, the specific factors in Indian setting as enumerated by *Gogtay et. al*. in their assiduous paper, merit a detailed investigation about any revised therapeutic window that may be applicable to Indian patients([12](#_ENREF_12)).

**Antibacterial drugs**

The TDM of this class of drugs are of increased importance in the critically ill patients where several disease factors modify the pharmacokinetic behaviour of the drugs unpredictably([47](#_ENREF_47), [48](#_ENREF_48)). The PK/PD principles and Bayesian dosing algorithms have been successfully employed for dose modification of these drugs leading to better clinical outcomes([49](#_ENREF_49)). According to the WHO report, the burden of infectious disease in India, is one of the highest in the world in 2014 and Indians were the highest consumer of antibiotics([50](#_ENREF_50)). The conundrum of antimicrobial resistance (AMR) is a result of several factors such as high burden of disease, poor public health infrastructure, unregulated sale of antibiotics leading to misuse of broad-spectrum antibiotics([51](#_ENREF_51)). Though the problem of AMR is multifactorial, TDM of antibiotics (at least for the ones with convincing outcome data), has the potential to eradicate the index infections and may help in containment of the multidrug resistant (MDR) organisms. Antimicrobial drugs are rarely found on the list of the commercial clinical chemistry laboratories in India, only a few academic TDM centres are engaged in this at present. There are studies suggesting that, employing TDM to treat severe infections will lead to better control of hospital acquired MDR infections ([47](#_ENREF_47), [48](#_ENREF_48), [52-55](#_ENREF_52)). Therefore, there is a possibility that the spread of MDR to the community may potentially be controlled by calling the TDM of antibiotics into action and facilitating it’s wide spread implementation.

**Antitubercular Drugs**

Tuberculosis (TB) is a significant health problem in India with the highest disease burden in the world . According to the WHO report, an estimated incidence in 2015 was 2790 thousand and about 423 thousand patients succumbed to the disease([56](#_ENREF_56)). Despite the implementation of DOTS (directly observed treatment short course) and DOTs-plus anti tubercular treatment regimens achieving a cure rate as high as 83% among the drug susceptible organisms, tubercular infection related deaths continue to be a threat due to emergence of MDR and XDR (extensively drug resistant) organisms ([57](#_ENREF_57)) . Several factors contribute to the development of resistance. Insufficient dose or dosing frequency of antituberculosis drugs ([1](#_ENREF_1)) and significant inter-individual differences in the pharmacokinetics (PK), among other factors, lead to low plasma concentrations of ATDs ([57-59](#_ENREF_57)). Studies have shown that inadequate exposure to the drug seem to be a much more important factor contributing to resistance than the patient non-compliance([60](#_ENREF_60)). PK variability is paramount given that emergence of drug resistance mainly in a subset of patients who are slow responders, patient with diabetes and MDR-TB strains ([61](#_ENREF_61)). Drug susceptibility testing addressing the pharmacodynamic variability (minimum inhibitory concentration, MIC) coupled with dose optimization by TDM has been the recommended strategy to overcome the problem of drug resistance in TB([62](#_ENREF_62), [63](#_ENREF_63)). Several studies have demonstrated that drug exposure is the key to treatment and patients with inadequate exposure are at greater risk of treatment failure, relapse and acquired rifamycin resistance ([64-66](#_ENREF_64)). Timely dose modification based on TDM has shown to be useful in several subset of patients including slow responders, patients with diabetes and MDR-TB([67-71](#_ENREF_67)). Although drug susceptibility testing is being performed at several centres, TDM of ATD is still not widely used for management of tuberculosis despite the evidence of improved clinical outcomes. A study by *Chawla et al.* from Mumbai, India have demonstrated that with standard doses of ATT, sub-therapeutic concentrations were achieved in 60% of patients attained for either of the first-line drugs (INH and rifampicin) and 18% to both the drugs. Among these patients 65% were slow responders([72](#_ENREF_72)). As *Peloquin et. al.*([63](#_ENREF_63)) suggest, these slow responder may subsequently be vulnerable to develop drug resistant TB due to selection pressure. Advocacy for TDM of the first-line ATD has also been proposed from several other centres in India to prevent relapse, to monitor therapy in the setting of malnutrition and HIV([73-77](#_ENREF_73)). *Swaminathan et. al.* have proposed a new population specific PK targets using artificial intelligence algorithm for Indian children([78](#_ENREF_78)). It has also been recommended that the WHO tuberculosis control program should incorporate TDM to aid its End-TB goal ([79](#_ENREF_79)). Informal pharmacoeconomic calculations conducted with data from Centre for Disease Control (CDC, USA) has suggested that TDM could be huge cost saving venture than treating the patients of MDR and XDR TB([80](#_ENREF_80), [81](#_ENREF_81)). TDM would certainly be rewarding in India, where the disease burden is much higher compared to the USA. Thus, TDM of ATD has enormous potential to add value to the National tuberculosis elimination program (NTEP) in India.

