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Original Research Article

Analysis of completeness of information in package inserts of Indian and foreign multinational pharmaceutical companies: an Indian perspective

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ABSTRACT

Background: A package insert (PI) should contain all the information required for safe and effective use of the medicine. The present study evaluated and compared the completeness of information in package inserts of Indian and foreign multinational pharmaceutical companies based in India.

Methods: A total 150 PI's consisting of 75 package inserts of Indian and foreign multinational pharmaceutical companies in India were collected and analyzed based on the criteria of Indian drugs and cosmetics rules, 1945 under section 6.2, 6.3 of schedule D, which consists of 25 parameters. Each criteria was scored for presence of information as '1', absence as '0'. Total score was 25, score >20 was graded as 'A', 10-20 as 'B' and <10 as 'C'. Data was expressed as numbers and percentage.

Results: Total 150 PI evaluated included antimicrobials, antipsychotics etc. Out of all the PIs 26% belonged to grade A, 70% belonged to grade B and 4% belonged to grade C. Lack of information was found in both the categories of PIs. Foreign PIs performed better in comparison to Indian PIs as in grade A, 27 out of 41 PIs were foreign whereas 56 PI's in grade B were Indian and 47 were foreign. Both categories of PI showed good information about active ingredient, dosage form, warnings, contraindications and lacked information about retail price and references etc.

Conclusions: Both categories of PIs were deficient in completeness of information. The pharmaceutical companies, both national and foreign, must provide the information as per regulatory norms.

Keywords: Package insert, Schedule D, Regulatory

INTRODUCTION

Accurate and reliable drug information is essential for safe and effective use of marketed products. In developing country like India where about 72% of the health care burden is borne by the patient and physician gets limited time to explain the drug peculiarities to patient, the role of package insert information becomes significant.¹ Package insert (PI) is a document provided along with drug in its manufactured container. It is primary source of drug information to any patient

containing details of drugs pharmacokinetics and pharmacodynamics properties, its adverse effects, overdose, drug interactions, special warnings and several other instructions. The information presented in the PIs is necessary for both the prescribers and the patients. In Indian scenario, due to inadequate doctor patient ratio, the accessibility to trained prescribers is difficult and physicians are not able to spend enough time with their patients. This gives rise to self-medication, medication errors, and adverse drug reactions. All these issues indicate the need for patient-oriented PIs. The United

States Pharmacopeia (USP) Medication Errors Reporting Program (MER) found 30% of the medication errors reported were due to wrong labelling of the medicine.² A good PI contains all the approved, essential, and accurate information required for safe and effective use of marketed products. Various studies have concluded that PIs can produce an important impact on patient's compliance and thus on the ultimate effectiveness of drug use. Sholomo et al observed that 51% of patients reading package inserts developed anxiety and 10% patients decreased the adherence to treatment.³ A survey based study done by Kafeel et al analyzed that 75.6% responders believed that reading package inserts affect health outcomes.⁴ It is written in a non-promotional, non-misleading and easy to understand language. In India, the standards of package insert are formalized by the 'drugs and cosmetics act (1940) and rules (1945). The section 6.2 of schedule D (II) of the rules lists the headings according to which information should be provided in the PIs. The 'section 6.3' mandates pharmaceutical information on list of excipients.

In spite of all the regulations, enforcing authorities, quite often these drug package inserts are found to have missing information about various parameters. Mahatme et al, conducted a study to evaluate the adherence of drug package inserts to the recommended guidelines and found the information provided in most of PI's was not uniform and could not be accessed easily. They also noted that government supply inserts are of poorer information than that of non-government package inserts.⁵ Shivkar et al noted, after studying 92 inserts, that most package inserts contained information related to undesirable effects but none of the inserts highlighted the serious adverse events, including ones that could be life-threatening or fatal.⁶

The information on PIs is updated time to time based upon the latest research data. In 2006, US food and drug administration have revised the guidelines for prescription drug information. To manage the risks of medication, use and to reduce medication error, these package inserts were made to provide up-to-date information in easy-to-read format.⁷ A regular audit of package inserts is necessary by the government and the local agencies to ensure that the pharmaceutical companies comply with the regulatory guidelines.

