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RESEARCH ARTICLE

Analysis of completeness of drug package inserts available in India

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ABSTRACT

Background: Information about the drug used can be obtained from various sources of drug information. One of the easily available sources of drug information is package insert (PI). The PI is the primary source of drug information. The PI or leaflet is the leaflet containing information about the medicinal product which accompanies the medicinal product. A good PI contains the approved, essential, and accurate information and it contains information in a language that is not promotional, false, or misleading. It is evidence based and periodically updated. However, not all PIs conform to all the above standards. Hence, the present study was undertaken to evaluate the appropriateness of presently available drug PIs. **Aims and Objectives:** The aim of this study is to evaluate the completeness of the presently available PIs and grade them. **Materials and Methods:** The present study was cross-sectional, observational, prospective study. 55 PIs were collected from various pharmacies in request. Out of them, 5 were found to be duplicated and were rejected. Remaining 50 PIs were analyzed based on criteria laid under the Drugs and Cosmetics Rules 1945 under section 6.2 and 6.3 of schedule D. **Results**: Among the 50 PIs, 35 (70%) were of Indian companies and 15 (30%) were of multinational companies. Furthermore, 31 (62%) were parenteral preparations, 15 (30%) were oral formulations, and 04 (8%) were topical preparations. PIs were inadequate as to retail price of drug (0%), references (14%), effect on ability to drive machines(26%), updated information, and provision of full information on request (38%). 52% of PIs were A category, 48% of PIs were B category, and none of PIs were C category. **Conclusions:** The present study shows that there is still paucity of information and requirement of standardization of the presently available PIs, especially with regard to the size and shape of PIs, font size, references, effect on ability to drive machines, updated information, and provision of full information on request. Furthermore, PIs should be made mandatory with all medications.

KEY WORDS: Package Inserts; Drug Information; India; Patient Information Leaflets; Patient Information Package Inserts

INTRODUCTION

Drugs are regularly prescribed by physicians to treat diseases. Most of these drugs are manufactured by pharmaceutical companies according to the industry standards of manufacturing. These drugs manufactured by pharmaceutical companies contain information about the drugs in them in the form of package insert (PI) as mandated in the Drugs and Cosmetics Rules (1945).[1] The PIs form the primary source of drug information for the physician, the pharmacist, and to the patient. These PIs are also known by different names, for example, package leaflet, prescription drug label, prescribing information,[2] prescription drug insert, professional labeling, etc. The PI was first introduced in the 1960 and 1970s for isoproterenol inhalators followed by oral contraceptives and other drugs.[3] The term PI should not be confused with the term drug label which implies all the printed information that accompanies the drug, including the label, wrapping, and the PI.[4]

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A package leaflet is a leaflet containing the information for the end user accompanying the medicinal product.[5,6] Other definitions of PI include that it is a document which is in the form of a printed leaflet approved by the drug regulatory authority and which is provided along with the package of drug. The PIs in India are regulated by the Drugs and Cosmetics Rules (1945) section 6.2 and 6.3 of Schedule D. Section 6.2 requires that the PIs should be in English and must include information on therapeutic indications, posology and method of administration, contraindications, special warnings and precautions drug interactions, contraindications in pregnancy and lactation, effects on ability to drive and use machines, undesirable effects, and antidote for overdosage. Section 6.3 includes pharmaceutical information about the list of excipients.[1]

A PI is said to be complete if it contains approved, correct, and essential information about the drug and be periodically updated from time to time as and when pre-clinical and clinical data about the drug become available.[2] Furthermore, it should be written in a language that is easily comprehensible, contains essential information related to drug, is evidence based and does not falsely promote the drug on the basis of false claims and promises.[2] The Drugs and Cosmetic Rules fail to specify the end user of the PI, however, it appears to be directed toward the health-care practitioner.