**Antifungal drugs**

Rising organ transplantations, use of cancer chemotherapy and the induced immunosuppression thereof, increasing prevalence of diabetes mellitus and HIV-AIDS; wide-spread use of antimicrobial drugs have led to reported surge in various types of opportunistic fungal infections in India ([82](#_ENREF_82)). The recommendation for TDM of antifungal drugs especially voriconazole, posaconazole, itraconazole and 5-flucytocine are growing stronger due to demonstration of high inter-patient variability and positive exposure-response relationship for efficacy as well as toxicity. Growing body of evidence suggests that TDM can provide better response to therapy and reduction in drug related adverse events([80](#_ENREF_80), [82](#_ENREF_82)). The impact of therapeutic optimization is certainly going to be proven rewarding in the long term.

**Neuropsychiatric drugs**

Changing life styles and increased average longevity in India has also led to increase in incidence of depression and other non-communicable chronic neuropsychiatric diseases. Improvement in health care facilities has led to better diagnosis and treatment options. Lithium is the most common drug monitored in psychiatry practice and it is one of the classical candidate drugs for TDM. The serum chemistry laboratories generally handle TDM of lithium. Because of the relative ease of measurement of lithium with electrolyte analysers measuring Na+/K+, it is included in almost all centres in providing TDM services. Among the other notable drugs needing TDM are clozapine, valproic acid and carbamazepine are part of the standard of care in developed countries ([83](#_ENREF_83)). Strong recommendation for TDM of several first and second generation antipsychotics have come up recently. Along with TDM, pharmacogenomics based dose selection for most tricyclic antidepressants has a potential to optimise the therapy further preventing the toxicities. In a consolidated clinical practice recommendation for TDM of neuropsychiatry drugs, *Hiemke et. al.* put forth strong recommendation for 19 out of 154 drugs and fair recommendation for another 39 drugs ([83](#_ENREF_83)). Moreover, TDM in these group of patients resolves other challenges like distinguishing between therapeutic inefficacy or treatment nonadherence arising due to concomitant comorbid conditions like dementia ([84](#_ENREF_84)).

**Miscellaneous Drugs**

Biologicals like anti TNF-alfa are increasingly being used in rheumatoid arthritis, psoriatic arthritis and inflammatory bowel disease (IBD) etc. Despite a growing body of evidence is in favour of employing TDM, to improve cost-effectiveness and prevent adverse events, it is only performed at a couple of centres in India. In a recent survey, Patel et. al. reported that, only 20% of the treating physicians were able to avail a TDM service assistance to treat their IBD patients. High cost and non-availability of the test were two important factors for such low prevalence of use([85](#_ENREF_85)).

**Availability of a sea of generics**

India has been one of the largest manufacturer and supplier of generic drugs and active pharmaceutical ingredients globally. The physicians in India are also encouraged to prescribe the generics as in the other parts of the world. This is owing to the substantial cost difference between the innovator drugs, even after the expiry of their patent ([86-88](#_ENREF_86)). However, there have been unremitting concerns in India, over the quality of generics in several quarters. The reported prevalence of not of standard quality medicines in India, range from as high as 30% to as low as 0.3% ([89-91](#_ENREF_89)). The greatest fear with generic substitution is therapeutic failure, which may initiate a vicious cycle further increasing the burden on the healthcare system. Moreover, when a generic is replaced for drug that traditionally requires TDM for dose optimization or monitoring of therapy like AED, ATD, antibiotics, antipsychotics etc. availability of TDM service is certainly desirable. This is of particular concern for drugs with narrow therapeutic index like tacrolimus, where a generic product can lead to serious fluctuation in drug concentration leading to adverse outcome like transplant rejection or nephrotoxicity ([92](#_ENREF_92)). These issues remain largely unaddressed, but wider availability and application of TDM would circumvent such problems and facilitate seamless generic substitution increasing the confidence of the physicians.