The present study was carried out to critically assess the completeness of information provided in the package inserts of the Indian and foreign multinational pharmaceutical companies in India according to the standards laid down by Indian drugs and cosmetics rules, 1945.

METHODS

Study design

This was a survey based observational study conducted by the Department of Pharmacology, Pt. B.D. Sharma

PGIMS, Rohtak (Haryana) from September to October 2019.

Methods

A total of 150 PIs belonging to different pharmacological classes and formulations were randomly collected from local and regional pharmacy stores, which included 75 package inserts each of Indian and foreign multinational pharmaceutical companies in India. An analysis of the contents of PI's were based on the criteria laid down by Indian drug and cosmetic rules, 1945 under section 6.2, 6.3 of schedule D (II), which consists of 25 parameters (Table 1) recommended for every package insert of drug.

Criteria of package inserts

The PIs were analyzed based on the following criteria: legibility, approved generic name of active ingredients, content of active ingredient per dosage form, generic names of other ingredients, 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, drug dose, over dosage, pharmacokinetic information, storage information, instructions for use and handling, shelf life, date on which information was last updated, name and address of manufacturer/distributor, provision of full information on request should be highlighted, retail price of the drug, and references.

Scoring and grading of PI's

A total score of 25 was assigned to each PI, based on 25 parameters. Presence of parameter on PI was awarded a score of '1' and absence was awarded '0'. Total score out of 25 was expressed in numbers and percentages.

The scores of package inserts, was classified into 3 grades for the completeness of information based upon the score out of 25. The classification based upon scores was as follows: grade A: score 21-25, grade B: score 11-20, and grade C: score 1-10.

The higher grade i.e. grade A, is representative of better completeness of information in PI while grade C with lower score represent grossly incomplete information provided in PI.^{11,13}

Apart from dividing the PIs into grades based upon the scores out of 25, they were also analyzed and compared for distribution of achieved score.

Percentage value for each item to calculate completeness of information was categorized accordingly - very good: 100-96%, good: 91-95%, fair: 75-90%, average: 50-74%, and poor: $\leq 50\%$.

Apart from dividing the PIs into grades based upon the scores out of 25, they were also analyzed and compared for distribution of achieved score. All the data was recorded, entered and analysed by a master chart prepared using microsoft excel 2013.

RESULTS

Total of 164 drug package inserts were collected and 14 were excluded due to duplication. The remaining PI's consisted of 75 each from Indian and foreign multinational companies. Among 150 PI's included in the study, there were 66 tablets, 26 capsules, 22 injections, 14 topicals, 6 eye drops, 2 nasal spray, 5 inhalational drugs and 9 syrups (Figure 1).

The package inserts belonged to various pharmacological classes of drugs (Figure 2). The most frequent classes being antimicrobials, analgesics and antipsychotics whereas PIs of drugs acting on gastrointestinal, skin and endocrinal disorders contributed to lesser extent.

According to section 6.2 the package inserts should be in English and it was found that all the inserts examined

were in English and not in regional languages. The presentation of information was not uniform and it was difficult to locate and retrieve the information easily due to lack of common layout and heading.

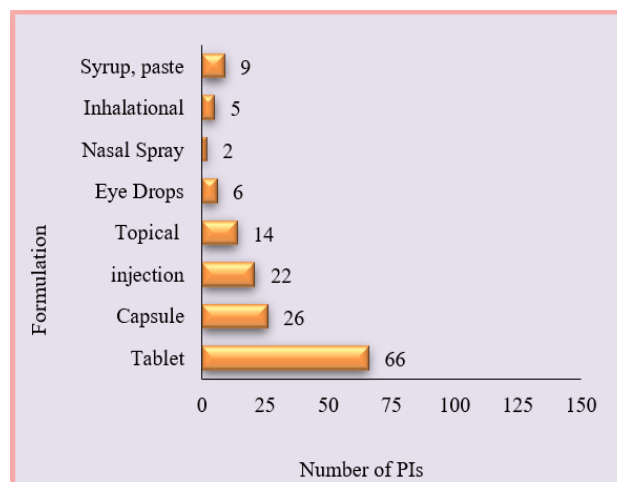


Figure 1: Types and number of formulations of the medicine analyzed for the PIs.

