Original Article

Information adequacy of medicine package inserts in India: A critical evaluation

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Abstract

Objectives: Package inserts (PIs) are used by physicians and other health-care providers as ready source of approved prescribing information. In India, they are subject to statutory regulations that specify the information to be provided under various headings. Uniformity of PIs with optimal level of information is desirable, the absence of which may lead to medication errors. This observational study aimed to evaluate the information adequacy and accuracy of PIs available in the Indian market.

Materials and Methods: PIs of drugs marketed in India, and approved by United States Food and Drug Administration, were collected from various retail pharmacies through purposive sampling. The adequacy and accuracy of the information in each PI were evaluated with the help of a 25-item checklist prepared as per stipulations mentioned in statutory guidelines. Each required item of information was scored 1 if present and appropriate or 0 if absent or deemed incomplete or inaccurate. A total information adequacy score (IAS), with maximum value 25, was thereby calculated.

Results: From the total 135 PIs analyzed, the median IAS was 17 (interquartile range 15–19). Deficiencies were observed under important headings. For example, "references" were mentioned in only 6.67% and "date of last updating" in only 19.26% of PIs. Other notable shortcomings were in "disposal" (not mentioned in 92.59%), "effects on ability to drive and use machines" (76.30%), "pharmaceutical incompatibilities" (66.67%), "shelf life" (62.96%), "excipients" (60.00%), and "overdose" (17.78%) information. Information on "generic name," "composition," and "indications" were however provided by all (100%) PIs.

Conclusions: The information provided by PIs in India being inadequate, may not be able to serve as a reliable source of information.

Keywords: Drug information, India, information adequacy score, package insert

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INTRODUCTION

A package insert (PI) is a printed product information leaflet enclosed with a pharmaceutical product pack that is intended to be a ready source of information for the prescriber and other health-care providers. Packages for prescription drugs may include a separate document written in nontechnical language and intended for the patient. This has been called a "patient package insert" or "patient information leaflet." A PI is derived as a concise

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summary of the detailed product information that is available as "full prescribing information" or "summary of product characteristics" from manufacturers or marketing authorization holders.[1]

The information that is provided in the PI is usually in accordance with statutes or guidelines applicable to the territory in which the product is marketed. It includes approved proprietary name and generic composition, classification and pharmacological description, clinical pharmacology, approved indications and usage, adverse drug reactions (ADRs), drug-drug interactions, special precautions in use, references, and other matters. Any wrong or misleading information here will have legal implication. Thus, PIs are regarded as a reliable source of drug information, shorn of exaggerated promotional claims, for both prescriber and patient. Further, PIs need to be updated regularly as new evidence is generated.

In India, a PI is mandated by the Drugs and Cosmetics Rules of 1945 framed under the Drugs and Cosmetics Act of 1940. Sections 6.2 and 6.3 of Schedule D (II) of the Rules[2] specify that the PI must be in English and the information it should contain. The rules do not specify the use of PI, but it appears to be intended for health-care professionals.[3] In practice, PIs are provided by pharmaceutical manufacturers in India for new products, that is, those that have been in the market for <4 years. However, PIs may continue to be provided for products that are expensive (e.g., botulinum neurotoxin, and biologics) or have complexities in use and administration (e.g., inhalational or self-administered injectable products). Studies previously published indicate that despite regulations, Indian PIs suffer from inadequacy of information.[3,4] Because PIs are intended to act as a buffer against prescribing, dispensing, and administration errors, this may be one of the contributory factors toward medication errors.[5,6]

We conducted a cross-sectional observational study to check the current completeness of PIs with respect to the format laid down by statutory guidelines and to compare the performance of PIs from multinational pharmaceutical companies and Indian manufacturers in this regard.

MATERIALS AND METHODS

This work was carried out collaboratively by the pharmacology departments of two tertiary care teaching hospitals in Kolkata. PIs were collected over a period of 6 months from September 2017 to February 2018. They were in English and were collected through purposive sampling from retail pharmacies. Two investigators approached pharmacies located near their institutions with the request to contribute 10–15 current PIs each, from packaging intended to be discarded. The contributions could include leaflets of oral, injectable, inhaled, or topical preparations of prescription medicines from various therapeutic segments. PIs of over-the-counter products, Ayurvedic and other indigenous medicine system formulations, and food supplements were excluded from the study.

