International Journal of Pharmacological Research
ISSN: 2277-3312
www.ssjournals.com
Journal DOI:10.7439/ijpr

A critical appraisal of medication package inserts

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Abstract

Introduction: Package Inserts (PIs) refers to officially specified document that accompanies a drug for relevant, updated and unbiased information for rational drug use based on regulatory guidelines as per section 6.2 and 6.3 of schedule D of Indian Drug and cosmetic Act 1945. But some studies had shown non-uniformity with sub-optimal level of information which frequently can lead to medication errors. Hence this study was conducted to evaluate the completeness of PIs.
Aim: To critically evaluate package inserts of allopathic medicines.
Material and Methods: 100 allopathic drug PIs were collected from pharmacies in Rohtak and were checked for the presence of each heading as per schedule D criteria, followed by scrutiny of the information included under the heading. Indian guidelines were also compared with US FDA guidelines for PIs.
Scoring of package inserts: The information were evaluated for completeness and scored as 1 if present otherwise scored as zero for no information or partial information. Scores for each heading were calculated by totaling the scores of all the package inserts. The total scores were expressed as absolute numbers and percentages.
Results: On an average PIs analyzed for the completeness of the criteria scored 10 (Mean± SD = 9.73±2.49) out of 16. Absence of common layout and headings caused inconvenience. In comparison to US FDA guidelines it lacked, disclaimer statement, boxed warning, revision date, approval date, toll-free number etc.
Conclusion: PIs don't seem to be serving effectively because of multiple deficiencies like completeness, uniformity, absence of headings.
Keywords: Critical, appraisal, package inserts.

1. Introduction

The term "package insert" (PIs) refers to officially specified document provided along with the drug for relevant, updated and unbiased information for rational drug use based on regulatory guidelines. It is a global term of reference for product's characteristics, risks, recommended doses and uses. PIs are the authentic source of information for the new molecules in the market.[1] Accurate and reliable drug product information are important for its safety and effectiveness. It is evidence based and updated time to time as and when the relevant pre-clinical and clinical data available.[2]

There is considerable variation in the information worldwide with different regulatory bodies controlling the genuineness of the information, like United States Food and Drug Administration (FDA) and Ministry of Health and Family Welfare in India. In India this information should be according to the guidelines mentioned as per section 6.2 and 6.3 of Schedule D, of the Indian Drug and cosmetic Act 1945. Section 6.2 mandates information under headings such as posology and method of administration, contraindications, special warnings etc. and section 6.3 mandates list of excipients, incompatibilities, shelf life etc.

The PIs are intended to guide the health care providers and patients who largely rely on the information provided by the manufacturers.[3] A study done in private practitioners observed that the majority of them found PIs extremely useful, reason being information on effects, indications and mechanism of action.[4] Patients do require certain amount of information in order to use their drugs optimally.[5] Indian healthcare professionals depend on a variety of sources, including textbooks and compendiums, for information on drugs.[6] Prescribers are also likely to depend on product information provided by pharmaceutical companies.[7] It promotes rational drug use and prevent self-medication related adverse events as mentioned by Zaghi *et al* in 'Survey of Safety and Efficacy Information in Drug Inserts for Topical Prescription Medications'. A study from northern India mentioned 56% of hospital admissions occurred in people aged over sixty years are due to adverse drug events.[8] Excipients which have often been implicated in drug reactions were mentioned in less than half of the inserts. [9] Study titled "Clinical information in drug package inserts in India" indicated that the information relevant for the safe and effective use of medications was not uniform with missing information on

drug over dosage, drug-interactions, and pregnancy and lactation.[10] PIs are still missing key information regarding drug safety and efficacy.[11] This drug product information commences early during the developmental phase of a pharmaceutical product with careful scrutiny of available information. FDA has designed PIs for most up-to-date information in an easy-to-read format that draws attention providing clear and concise information. Some of the changes are initial date for product approval, toll-free number, Internet reporting of adverse events, electronic format leaflets etc. Product information provided by pharmaceutical companies in India has been determined to be far from adequate and not conforming with the WHO recommendations. [12,13]

Keeping this in mind, this study was designed to critically evaluate completeness of PIs and to compare with US FDA guidelines for necessary modifications.