Table 1: Parameters recommended for package inserts in Indian drugs and cosmetics rules 1945 under section 6.2, 6.3 of schedule D (II).

S. no.	Parameters	% Foreign PIs (n=75)	% Indian PIs (n=75)
1	Legibility	100	100
2	Approved generic name of active ingredient	100	100
3	Content of active ingredient per dosage form	100	100
4	Generic names of other ingredients	97	78
5	Therapeutic indications	98	92
6	Posology and method of administration	100	88
7	Contraindications	96	94
8	Special warnings and precautions	98	94
9	Drug interactions	96	75
10	Pregnancy and lactation	96	75
11	Pediatrics and geriatric indications	96	75
12	Special conditions and contraindications	97	88
13	Effect on ability to drive and use machines	37	20
14	Undesirable effects	98	97
15	Drug dose	97	92
16	Antidote for over dosage	48	37
17	Pharmacokinetic information	94	93
18	Storage information	96	90
19	Instructions for use and handling	100	89
20	Shelf life	41	41
21	Date on which information was last updated	17	12
22	Name and address of manufacturer/distributor	81	76
23	Provision of full information on request should be highlighted	13	13
24	Retail price of the drug	8	10
25	References	26	20

Table 2: Comparison of parameters of completeness of information of Indian and foreign PIs.

Category	Parameters of foreign PIs	Parameters of Indian PIs
Very good	Legibility	
	Approved generic name of active ingredient	
	Content of active ingredient per dosage form	
	Generic names of other ingredients	
	Therapeutic indications	Legibility
	Special conditions and contraindications	Approved generic name of active ingredient
	Posology and method of administration	Content of active ingredient per dosage form
	Contraindications	Undesirable effects
	Special warnings and precautions	
	Drug interactions	
	Pregnancy and lactation	
	Pediatrics and geriatric indications	
	Undesirable effects	
	Drug dose	
	Storage information	
	Instructions for use and handling	
Good	Pharmacokinetic information	Therapeutic indications
		Contraindications
		Special warnings and precautions
		Drug dose
		Pharmacokinetic information
Fair	Name and address of manufacturer/distributor	Generic names of other ingredients
		Posology and method of administration
		Drug interactions
		Pregnancy and lactation
		Pediatrics and geriatric indications
		Special conditions and contraindications
		Storage information
		Instructions for use and handling
Poor	Effect on ability to drive and use machines	Effect on ability to drive and use machines
	Antidote for over dosage	Antidote for over dosage
	Shelf life	Shelf life
	Date on which information was last updated	Date on which information was last updated
	Provision of full information on request should be highlighted	Provision of full information on request should be highlighted
	Retail price of the drug	Retail price of the drug
	References	References

Moreover, the package inserts were of different shapes and sizes with different font size which made it inconvenient for analyzing (Table 1).

The highest score achieved by any package insert was 24 out of 25 and lowest was 9. Based on their scores out of 25, PI's were divided into A, B and C grades. Out of 150, 41 (27%) belonged to grade 'A', 103 (69%) belonged to grade B and remaining 6 (4%) belonged to grade 'C'. The foreign PIs performed better in grade A. 27 out of 41 PIs in grade A belonged to foreign MNCs whereas 56 PI's in grade B were Indian and 47 were foreign PI's. The

grading and score distribution of PIs from Indian and foreign companies is shown in (Figure 3 and 4).

A comparison was made between completeness of each item in both the categories of PI. The completeness was further classified ranging from very good to poor availability of information (Table 2).

Both categories of PIs show very good information about legibility, approved generic name of active ingredient, content of active ingredient per dosage form, undesirable effects and poor information about retail price, date on

which information was last updated, references and provision of full information on request. In a general comparison between two categories it was found that foreign PIs performed better in extent of providing the information in very good category whereas both performed equally bad in poor category.