**Weakness**

We believe that, the weakness that TDM may have in the Indian context could be categorized into three broad areas viz. related to TDM *per se*, the logistic shortcomings, and matters related to the quality of the services.

**Ethnicity specific therapeutic ranges**

The ‘acceptable therapeutic ranges’ used in interpreting the TDM results are usually adopted from the studies conducted in other geographic and ethnic population, which may be different from the ‘Asian’ population at large. The Indian population has been designated as a genetically unique sub group by the US-FDA as ‘Asian Indian’ who are different than *Chinese, Filipinos, Koreans,* *Japanese* or the *Arabs, Turks, Hebrews* and *Persians*([93](#_ENREF_93)), and consequently a bridging study is mandatory to market a drug in India for the possible ethnic differences. However, it is not mandatory to look for the possible concentration effect relationship or any specific ethnicity specific dosing that may be needed. Similarly for the older drugs which are in the market for several years, it has not been considered essential to demonstrate the ethnicity specific therapeutic window. However, studies conducted in India show, only a fewer proportion of patients (<50%) were found to be within the therapeutic window for AEDs who had clinically controlled seizure ([94](#_ENREF_94), [95](#_ENREF_95)). Similarly, emerging evidence also suggests that the dose requirement and therapeutic range of mycophenolate for *Indians* may be less compared to the *Caucasians* ([96](#_ENREF_96), [97](#_ENREF_97)). Nevertheless, these aspect of ethnicity based dosing is still unexplored and drug use in clinical practice continues as per the International best practice guidelines. Apart from ethnicity, the other confounders for the therapeutic range are poor nutritional status and presence of tropical diseases. Generating the relevant data for a potentially altered concentration-response relationship with such effect modifiers requires substantial capital investment. As it does not add to commercial benefit, such studies are only of academic interest and seldom find sponsors. In the absence of population specific data, the current practice of TDM in India employs the recommended values for therapeutic window from the international guidance or consensus statements.

**Logistic challenges**

Performing TDM is resource intensive. The equipments or platfoms (as they are popularly referred as) that are required for drug estimation are broadly divided into two classes viz. immunoassay or chemistry analysers, chromatography based systems. Additionally, supportive laboratory equipments for sample storage and preparation etc. are also required. The first two class of equipment are too expensive as there are no indigenous manufacturers and most of them have to be imported. In addition, the recurring cost of consumables for running a service and employment of competent personnel to deliver the service is also significant. Therefore, rationalisation of TDM services, as an economically viable add-on in the management of diseases in the face of enormous health care demands is the greatest challenge in India. The opportunity cost associated with TDM is therefore could be major a deterrent to the wide spread penetration of TDM services to semi-urban areas. The putative counter argument is, these resources may be utilized in improving the basic healthcare facilities in these areas. However, to prove the worth one may have to wait patiently, may be as long as half to one decade, to demonstrate that implementation on TDM has actually prevented therapeutic failures, adverse events, improved outcomes and reduced health care expenditures by adding a positive pharmacoeconomic value.

**Lack of formally trained manpower**

Development of TDM in the country has been limited to specific regions. Scarcity of competent skillset has been recognised as one of the important limitations to the growth of TDM. There is only a few TDM oriented training program run by the academic TDM centres. Moreover, these are of short courses and may not be adequate for running independent centres. There has been no upgrades in these training programs and one of the reasons may be number of upcoming TDM establishments have been very few in the recent times. Therefore, the manpower engaged in current TDM framework has largely acquired these skill on the go and there is limited avenue for passing it on to the future generation. Apart from the technical skills (analytical chemistry) of performing TDM, the operational skills for procurement of necessary equipments, consumables and overall management of a centre is also important for the laboratory managers and directors. Robust technical training programs and specific leadership programs are currently needed in the country to strengthen TDM as an independent clinical service.