The PIs by providing reliable, accurate, and essential information about the medication are an important source of drug information to the health-care practitioners thus decreasing and avoiding medication errors. They bridge the gap between the prescriber and the patient[7-9] and improve medication use and patient's compliance.[10,11] According to a study by Joubert and Skene, various reasons for consulting the PI were for information on untoward effects (64%), indications and mechanism of action (33%).[11]

Various countries have framed their own guidelines regarding the information that should be included in the PIs and there is a slight variation in the terminologies used as to the name of the PIs. The US Food and Drug Administration mentions them as "patients PI" while in the European Union, they are known as "patient information leaflets."[2]

The PIs have received their due attention in the developed countries but still have not received the complete attention in developing countries like India and there is still scope for improvement of these PIs.[12] In the developing countries, PIs are still an important source of drug information even for prescribing doctors, as they sometimes have limited access for up-to-date details of newer drugs. Even from the patients, perspective PIs are an important source of drug information as many patients tend to use over the counter drugs and PIs are helpful in providing the correct information to the patient about the drug. Despite repeated attempts to sensitize the authorities regarding inadequacy of information of presently available PI at both national and international level, there is still a lot of deficiencies in the presently available regulations for designing the PI, especially in a developing country like India.[13-17] Therefore, the present study was carried out to further emphasize these differences in the presently available PIs by measuring the completeness (availability of key information) of PIs in India according to a set of standard criteria and grade them according to the scores obtained.

MATERIALS AND METHODS

Collection of PIs

The present study is a cross-sectional, observational, prospective study. A total of 55 PIs were collected from various pharmacies on request in the months of January-February 2017. Out of these, 5 were found to be duplicated and hence were not included in the study.

Analysis of Content of PIs

These PIs so obtained were analyzed for the presentation and completeness of clinical and pharmaceutical formulation based on the criteria laid down by the Indian Drugs and Cosmetics Rules 1945 under section 6.2 and 6.3 of Schedule D.

The following points were investigated for each of these PIs:[18] Legibility, approved generic name of active ingredients, content of active ingredient per dosage form, list of excipients, therapeutic indications, posology and method of administration, contraindications, special warnings and precautions, drug interactions, pregnancy and lactation, pediatric and geriatric indications, special conditions and contraindications, effect on ability to drive and use machines, undesirable effects, antidote for overdosage, pharmaceutical information, storage information, instructions for use and handling, shelf life, date on which information last updated, name and address of the manufacturer/distributor, provision of full information on request should be highlighted, retail price of drug, and references.

Scoring and Grading of PIs

A total score of 24 was assigned for each of these PIs based on the criteria laid down in the Drugs and Cosmetics Rules 1945.

- Score of >20 graded as "A."
- Score of 10-20 graded as "B."
- Score of <10 graded as "C."

If a heading was not present in a PI, the entire insert was checked for the presence or absence of information relevant to concerned heading.

RESULTS

Information about legibility, generic name and active ingredient, therapeutic indications, posology and method of administration, contraindications, special warning and precautions, side effects, name and address of manufacturer/distributor, information about drug interactions, contraindications during pregnancy and lactation, special conditions and confidence interval (C/I), and storage information was present in ≥90% of PIs. While information of pediatric and geriatric indications, antidote for overdosage, pharmacokinetic information, and instructions for use and handling was present in 70-80% of patients.

Other information regarding list of excipients (68%), effect on ability to drive and use machines (26%), shelf life (54%), date on which last information last updated (38%), provision of full information on request (38%), and references (14%) were present in only a few of these PIs (mentioned in brackets). None of the PIs contained information about the retail price of drug (Table 1).

Of the 50 PIs, 26 (52%) belonged to Grade A and the remaining 24 (48%) PIs belonged to Grade B. None of the PIs belonged to Grade C (Table 2).

Furthermore, on further analysis of these 50 PIs based on drug groups, they were found to be as follows: 13(26%) were for antibiotics, 11 (22%) were for endocrinal conditions, 5 (10%) for cardiovascular conditions, 4 (8%) for autonomic conditions, 3 each for central nervous disorders (6%), vaccines (6%) and miscellaneous conditions (6%), 2 for gastrointestinal disorders (4%), 1 each for snake venom antisera (2%), respiratory condition (2%), local anesthetic (2%), dermatological conditions (2%), NSAID's (2%), and skeletal muscle relaxants (2%) (Table 3).