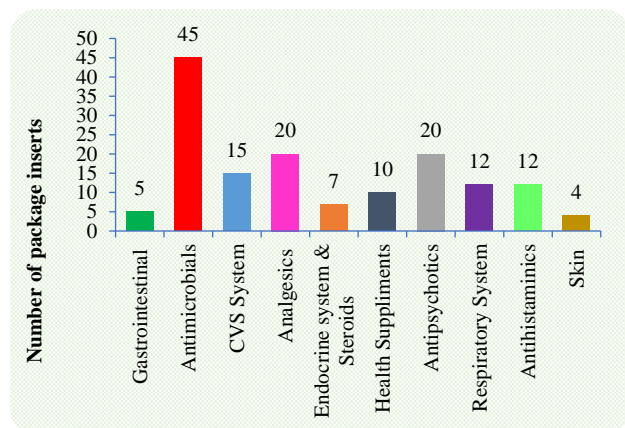


Figure 2: Number and pharmacological classes of the medicines analysed for PIs.

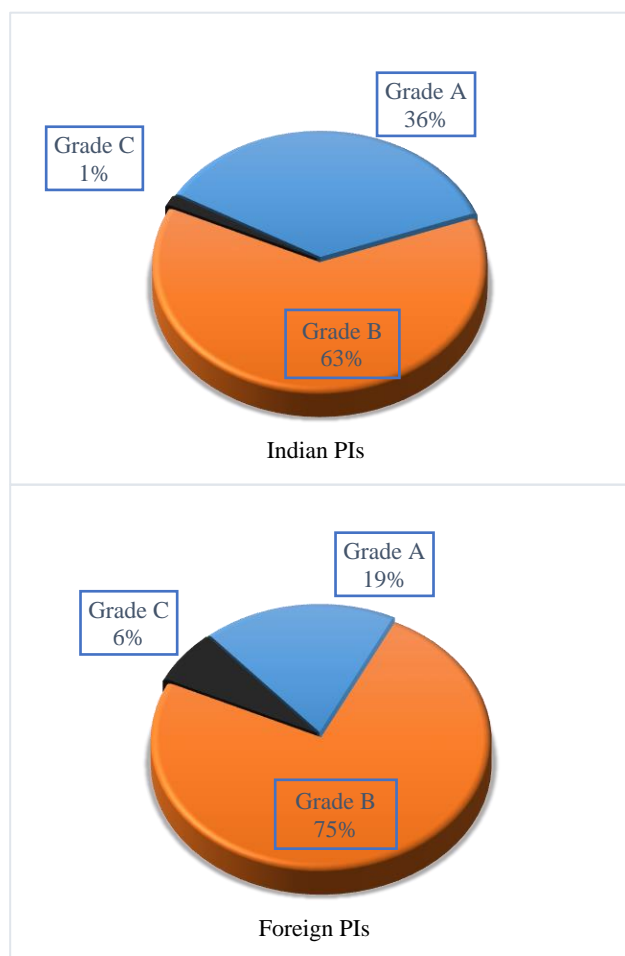


Figure 3: Comparison of grading of completeness of information (percentage) in Indian and foreign PIs.

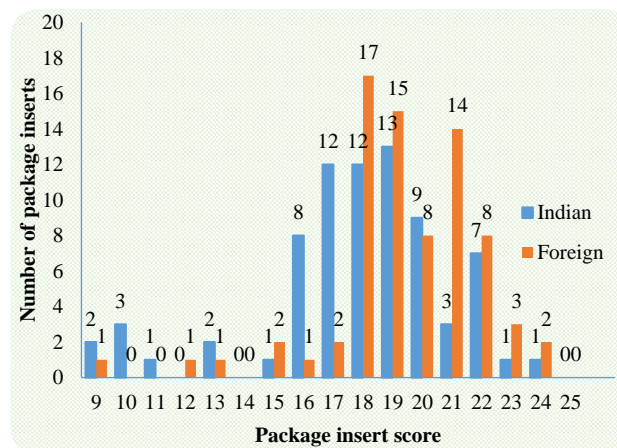


Figure 4: Comparison of scores of PIs achieving score between 9 to 25 as per parameters of the drugs and cosmetics rules 1945.

