Medication package inserts: Complete, accurate, and up-to-date

While technical definition of package insert (PI) of a medication/device is – “printed leaflets accompanying marketed drug products and contain information approved by regulatory authorities,”[1] it is the key summary of all the research done while developing the product and the information generated during the process. Updated, accurate PI, duly approved by regulatory authorities in each territory, is an important source that provides the physician with reliable framework to correctly prescribe and dispense the medication for safe and effective use.

Approval and up-dation of PI is a well-defined regulatory process. United States Food and Drug Administration (US FDA) has a website with over 150 labelling resources – containing regulations, guidance, templates, format tools databases, etc. Taking cognizance of the fact that PIs, over a period, have increased in length, details, and complexity, 2006 amendment to US FDA regulations requires concise, half page summary in the full prescribing information for easy reference.

According to the US FDA, three key essential elements in the PI should:
• Contain summary of essential scientific information needed for safe and effective use
• Be informative, accurate and neither promotional, false or misleading
• Be updated when important new information is available.[2]

Indian regulations around PI are laid down in Drugs and Cosmetics Rules and the information under two categories (broadly pharmaceutical and therapeutic) is expected to be included.

It is important to assess and analyze accuracy and completeness of PI in a country like India where there are thousands of manufacturers and each product may have several generic brands. PIs, deficient in information, inaccurate, and not updated timely, can lead to medication errors with adverse consequences for the patients.

A cross-sectional observational study by Barkondai et al.[3] published in this issue assessing adequacy of PIs in India, is a relevant addition to the studies conducted so far. In investigator blinded (to manufacturer) assessment of 135 PIs of medications in different therapy areas and with different routes of administration, completeness of PIs with respect to statutory guidelines was checked under 25 headings. The study identified important gaps. To highlight few key areas where information was either missing or inadequate, inaccurate were-patient information (87.41% PIs), disposal instructions (92.59%), last updated date (80.74%), and references (94%). The article quotes other studies that show similar trends, though the lacunae may be in different areas.[3]

Another study on clinical information in drug PIs in India was published in 2009 by Shivkar.[1] The author did a qualitative analysis of missing information in 80 PIs and compared his findings with studies published a decade ago. While he found improvements in many areas, important deficiencies remained. For e.g., though majority PIs included warnings and precautions, they frequently lacked information on use in pediatric and geriatric patients, other special conditions (e.g., liver, renal, and cardiac illnesses). Drug dose to be administered was missing in three PIs – including those of rosiglitazone and norepinephrine, and dosing interval was missing from 6 PIs (including PI of methyl prednisolone tablets, and ampicillin-sulbactam injections). Information of adverse events was summarily mentioned in most leaflets, none highlighting serious adverse drug reactions (ADRs) associated with the product.

US FDA requires that PI includes clinically significant adverse reactions that,
• Require discontinuation, dose adjustment, or addition of another agent
• Could be prevented or managed with appropriate patient selection or avoidance of concomitant therapy
• Significantly affects patient compliance.[4]

Majority of updates to PI are linked to new safety information emerging as more and more patients are given the medication. It is important that they are updated timely (hence importance of “last updated” date), to enable the physicians to re-assess the risk-benefit ratio for their patients.
One important lacuna highlighted in the current study is the lack of or inadequate patient information sheet, which forms the integral part of PI in developed countries. Patients are critical stakeholders and their understanding of treatment is the key to success in disease management. The patient assumes primary responsibility in taking the medicines dispensed on outpatient basis. As comprehensively described by Hermann et al., the minimum information the patient information sheet should contain is—how to take the drug, how to store the drug, how it is expected to help the illness, how to recognize problems (side effects) that can arise, and what to do about them. We, in India, must move toward a scenario where patient information sheet is prepared, approved, and enclosed with every medication.

Another focus area of research should be surveying physicians to find out whether they regularly read, use the PI and their perception about its quality and utility while they prescribe the medicines. Their perceptions can have a powerful positive or negative impact on prescribing habits.

Top et al. published a study in The Lancet. They surveyed 141 health-care professionals from four African countries to capture their perceptions about influenza vaccine safety in pregnant women, based on the language in PI. PIs from three companies that had framed information in three different ways were shown to the participants. Negatively framed sentence read, “safety and efficacy in pregnancy not clearly established,……use (only) if clearly needed,” while positively framed sentences read, “use only following advice of a healthcare professional, based on the risk-benefit considerations to mother and fetus” and “Use only from the 2nd trimester of pregnancy …..at the risk of complications of infections.” 44% (nearly half) perceived vaccine as unsafe in pregnancy after reading negatively framed sentence, while 30% (about one third) perceived the vaccine as unsafe after reading the positively framed sentences.[6]

It is important to mention the US FDA position that it does not consider PI establishes medical standard of care. It recognizes the fact that there are situations where the appropriate and rational use of medication may be reflected by experience of prescriber and reports in the medical literature.[7] However, PI provides important framework of evidence-based information derived from clinical trials and postmarketing pharmacovigilance to plan the therapy. There should be very good reason/evidence to deviate from its recommendations and prescriber needs to take the responsibility for the same.

Chayet published a case in New England Journal of Medicine in 1967 titled “Power of the PI.”[8] A hypertensive lady patient died after xylocaine (epinephrine + lidocaine) was administered to her by dentist. Her estate brought a lawsuit alleging the dentist that injection of xylocaine led to her death but were unable to get a medical expert to testify in court that the dentist was negligent in administering the drug. However, the jury could give a guilty verdict on the ground that the PI stated that lidocaine and epinephrine may be contraindicated in patients with hypertension!

To summarize, there are now many sources from which a prescriber can obtain information about medications. However, PI, duly reviewed and approved by regulators remains the most important source. In the Indian context, we still need to do much more to consistently make PIs comprehensive, accurate and up-to-date as evidenced from the study published in the current issue and several others before that. It will require many pronged approach—further refinement and strengthening of regulations—importantly their consistent implementation, more proactive approach and responsibility from the manufacturers, active role played by physician community, and lot of efforts on ground to educate the patients.

One medical dictionary cynically describes PI as “hard-to-handle, and difficult to read package ‘stuffer’ printed in Lilliputian type of Bible paper”[9] All stakeholders need to work to move PIs from cumbersome to an easy to refer, accurate, up-to-date, scientific reference tool to a medication that will lead to correct prescriptions benefiting the patients.

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