Once the PIs had been collected they were screened and duplicate PIs, that is, those of the same product and brand were excluded from the study. The PIs were then photocopied, with enlargement of size if the writing was deemed too small, and after the name of the manufacturer/distributor was obscured with black indelible marker. The photocopied PIs were then categorized into therapeutic segments, assigned serial numbers, and handed over to other investigators for scrutiny and analysis. Thus, we achieved blinding with respect to the source of the PI, that is, whether from an Indian or a multinational pharmaceutical manufacturer.

The information contained in each PI was analyzed under 25 headings, as shown in the checklist provided in Table 1. This 25-item checklist was drawn up by merging Drugs and Cosmetics Rules 1945 (sections 6.2 and 6.3 of Schedule D [II]) criteria with some additional points taken from Schedule Y of the Rules[2] and United States Food and Drug Administration guidelines[7,8] and was categorized into three sections as shown. Each required item of information was scored 1 if present and appropriate or 0 if absent or deemed incomplete or inaccurate. A total information adequacy score (IAS), with maximum possible value 25, was thereby calculated for each PI.

The results have been summarized by descriptive statistics. Normality of numerical variables was assessed by Shapiro–Wilk test, and the variables were found to be skewed. Subgroup comparisons of total IAS and IAS for the three sections were done between PIs obtained from Indian manufacturers and multinational pharmaceutical companies by Mann–Whitney U-test. $P < 0.05$ implied statistical significance. MedCalc version 15.8 (MedCalc Software; 2015, Ostend, Belgium) software was employed for statistical analysis.

RESULTS

We screened 139 PIs voluntarily contributed by 11 retail pharmacies. Of these 4 were discarded as they were duplicates pertaining to the same product and brand. The analysis cohort therefore comprised 135 PIs. This covered 88 oral, 40 injectable, and 7 topical preparations spread

Table 1: Frequency distribution of individual items in the 25-item checklist for 135 package inserts

Information category	Serial number	Item	Absent (%)
Pharmaceutical information	1	Generic name	0 (0.00)
	2	Composition	0 (0.00)
	3	Dosage form	1 (0.74)
	4	List of excipients	81 (60.00)
	5	Incompatibilities	90 (66.67)
	6	Shelf life	85 (62.96)
	7	Packaging information	24 (17.78)
	8	Storage and handling instructions	13 (9.63)
	9	Disposal	125 (92.59)
Therapeutic information	10	Indications	0 (0.00)
	11	Posology and method of administration	1 (0.74)
	12	Contraindications	2 (1.48)
	13	Special warnings and precautions	6 (4.44)
	14	Drug interactions	10 (7.41)
	15	Use in pregnancy and lactation	10 (7.41)
	16	Pediatric and geriatric use	25 (18.52)
	17	Undesirable effects	5 (3.70)
	18	Effects on ability to drive and use machines	103 (76.30)
	19	Overdose	24 (17.78)
	20	Pharmacodynamics and pharmacokinetics	6 (4.44)
Miscellaneous information	21	Marketing authorization holder	2 (1.48)
	22	Provision for further information	105 (77.78)
	23	Date on which information last updated	109 (80.74)
	24	References	126 (93.33)
	25	Less technical patient information	118 (87.41)

across 10 therapeutic segments plus one miscellaneous segment that clubbed together products (respiratory, anti-inflammatory, and ocular formulations) not fitting into the other 10 segments.

Table 1 shows that the frequencies with which individual items of information, from the 25-item checklist, were found missing in the study cohort. Notably, "references" were mentioned in only 6.67% and "date of last updating" in only 19.26% of PIs. Other notable shortcomings were in "disposal" (mot mentioned in 92.59%), "less technical patient information" (87.41%), "provision for further information" (77.41%), "effects on ability to drive and use machines" (76.30%), "pharmaceutical incompatibilities" (66.67%), "shelf life" (62.96%), "excipients" (60.00%), and "overdose" (17.78%) information. However, information on "generic name," "composition," and "indications" were provided by all (100%) PIs, and "dosage form," "posology and method of administration," "undesirable effects," "contraindications," and "special warnings and precautions" were mentioned by nearly all.