DISCUSSION

On analyzing the package inserts, it was found that way of presentation of information varied from one package insert to another. The size and fonts of all the package inserts were not uniform and standardized and this causes inconvenience for reader. A common layout of posology could have made it easier to retrieve information. The variations in layout of PI's is not only in India, studies from abroad have also shown same. Sawalha et al study from Palestine compared local and imported PI's of anti-infective and found that the overall design of PI was different from one local company to another and even between different medications produced by the same company.⁸

The information presented in the PIs is necessary for both the prescribers and the patients. A study assessing private health care providers attitude toward package inserts showed that prescribers consult PI's frequently to know untoward effects and therapeutic indications. 72% of practitioners found PI's extremely useful.⁹ PIs can help a practitioner only when information in it is well complied with regulatory recommendations. Deficit of information on any parameter can prove consequential. Items in PIs are focused to target physician, pharmacist and patients so all of them can make use of information provided in it. Package inserts have an important impact on patient's compliance and thus on the effectiveness of drug use. Insufficient information in PIs is matter of concern and various studies over the globe have found scarcity of information time to time. A German study conducted to analyze PI's based upon 104 quality criterias showed that in 73.5% of cases, daily maximum dose was missing, 66.2% of package inserts provided no instructions about the correct storage.¹⁰ In present study only 48% and 37% Foreign and Indian PI's respectively showed over dosage information. Which has large scope of improvement. The storage information was present in 90 to 96% of the

package inserts which is better than above compared study from Germany.

The PI's from Indian and foreign pharmaceutical companies showed poor information particularly about effect of ability to drive and use machine 20% to 37%, over dosage 37% to 48%, shelf life (41%), date on which information was last updated 12% to 17%, provision for full information on request (13%) retail price 8% to 10% and references 20% to 26%. Information on shelf life is important as the drug that has passed its shelf life might still be safe for consumption but its quality cannot be guaranteed. This can lead to poor control of diseases. Also, patients should be well-informed about the retail price of the drugs and should be able to confer to references whenever required. The compromised information about retail price (3%), references (2%), information update date (12%) and shelf life (26%) was also shown previously by Mahajan et al. who analyzed completeness of PIs in Maharashtra.¹¹ However, comparing present to previous study of package inserts analysis from Rohtak by Pranjit et al, these parameters have shown improvement. Previous study had assessed lower shelf life (9%) and ability to drive (19%).¹²

In overall comparison of completeness of Indian and foreign PI's it was found that foreign PI's are providing relatively more information and achieved higher overall scores. The 27 out of 41 PI's in grade 'A' were foreign PI's whereas grade B was dominated by Indian PI's in number. One such comparison between Indian and Foreign PI's was attempted by Ramdas et al in southern India who studied 134 PIs (96 Indian and 38 foreign) and found more number of Indian PI's in grade A.¹³ As a whole nearly 69% of the package inserts in present study belonged to grade B which is comparable to above mentioned study who found 76% of PIs in grade B. Both the studies indicate that Indian as well as foreign PIs are performing poor in providing the information. There are various reasons for not providing complete PI information, one of which is casual attitude of pharmaceutical companies because of laxity in guidelines implementation. Superlative guidelines are indeed necessary but their reinforcement is equally important too. The implementation of guidelines by concerned authorities is as essential as defining the guidelines. Even excellent standard guidelines turn futile without the genuine implementation efforts. Paucity in monitoring of the PIs in post-marketing surveillance by regulatory bodies and lack of robust punishment process empowers pharmaceutical companies to dodge the guidelines. Pharmaceutical companies smartly hide the information which can adversely affect the sales of medicine like adverse effects, contraindications or drug interactions and promote the positive effects of drug like therapeutic indications. It is necessary that PIs must be optimized and tested by selected groups of experts prior to the approval of the drug. This will ensure the avoidance of the lack of

information and will guide towards informed and better treatment outcomes.

CONCLUSION

In this study, it was found that many drugs come with major lacunas in information of package insert. Majority of the PIs were of grade B which suggests relevant information was mentioned but there is sufficient amount of information which was mandatory to mention but was absent from PI's. The Indian PI's need to improve more than foreign PI's.

The current concept of package inserts, which is followed in India, is inadequately serving its purpose of providing satisfactory prescribing guidance in an effective manner. There is a wide variation in the information available on the package inserts of drugs available in the Indian market. A post publishing surveillance to avoid such confusion would be beneficial. A strict watch on such a practice is the need of the hour for the benefit of the patient as well as the society.

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Ethical approval: The study was approved by the Institutional review board

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