Furthermore, analysis of PIs based on the nationality of manufacturers revealed that out of 50 PIs, 35 (70%) were of Indian nationality and 15 (30%) were of multinational companies (Table 4).

Categorization of these PIs according to the route of administration of the drug in them showed that 31 were parenteral preparations (62%), 15 were oral preparations (30%), and 04 (8%) were topical preparations (Table 5).

Table 1: Scoring of PIs (*n*=50)

Criteria	Present (%)	Absent (%)
Legibility	50 (100)	0 (0)
Generic name of active ingredient	50 (100)	0 (0)
Content of active ingredient per dosage form	50 (100)	0 (0)
Generic name of other ingredients (list of excipients)	34 (68)	16 (32)
Therapeutic indications	50 (100)	0 (0)
Posology and method of administration	50 (100)	0 (0)
Contraindications	50 (100)	0 (0)
Special warnings and precautions	50 (100)	0 (0)
Drug interactions	45 (90)	5 (10)
Pregnancy and lactation	48 (96)	2 (4)
Pediatric and geriatric indications	36 (72)	14 (28)
Special conditions and contraindications	46 (92)	4 (81)
Effect on ability to drive and use machines	13 (26)	37 (74)
Undesirable effects	50 (100)	0 (0)
Antidote for overdosage	39 (88)	11 (22)
Pharmaceutical information	36 (72)	14 (28)
Storage information	47 (94)	3 (6)
Instructions for use and handling	44 (88)	6 (12)
Shelf life	27 (54)	23 (46)
Date on which information last updated	19 (38)	31 (62)
Name and address of the manufacturer/distributor	50 (100)	0 (0)
Provision of full information on request should be highlighted	19 (38)	31 (62)
Retail price of drug	0 (0)	50 (100)
References	7 (14)	43 (86)

PI: Package insert

Table 2: Grades of PIs

Score	Grade	*n* (%)
>20	A	26 (52)
20-10	B	24 (48)
<10	C	00 (0)

PI: Package insert

DISCUSSION

Over 90% of PIs contained information about legibility, generic name and active ingredient, therapeutic indications, posology and method of administration, contraindications, special warning and precautions, side effects, name and address of manufacturer/distributor, information about drug interactions, contraindications during pregnancy and lactation, special conditions and contraindications, storage information, etc. While in 70-80% of PIs, information of pediatric and geriatric indications, antidote for overdosage, pharmacokinetic information, instructions for use, and handling was present. Other information regarding list of excipients(68%), effect on ability to drive and use machines (26%), shelf life (54%), date on which last information last updated(38%), provision of full information on request (38%), and references (14%) were present in only a few of these PIs (mentioned in brackets). None of the PIs contained information about the retail price of drug (Table 1).

Table 3: Percentage of various classes of PIs (*n*=50)

Drug category	*n* (%)
Antibiotics	13 (26)
Endocrinal drugs	11 (22)
Cardiovascular drugs	5 (10)
Autonomic nervous system drugs	4 (8)
Central nervous drugs	3 (6)
Vaccines	3 (6)
Multivitamins (miscellaneous)	3 (6)
GIT drugs	2 (4)
Snake venom antisera	1 (2)
Respiratory drugs	1 (2)
Local anesthetics	1 (2)
Dermatological drugs	1 (2)
NSAIDs	1 (2)
Skeletal muscle relaxants	1 (2)

PI: Package insert

Table 4: Percentage of PIs by Indian and multinational companies

Company	*n* (%)
Indian	35 (70)
Multinational	15 (30)

PI: Package insert

Table 5: Percentage of PIs based on route of drug administration (*n*=50)

Route of administration of drug in PI	*n* (%)
Parenteral preparations	31 (62)
Oral formulations	15 (30)
Topical formulations	04 (8)