**Quality of service**

Quality of TDM services is another area of concern. The quality of the report is ensured when the tests are conducted in an accredited laboratories with the proficiency testing in place. Improved diagnostic tools and rigorous quality control provide assurance of quality and hence the degree of variability is reduced to <10% of the true value of the drug concentration([98](#_ENREF_98)). The commercial clinical biochemistry laboratories, which conduct drug estimation from biological fluids, have both these requirements in place, as it is in part essential for medical tourism([11](#_ENREF_11)). However, as we mentioned previously, they are essentially not conducting TDM but a random drug measurement. The logistic challenges and restricted funding in the public sector hospitals prevent implementation of the procedures that assures quality of the TDM services. Moreover, as there is no regulatory requirement in India for clinical laboratories providing TDM service, compliance to appropriate quality standards has been a voluntary. Therefore, despite providing the best of care with the available resources and producing good quality research and answering some of the fundamental issues in the developing countries with regard to TDM, the quality of TDM service in the major teaching hospitals in India appear to fall short of the international standards.

In summary, apart from the logistic bottleneck, lack of a co-operative network, and facilitated cross-talk for operational troubleshooting and organised development of TDM strategies is lacking in the country. Most of the weaknesses listed here are surmountable, provided reasonable infrastructures are developed, a well thought though action plan and able leadership is required for executing and building the TDM programs.

**Opportunities**

The broad purpose of TDM is to identify the population who may respond differently to a given drug. India fits into this quite well because of its unique ethnicity, genetic diversity, prevalence of nutritional deficiencies, and tropical infectious diseases and other significant public health problems like, tuberculosis and HIV. It has been recognised that the therapeutic windows for many drugs may be different in this part of the world compared to others ([16](#_ENREF_16), [17](#_ENREF_17)). Wide spread use of alternative system of medicines (Ayurveda, Unani, Siddha and others) carry the potential for altering the pharmacokinetics of modern medicines and thus add another level of complexity ([12](#_ENREF_12)).

Moreover, with a population of more than 1.3 billion, the magnitude in terms of numbers is enormous. Rising burden of chronic non-communicable diseases such as diabetes mellitus, chronic renal failures needing renal transplantations, cancers and infectious diseases will further increase the need for TDM with improvement in the healthcare standards and rising investments in the healthcare infrastructure. The growing elderly population shall also require these services as the use of antidepressant, antiepileptic and antipsychotic drug use will increase.

**COVID-19 pandemic and the strengthening of healthcare infrastructure**

The outbreak of the COVID-19 has overwhelmed the healthcare system throughout the world and it has forced us to think about our extent of pandemic preparedness. The healthcare infrastructure has got a boost in India due to the pandemic([14](#_ENREF_14)). Strengthening of the laboratory testing facilitates have been achieved due to increased public and private sector investments. This can to be turned into an advantage and these newly functional laboratories can be further be equipped to provide special analytical chemistry services.

**Improving the quality**

The usefulness of TDM in many therapeutic areas is well proven; one such is TDM of ISDs. There are many centres in India performing renal transplantation without in-house facility for TDM. The sample is transported to a distant laboratory and report is communicated telephonically or by email. Most of the times the onus of validity of the sample and its interpretation rests on the treating physician, who does not have a choice but to trust the quality of analysis from a private laboratory. On the other hand, due to lack of accreditation, the academic TDM centres refrain from commenting on the quality of testing. It is therefore not surprising that a survey on the ‘quality of TDM services’ received no responses from India([99](#_ENREF_99)). Establishing accredited regional TDM centres providing optimal quality service to a is the right strategy as having centres in each hospital is not a viable option. Strengthening the TDM services by improving the quality of service is the greatest opportunity. We understand that the most fruitful initiative would be from the government to strengthen the program and enforce some standards. The national accreditation board for testing and calibration of laboratories (NABL) for clinical laboratories still are voluntary in India. It is resource intensive and is at par with the international accreditations. Regulatory and policy reforms for facilitating accreditation of the TDM laboratories in academic set ups. There is also need for provision of funding for upgradation and training of the laboratory personnel in TDM facilities. Many TDM laboratories have to subscribe to external proficiency testing from agencies outside India that are prohibitively expensive posing substantial financial burden. Therefore, there is a great opportunity to develop our own national proficiency testing programs, which could be subscribed by the laboratories in the country at a reasonable cost. Quality improvement is a continuous process, and if TDM has to grow both in depth and breadth, capacity building should be the strategy. Moreover, the cost-effectiveness and cost-utility of such service must be demonstrated as has been in other parts of the world (table 1)([100-102](#_ENREF_100)).

