One of the fundamental aims of developing a new molecular entity (NME) is to fulfill an unmet medical need in a therapeutic area. Recently, Central Drugs Standard Control Organization (CDSCO) issued an office order directing all sponsors, Contract Research Organizations (CRO), and medical institutions applying for conduct of clinical trials to provide information on unmet medical need in the country[1]. In the absence of any regulatory guidance, the challenge for the applicant would be how to fulfill this regulatory requirement.

Food and Drug Administration (FDA) defines unmet medical need as a condition whose treatment or diagnosis is not addressed adequately by available therapy.[2] Priority medicines for Europe focuses on conditions for which some treatments exist, but the delivery mechanism, or formulation may be inappropriate for the target patient group and conditions for which no effective treatment is available.[3]

An unmet medical need includes an immediate need for a defined population e.g. to treat a serious condition with no or limited treatment or a longer-term need for society, e.g. to address the development of resistance to antibacterial drugs).[2] Hence, assessment of an unmet medical in a population need would depend on the target population for whom the need is to be assessed.

If the purpose of estimating medical need to is to meet societal or public health requirements, it would require consideration of disease burden and clinical efficacy and safety of available therapeutic interventions.

Burden of disease is usually measured by estimating the disability adjusted life years (DALYs)[3] an integrated measure of mortality and disability due to a particular disease or condition.

For the priority medicines for Europe report, the criteria considered were:[3]

- The estimated European and global burdens of disease
- The common risk factors amenable to pharmacological intervention that have an impact on many high-burden diseases
- The prediction of disease burden trends, based on epidemiological and demographic changes in Europe and the world
- The principle of “social solidarity” applied to diseases for which there are currently no market incentives to develop treatments.

Priority medicines for Europe report also considered pharmaceutical gaps for the diseases and the risk factors identified. A pharmaceutical gap exists.[3] (1) when pharmaceutical treatments are likely to become ineffective, e.g., due to resistance or (2) if an effective medicine either does not exist or is not sufficiently effective or (3) when the delivery mechanism or formulation is not appropriate for the target patient group. Pharmaceutical gap was identified by using data on the effectiveness of available treatments from multiple sources such as Cochrane and other databases, the National Institute for Health and Care Excellence, WHO reports and industry sources.[3]

In contrast to public health perspective, the regulatory authorities determine whether medicine should be a “priority” for regulatory purposes, based on whether or not an NME demonstrates improvement over existing medicines. The FDAs fast track process is designed to facilitate and expedite the development, and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition.[3] A serious disease or condition is defined as a disease or condition associated with morbidity that has a substantial impact on day-to-day functioning.

The FDA, while reviewing a drug for fast track approval, applies following criteria for an NME claiming to fill and unmet medical need.

- If a new treatment is for a serious condition, for which no therapy is available.

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If an available therapy exists for the condition, a new treatment must show some advantage over existing therapy such as:

- Superior or improved effect on serious outcome(s) of the condition
- Effective in patients who are unable to tolerate or failed to respond to available therapy
- Better safety profile, e.g. avoiding serious toxicity
- Improved compliance
- Reduced potential for drug interactions.

In contrast, the pharmaceutical industry’s approach in setting drug development priority is driven by scientific opportunity, market assessment, available and required resources, and medical need. The industry experts review the market to identify unmet medical needs, and benchmark competitor products to understand the competitive landscape. This approach helps in clearly identifying the market segments and patient populations an NME can target.

The CDSCO expects information on unmet medical need in the country. This probably implies a preference for societal need over the immediate need for a defined population. Estimating an unmet medical need in Indian population would be challenging for clinical trial applicants.

Indian pharmaceutical and CRO professionals have managed global clinical trials protocols, which provide justification of unmet medical need in the rationale of the clinical trial. But this justification is prepared by European/US experts with consideration of unmet medical needs in the Western population. Hence, Indian pharmaceutical and CRO professionals have to develop competence in preparing justification of unmet medical need in Indian population.

India has a huge burden of diseases. In 2012, 9,816,000 Indians succumbed to medical illnesses. Noncommunicable diseases (NCD) are estimated to account for 60% of total deaths. Among NCD, most common are cardiovascular disease, chronic respiratory conditions, cancers, and diabetes. However, in recent years the focus of industry clinical trials has been niche indications such as mild-to-moderate systolic hypertension, diabetes patient on metformin therapy, nonST-segment elevation myocardial infarction, genotype 2/3 hepatitis C, triple negative metastatic breast cancer, hormone resistant prostate cancer with bone metastases etc., DALY estimates are available at macro level but not for a subset of the disease. One option would be to extrapolate the number of Indian patients suffering from such conditions by using estimates from published literature. However, this approach would not reflect Indian reality as the published studies are likely to be from Western countries.

In a recent study, Mattheij et al. challenged the justification for the need of human papillomavirus (HPV) vaccine in India. The authors concluded that neither the epidemiological evidence nor current cancer surveillance systems justify the general rollout of a HPV vaccination program either in India or in the two states – Gujarat and Andhra Pradesh where the trials were conducted.

The question for the Indian pharmaceutical sponsor would be: How to estimate the burden of disease when the therapeutic target is subset of the disease?

Another difficulty would be how to assess potential clinical benefits of the new therapy in comparison with therapy available in India. Although Cochrane is considered the gold standard for systematic reviews of medical evidence, these reviews are retrospective and may not include recent products. Furthermore, most trials in the Cochrane database are randomized placebo-controlled trials. What is important from a public health perspective is not whether a new intervention is better than placebo but whether it is better than the current best available treatment. More often than not, randomized controlled trials (RCT) of head-to-head comparisons between new intervention and current best available treatment are not done. Another drawback of the Cochrane Database is the limited data on adverse events. In addition, the Cochrane reviews may not be available for a specific medical condition for which the trial is designed. Even when Cochrane review is available it is unlikely to include Indian data, as India did not participate in global clinical trials prior to 2005. We also lack Indian data based on RCTs, as industry clinical trials conducted for regulatory approval are open noncomparative in a small number – usually 100 – patients.

The CDSCO mandates that at least 50% of clinical trial sites should in public or government hospitals. This population is from lower socioeconomic strata whose prime medical need is access to available therapy. It would be difficult to justify that unmet medical need in this population can be met by a new therapy.

There seem to be diverse approaches to assessing unmet medical need for prioritizing pharmaceutical research and development in the country. However, unless the regulatory authorities provide guidance as to what is expected from the applicant, this regulatory requirement would become a riddle for the industry.
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