2. Material and methods

2.1 Collection of package inserts

Package inserts from various drugs packages were collected from various pharmacies on request over a period of four weeks in the month of august 2014. A total of 100 package inserts in English were collected from pharmacies near PGIMS Rohtak. The collections included leaflets from 54 oral, 40 injectable, and 6 topical preparations from various categories like antidiabetic, antibiotic, antihypertensive, anti-malarial, hormonal agent, anti-allergic, anti-emetic, analgesic drugs marketed by different pharmaceutical companies in India. Package inserts from ayurvedic products, those from the same brand, others which are in regional languages only, were identified and excluded from the study. However those with both English and regional Indian languages were included in the study.

2.2 Analysis of content of PIs

Package inserts were scored based on criteria laid down by Indian Drug and Cosmetic Rules, 1945 under section 6.2 and 6.3 of schedule D. Data were extracted twice to minimize chances of missing any information. The clinical information included in the package inserts was analyzed according to the headings mentioned in Section 6.2 and 6.3 of Schedule D of Drugs and Cosmetics Rules, 1945. The package inserts were checked for the presence of each heading mentioned in Section 6.2 and 6.3, followed by scrutiny of the information included under the heading. If a heading was not present, the content was searched for relevant informations. The extracted informations were also analyzed in comparison to US FDA package inserts guidelines for presence of any deficiencies.

The Package Inserts were analyzed based on the following criteria:

1) Posology and method of administration
2) Contraindications
3) Special warning and special pre-caution for use, if any:
4) Interaction with other medicaments and other forms of interaction
5) Pregnancy and lactation, if contraindicated
6) Effects on ability to drive and use machines, if contraindicated
7) Undesirable effects and side effects
8) Antidote for overdosing
9) List of excipients
10) Incompatibilities
11) Shelf life in the medical product as packaged for sale
12) Shelf life after dilution or reconstitution according to direction
13) Shelf life after first opening the container
14) Special precautions for storage
15) Nature and specification of the container
16) Instructions for use / handling

2.3 Scoring of package inserts

The information under the relevant heading or elsewhere in the package insert were evaluated for completeness and scored as 1 if present otherwise scored as zero for no information or partial information. After each of the selected package inserts had been scored, the total scores for each heading were calculated by totaling the scores from individual package inserts. The total scores were expressed in absolute numbers and percentages.

3. Results

On critical evaluation package inserts were found to be inadequate in many aspects. On an average package inserts analyzed for the completeness of the criteria were 10 out of 16 (Mean± SD = 9.73±2.49). It lacked uniformity in shape and font size. Absence of common layout and headings caused inconvenience to obtain the necessary information. Although presentation of information regarding posology, methods of administration, instructions for use,

contraindications, adverse drug reactions, special warnings and precautions were present in majority of the leaflets but still they are lacking in many. One of the very important information regarding the use of drugs during pregnancy, lactation and the drug interactions were absent in many of the leaflets. Effect of the drug on ability to drive, management for overdosing, expiry date or shelf life for the medical product which constitutes its effectiveness were absent in most of the leaflets. Table 1 represents the criteria as per section 6.2 and 6.3 of schedule D of Indian Drug and Cosmetic Act 1945 and the corresponding percentage represent the presence of the information under the heading. In comparison to Indian guidelines for PIs the US FDA labeling design makes it easier for the prescriber as well as the patient to get access to important information about drug safety and benefits and also this in turn help them to have more meaningful discussions. Table 2 represents the comparison of criteria as per Indian guidelines with US FDA guidelines.

Table 1: Percentage of information present under the heading as per section 6.2 and 6.3 of schedule D of Indian Drug and Cosmetic Act 1945.