**Alternative sampling strategies**

India is a large and populous country with more than two thirds of its population residing in the rural areas ([103](#_ENREF_103)). The accessibility of the rural population to a good TDM laboratory facility may seem a little too far-fetched. However, there is a great opportunity to explore the utility of alternative sampling methods like dried blood spots to make TDM available to the rural population. There are certain issues specific to the tropical countries like higher temperature and high humidity condition for stability of these samples during their transport. These must be specifically addressed during the validation process of the method. The proof of concept for this application has been provided by *Das et. al,* where carbamazepine from dried blood spot assay was demonstrated to be comparable to liquid blood assay quantified by liquid chromatographic method in a distant laboratory in a tertiary care hospital ([104](#_ENREF_104)). There is a an evidence for available expertise in in the country for developing the bioanalytical method ([99](#_ENREF_99), [103](#_ENREF_103), [105-110](#_ENREF_105)), but it needs a goal oriented organized effort to standardize as many drugs as possible to make TDM available even in the remote parts of the country. This would reduce the cost of establishing multiple TDM facilities in addition to saving the cost related to the travel, loss of wages etc. Moreover, it will also provide business opportunity for small industries to develop sample collection devices and market them in the country.

**Integration with pharmacogenomics**

As precision medicine is increasing being practised worldwide, as we progress towards individually tailored therapeutic regimens, pharmacogenomics as a clinical diagnostic service is slowly catching up in the country. This is also backed by the effort of the public sector agencies for generation *Indian* ethnicity specific genome data. In a recent endeavour by the Council of Scientific and Industrial Research (CSIR) a government of India enterprise has been commissioned to develop the Indian Genome Variation (IGV) Consortium([111](#_ENREF_111)). In addition, scientists at the Institute of Genomics and Integrative Biology (IGIB), New Delhi have, recently concluded the first ever human genome-sequencing project in India ([112](#_ENREF_112)). The Indian Council of Medical Research (ICMR) has also set up a new task force on pharmacogenomics to focus on specific disease areas to develop an ‘Indian pharmacogenomics chip’ ([113](#_ENREF_113)). The request for pharmacogenomics is largely centred in the tertiary care hospitals. This information coupled with TDM and with expert therapeutic advice is an ideal setting for delivering precision medicine (figure 2). This kind of integrated facility could prove to be potentially rewarding in many therapeutic areas like organ transplantation, oncology, neuropsychiatry etc. However, such one stop service is exceedingly rare in India. And is at best a near-future dream. The academic clinical centres engaged in TDM services face logistic challenges to implement this. Many commercial laboratories are providing pharmacogenomic services using contemporary cutting edge technologies like DNA chips microarrays and next generation sequencing ([114-116](#_ENREF_114)). However, very few of them are also using the TDM data simultaneously to make dosage recommendation though they may be able provide drug sensitivity for a personalized oncology treatment. There is a great opportunity for strengthening these sectors. The diagnostic laboratory facilities have been boosted during the COVID-19 pandemic throughout the country with increased capital investments. Strengthening of these diagnostic laboratory facilities further for TDM capabilities, may be a worthwhile proposition, so as to provide opportunity for growth of TDM and pharmacogenomics together in India.

**Threats**

**Existential crisis**

TDM is facing a great challenge to make it’s presence as an independent branch of healthcare service science in the country. It is a highly unorganized sector in India. Since presently only a few of the pharmacology and clinical pharmacology departments in the teaching and research institutes in India are providing the most purposeful TDM services, the clinical biochemistry laboratories (both inside or outside of the teaching hospitals) have engaged in filling the gap to meet the demands. TDM has not grown substantially as a multidisciplinary science in India despite the tremendous transformation globally. The best practices for TDM process like the decision to request a drug level, the biological sample, laboratory measurement, communication of results to laboratory, clinical interpretations and therapeutic management as described by *Gross et. al. .* are far from being optimally achieved in India ([117](#_ENREF_117)). It is nearly three decades now since the pioneers of TDM in India published the challenges and opportunities for in a developing country([12](#_ENREF_12)) but it could never acquire a desired momentum. Currently, the centres, which are delivering TDM, are resource constraint and are running the program with local administrative support. These centres have done a commendable contribution to TDM science pertinent in the context of a developing country. However, these efforts are isolated and limited to few centres. More recently, a group of academicians have joined hands and started a web-based educational program known as ‘TDM education in India’ with support from the International Association of Therapeutic Drug Monitoring and Clinical Toxicology ([1](#_ENREF_1), [118](#_ENREF_118)). This movement needs consolidation with creation of a designated professional society for TDM in India and nurturing the efforts with logistics support for a committed goal of fostering its growth towards a well-recognised clinical science in India.