With respect to the whole cohort, the median total IAS was 17 (range 6–24; interquartile range [IQR] 6–19) while the corresponding scores for pharmaceutical information were median 6 (range 3–9; IQR 5–5), therapeutic information were median 10 (range 1–11; IQR 9–10), and miscellaneous information were median 1 (range 0–4; IQR 1–2).

Table 2 summarizes the total IAS for the whole cohort as well as across the various therapeutic segments covered by the analyzed PIs. Evidently, the median scores were quite similar with the exception of the 3 PIs of monoclonal antibodies which were detailed and returned a median score of 22. The lowest median score, at 15, was for the vitamins and minerals segment. However, because of the disparity in numbers, we did not attempt a formal statistical comparison in this regard. Figure 1 presents the median scores graphically as box and whiskers plots.

Table 3 and Figure 2 provide a comparison of IAS for PIs from Indian versus multinational pharmaceutical manufacturers. There was a modest but statistically significant difference in median total IAS in favor of multinational companies, and this was mainly due to better performance in the pharmaceutical information category.

Finally, although the size of the inserts was commensurate with the information presented therein, in many cases, the font size of the printing was too small to allow comfortable reading.

DISCUSSION

The increasing complexity of modern medicine and the ever-expanding number of pharmaceuticals in use implies that the need for ready sources of drug information is even more acute today than earlier. Although a profusion of drug information resources is available to today's practitioner

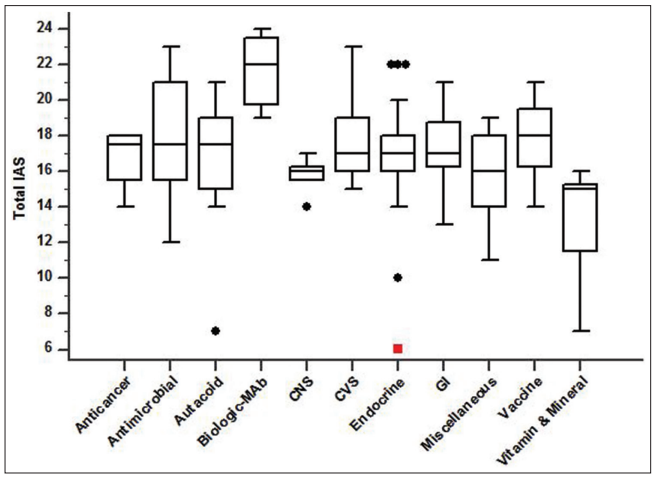

Figure 1: Comparison of information adequacy scores (IAS) of package inserts across various therapeutic segments. The box and whisker plots denote median, interquartile range, and range. The dots indicate outlier values

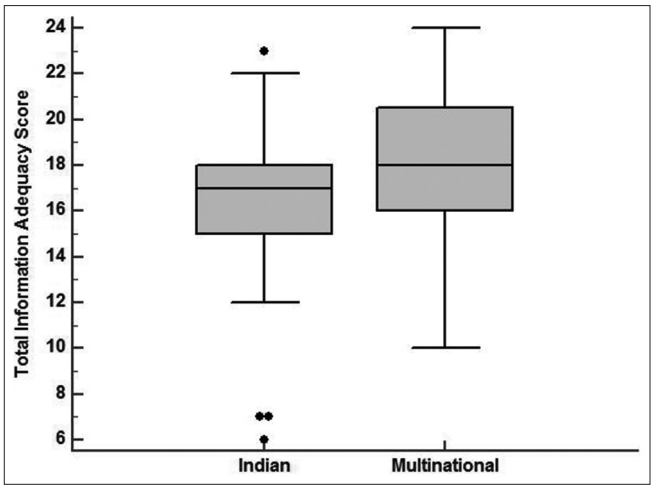

Figure 2: Comparison of information adequacy scores of package inserts from Indian and multinational pharmaceutical manufacturers. The box and whisker plots denote median, interquartile range, and range. The dots indicate outlier values

Table 2: Information adequacy score across various therapeutic segments covered in the study