Criteria as per Section 6.2 and 6.3 of schedule D (Total 16)	Total score of package inserts in percentage (N=100)

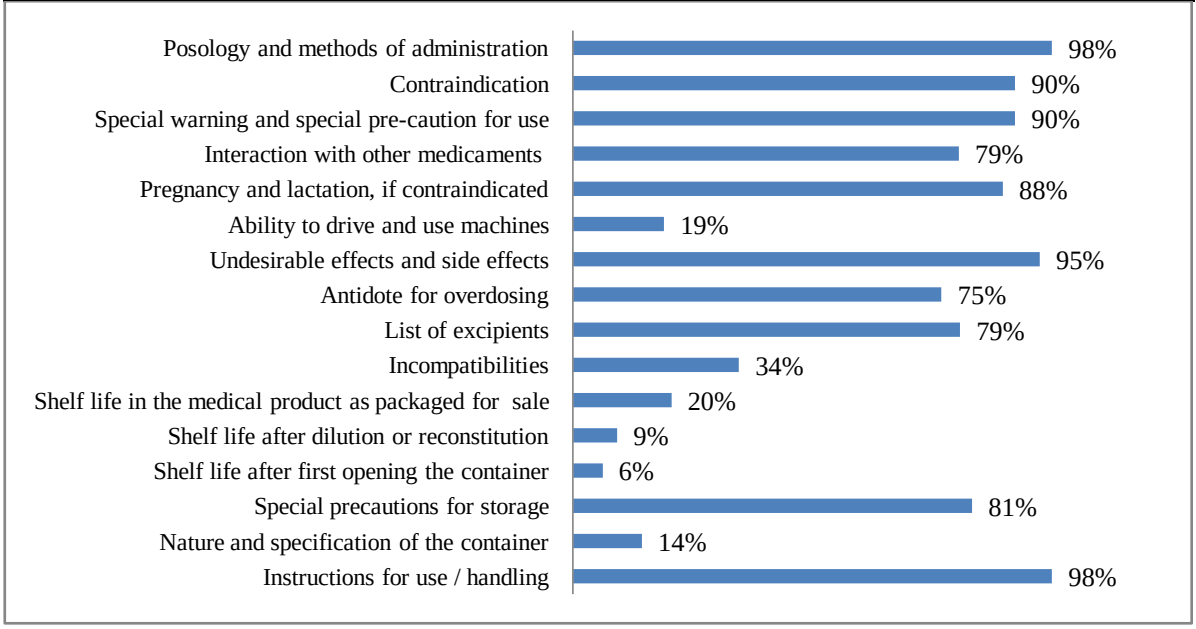

Table 2: Comparison of Indian guidelines with US FDA guidelines for PIs

Guidelines for labeling as per section 6.2 and 6.3 of schedule D of Indian Drug and Cosmetic Act 1945	US FDA guidelines for labeling
1. Posology and method of administration 2. Contraindications 3. Special warning and special pre-caution for use, if any: 4. Interaction with other medicaments and other forms of interaction 5. Pregnancy and lactation, if contraindicated 6. Effects on ability to drive and use machines, if contraindicated 7. Undesirable effects and side effects 8. Antidote for overdosing 9. List of excipients 10. Incompatibilities 11. Shelf life in the medical product as packaged for sale 12. Shelf life after dilution or reconstitution according to direction 13. Shelf life after first opening the container 14. Special precautions for storage 15. Nature and specification of the container 16. Instructions for use / handling	1. Highlight title and limitation statement 2. Product title: drug name, dosage form, route of administration, and controlled substance symbol 3. Initial U.S. approval 4. Boxed warning 5. Recent major changes 6. Indications and usage 7. Dosage and administration 8. Dosage forms and strengths 9. Contraindications 10. Warnings and precautions : special care precautions, monitoring by laboratory tests, and interference with laboratory test 11. Adverse reactions: categorization of adverse drug reactions, clinical trial experience and post marketing experience 12. Drug interactions 13. Use in specific population: pregnancy (teratogenicity), labour and delivery, nursing mother, pediatric use, geriatric use 14. Drug abuse and dependence 15. Overdosage 16. Clinical pharmacology: mechanism of action, pharmacodynamics, pharmacokinetics 17. Nonclinical toxicology: carcinogenesis, mutagenesis, impairment of fertility 18. Animal toxicology and /or pharmacology