**Need for a nation-wide initiative to strengthen TDM in India**

Prof. Phillip Walson, a founding member of the International Association of Therapeutic Drug Monitoring and Clinical Toxicity had rightly stated *“the greatest challenge is from hospital administrators and other business oriented people who simply do not understand (and may not even care) how TDM/CT (clinical toxicity) can improve patient outcomes. As long as TDM/CT results are considered the same as an AST “number” that need only be compared to some “normal range” these people who control budgets will resist assigning resources to provide true TDM/CT services that must include collection of patient, drug and dosing specific information and utilizing it to individualize the interpretation of results”*([119](#_ENREF_119))*.* TDM is resource intensive and hence the administrators must be first convinced about the purpose and its potential in patient care. We must learn from our able neighbour China, where TDM now a National policy since 2011 and expanded tremendously in last four to five years with 170 tertiary care hospitals providing TDM services throughout the country([120](#_ENREF_120), [121](#_ENREF_121)).

There is a need for a forum in India to bring together all the stakeholders viz. pharmacologists, clinicians, analytical chemists, hospital pharmacists, clinical biochemists, expert professionals in pharmacometrics and pharmacoeconomics on a common platform. Seeking guidance, professional support and mentorship from the IATDMCT towards fostering TDM and CT in India, as has been started in July 2022 is a timely step. However, it needs a fundings from a federal sources to continue the process, which is slow and time as well as effort intensive. The mandate of this cooperative TDM group should be (a) to offer TDM services to their strength, (b) to develop strategies for TDM through multicentric studies and (c) to publish multicentric data for wider dissemination of TDM.

**Action plan to revive TDM in India**

Capacity building should be the first step to revive TDM in India. The greatest strength we have currently is a vast, trainable cohort of professionals. India has 650 medical schools offering MBBS (Bachelor in Medicine and Bachelor in Surgery) courses and training more than 80000 physicians every year. Out of these schools, post-graduation in pharmacology is offered in 169, clinical biochemistry in 161, pathology and laboratory medicine in one, and laboratory medicine in one([122](#_ENREF_122)). These academic institutes, especially the centres running postgraduation courses, are the potential site of training for the TDM professionals at all levels. The physician clinical practitioners need to be sensitised about the latest developments in the TDM of drugs pertaining to his speciality and other specialities and therapeutic areas, with regard to the evolving clinical evidence. The physician laboratory scientists need training for manging the TDM program as laboratory directors. The laboratory personnel need technical training to manage the clinical sample workflow and conduct the clinical chemistry analysis. The clinical pharmacists in the hospitals should also be involved in the process of TDM service delivery. The clinical pharmacology centres which have been delivering TDM services for a few decades now, could adopt the leadership roles, sharing their experiences in managing the TDM programs at their centres. A national professional body may be constituted . A proposed tentative action plan in the order of priority for this professional body is depicted in figure 3. (i) A national action plan is to be drafted, (ii) list of priority drugs for TDM based on their utility to the Indian context, keeping in mind the disease prevalence in that region of India and the unanswered questions, (iii) A representation to government should be made with a 5-year action plan to seek the seeding fund to initiate a National TDM Program to strengthen TDM in India, (iv) nodal TDM centres are to be established and pilot programs for capacity building is to be run (v) finally, the assessment for performance of the program should be done at the end of 5 years to take plan the next 10-years.

**Epilogue**

For further growth in India, TDM needs logistic support, adequate funding and above all proper milieu – administrative and academic. With increasing awareness among clinicians about personalized medicine, TDM has the potential to emerge as an indispensable tool. The right interpretation of the drug concentrations in body fluids for each patient, considering the pharmacological, pharmacokinetic and pharmacodynamic aspects can be done by an insightful clinical pharmacologist who can convey necessary recommendation to the physician for dose adjustment; and this is the key to an effective TDM service. A successful integration of TDM into the routine clinical practise is much needed in the fast-changing healthcare delivery in India in the twenty-first century

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