PI: Package insert

Of the 50 PIs, 26(52%) belonged to Grade A and the remaining 24 (48%) PIs belonged to Grade B. None of the PIs belonged to Grade C (Table 2). This is different in comparison to the study by Deep et al.[18] in which the grade A PIs were only 3.14% and grade B PIs comprised 94.33% of the total PIs. This could be because of different nature of the PIs analyzed. On further analysis of PIs, it was found that they were of different shapes and sizes which gives rise to non-uniformity of these PIs. Furthermore, the information was not presented in a uniform manner as prescribed by the Drugs and Cosmetics Rules 1945 and it was difficult to locate and retrieve information that was not included clearly under different headings as mentioned in the Drugs and Cosmetics Rules 1945. As per Schedule D, it is mandatory to give importance to both sections 6.2 and 6.3 of section 6. However, it was found that much importance was given to 6.2 of section D with less emphasis on 6.3 of section D as can be seen in the results section.

The results of this study correlate with other similar studies in this aspect[18,19] with regard to criteria mentioned for measuring these PIs with some differences in results as to the antidote for overdosage in which the study by Kalam et al.[19] mentions only 4% of PIs containing the details of antidote for overdosage whereas in our study, it was present in 88% of PIs, this difference could be because of different types of PIs included for these studies. One similarity that was found in all the studies of PIs was that references were mentioned in only a very few PIs and this aspect should be improved on by providing full reference for the various claims in these PIs.

The use of PIs in India is governed by the Drugs and Cosmetic Rules 1945 as amended up to 30th June 2005. However, the information about labeling and packaging of drugs is further divided into subsections as 6.2 and 6.3. This can be further simplified by including all the information under a single section and dividing that section into different points for consideration. Some important aspects that could be considered for further improving the PIs include:[5,6] Readability of PIs clarified by standardizing the font size and type (e.g., size 9 and times new roman), use of capitals, italics, and underlining to be minimized, line spacing to be at least 1.5 times, headings should stand out by choosing a bold typeface or a different color, dark text should be printed on a light background, bullet point is preferable over long paragraphs, thick paper can be used to reduce transparency and glossy paper is discouraged as it causes glare in bright light, symbols and pictograms can be used provided they do not replace the actual text in leaflet, if the pictogram meaning is doubtful then it should not be used, hints regarding the application errors can be included, preclinical safety data to be included for drugs which have been recently introduced into market, also medicinal products whose safety data requires additional monitoring, and it should be clearly mentioned that use of this product requires additional precautions.

As mentioned by Shivkar,[17] pharmaceutical companies and drug regulatory authorities both have equal obligation to ensure that the PIs contain all the information required by medical practitioners and patients and that this information should be periodically updated from time to time. Self-regulation by pharmaceutical authorities can be of some help but the drug regulatory authorities should ensure that the guidelines for PIs are up to date and that these guidelines are strictly enforced in the preparation of PIs. Furthermore, PIs should be made mandatory with all those medications which require packaging.

The main strengths of this study was that its results (in terms of deficiency of information regarding section 6.3 of Schedule D of Drugs and Cosmetics Rules 1945) corroborate with other studies done researching the completeness of PIs with regard to deficiencies and guidelines required for improving the quality of presently available PIs.[17,20-22]

The limitation of this study could be that only 50 PIs were evaluated. However, this could be compensated because the PIs used for analysis were from different group of drugs and duplication of PIs for analysis was avoided by removing them at the start of the study. Another difficulty was the non-availability of a uniform reference standard (no gold standard) [23] for comparison and the criteria used in this study for analysis of drug PIs although used in previous studies has its own merits and demerits as different authorities lay emphasis on particular aspects of PIs. Hence, the various guidelines should be compared with each other for the development of a complete PI so that it can highlight all the salient features of a standard PI.

CONCLUSION

PIs are an important source of drug information for both the prescriber and user of the medication. These PIs are deficient in many aspects which can be rectified by following the rules and regulations properly and correctly. This in turn helps to prevent medication errors which are an important cause of drugs adverse effects and will also help to improve the patient's compliance.

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