	19. Clinical studies 20. References 21. How supplied /storage and handling 22. Patient counseling information 23. Revision date 24. Contents for easy reference to detailed safety and efficacy information 25. Toll-free number and internet reporting information for suspected adverse events 26. PIs in electronic format

4. Discussion

PIs have an important impact on the patients compliance and thus on the effectiveness of drug use. In our study it was observed that the PIs were inadequate in many aspects with lack of uniformity in presentations of information. It was difficult to locate and find the necessary information easily due to variable layout and heading, differences in the font size and shape, making it inconvenient for the users to use it as a reference. These findings depict that despite of the regulatory guidelines laid by Central Drugs Standard Control Organization (CDSCO) of India the current concept of PIs is not serving its purpose satisfactorily. Prevalence of self-prescribed medications and use of 'over the counter' drug is also on rise making the package inserts an essential tool for extracting the basic knowledge for understanding the drug. The language that was used in the PIs to describe its content was mostly related to scientific terminologies which could be difficult for a layman to understand. Therefore, use of simplified language could be more beneficial. For a country like India, with diverse culture and languages, introducing the regional language in combination with English language for a pre-specified region where the drug is to be supplied can be useful.

Patients need to be made aware of their therapeutic interventions in order to minimize medication related adverse events. But some of the pharmaceutical companies have failed to provide complete information in their PIs, the probable reason could be that providing such information can affect the off-label use of the drug and also there is no strict vigilance over the discrepancies by the concerned authorities. Therefore, strict rules should be made with the unique format of the package insert, so that all the discrepancies whether related to the paper size, shape, font size or others could be removed irrespective of drug preparations i.e. solid, liquid, cream, suspension or gel form. A governing body should be formed to ensure the implementation of these rules and for regular verification of the data. To improve the readability and comprehensiveness of PIs, they must be optimized and tested by selected groups of experts prior to marketing. This will ensure the avoidance of the lack of information and will give the best possible outcome to access the information content by the patients and to avoid safety related risks. This can be best exemplified by the U.S. Food and Drug Administration, where format for PIs are regularly revised, providing clear and concise information. In comparison to US FDA guidelines for package inserts there are certain deficiencies seen, for example if the information is not present, a disclaimer statement regarding the lack of such information should be made by the company, there were no criteria for mentioning of boxed warning drugs, use in specific populations has covered only pregnancy and lactation, however drug usage during labor, in pediatric and geriatric has not been mentioned in many of the PIs.

Under warning and precautions there are no specific criteria such as special care precautions, monitoring by laboratory tests, and interference with laboratory test. Under adverse drug reactions categorization of adverse drug reactions like clinical trial experience and post marketing experience has not been clearly defined. Patient counseling information which highlights to provide immediate access to the most important prescribing information about benefits and risks by providing a table of contents for easy reference to detailed safety and efficacy information were not included. Other criteria not mentioned are clinical pharmacology, nonclinical toxicology, clinical studies, drug abuse and dependence, revision date, references, date of initial product approval, making it easier to determine how long a product has been on the market, toll free number and internet reporting information for suspected adverse events, to encourage more widespread reporting of suspected side effects. Therefore, the current concept can be modified such that it can serve as a better tool for the dissemination of up-to-date information to the patients, as well as the prescribers. All these issues indicate a need for a 'patient-oriented package insert' in order to serve the population in an efficient way.

5. Conclusion

The current concept of package inserts is not serving its purpose satisfactorily and there is a need for revision. It can also be further improved by incorporation of some of the concepts, currently being followed in the developed countries and reformulate it in such a way to make it more patient oriented.

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