Therapeutic segment	*n*	Range	Median	IQR
Anticancer	4	14.0-18.0	17.5	15.5-18.0
Antimicrobial	20	12.0-23.0	17.5	15.5-21.0
Autacoid	8	7.0-21.0	17.5	15.0-19.0
Biologic (monoclonal antibody)	3	19.0-24.0	22.0	19.75-23.5
Central nervous system	5	14.0-17.0	16.0	15.5-16.25
Cardiovascular system	22	15.0-23.0	17.0	16.0-19.0
Endocrine system	34	6.0-22.0	17.0	16.0-18.0
Gastrointestinal	15	13.0-21.0	17.0	16.25-18.75
Vaccine	5	14.0-21.0	18.0	16.25-19.5
Vitamin and mineral	5	7.0-16.0	15.0	11.5-15.25
Miscellaneous	14	11.0-19.0	16.0	14.0-18.0
All categories	135	6.0-24.0	17.0	15.0-19.0

IQR=Interquartile range

Table 3: Comparison of information adequacy performance of package inserts of different origin

Information category	Indian manufacturers (*n*=91)	Multinational manufacturers (*n*=44)	*P*
Pharmaceutical information			
Range	3.0-9.0	4.0-9.0	<0.001
Median	5.0	6.5	
IQR	5.0-6.0	6.0-8.0	
Therapeutic information			
Range	1.0-11.0	4.0-11.0	0.669
Median	10.0	10.0	
IQR	10.0-10.0	9.0-11.0	
Miscellaneous information			
Range	0.0-4.0	1.0-4.0	0.074
Median	1.0	1.0	
IQR	1.0-2.0	1.0-3.0	
Overall information			
Range	6.0-23.0	10.0-24.0	0.004
Median	17.0	18.0	
IQR	15.0-18.0	16.0-20.5	

P value in the last column is from intergroup comparison by Mann–Whitney U-test. IQR=Interquartile range

and health-care provider, in the form of pharmacopeias, formularies, books, electronic compendia, and the internet, the PI will continue to be a useful ready reference due to its wide availability, ease of use, and legal weight.[1] Indeed countries such as UK and South Africa provide electronic access to database of thousands of PIs for the benefit of prescribers. In UK, this database is called the electronic medicine compendium (https://www.medicines.org.uk/emc) while in South Africa it is called South African Electronic PIs (http://home.intekom.com/pharm/). Their utility is now established.[9]

It is therefore imperative that PIs available in India must contain adequate and accurate information to play the ready reference role for which they are intended. Therefore, periodic evaluation of their quality is a worthwhile exercise. We have followed a simple checklist based evaluation scheme, based on statutory guidelines, which can be readily replicated in future studies. We also performed a blinded comparison of the PIs from Indian and multinational pharmaceutical manufacturers. These are the strengths of our study.

Sudhamadhuri and Kalsker[4] have recently published an evaluation of 120 PIs of allopathic medicines available in the South Indian market. Their analysis was restricted to the 12 elements specified in the drugs and cosmetics rules. They found no PI to be complete with respect to all the elements with the major deficiencies being in the list of excipients, incompatibilities, effect on the ability to drive, and overdose information. Earlier, Shivkar[10] and Kalam *et al*.,[11] in separate studies, reported that most PIs did contain information on therapeutic indications, contraindications, undesirable effects, etc., but there were also important gaps in clinically important information. In

a more recently published study on PIs of oral drugs,[12] the author reported broadly similar findings and concluded that there is wide variation in the information available in PIs circulating in the Indian market.

Studies from abroad have also revealed clinically important deficiencies in PIs intended for health-care professionals. Such deficiencies have been reported from Abu Dhabi,[13] Saudi Arabia,[14] and Germany.[15] Fuchs *et al*.[16] have made the interesting suggestion that PIs must be optimized and tested by selected groups of patients before approval of the drug. This will avoid misunderstandings and lack of information and ensure that use of the drug will give the best possible outcome and avoid safety risks. Instead of patients, pretesting by responsible pharmacists and physicians may be a viable option in India.

We found that the quality of the PIs was good overall with respect to the therapeutic information, but there were large gaps in the essential pharmaceutical information, particularly with respect to list of excipients, incompatibilities, shelf life, and disposal. However, with the exception of the identity of the marketing authorization holder, most elements of essential miscellaneous information were lacking such as provision for further information, date on which information last updated, references, and less technical patient information. These have contributed to the lowering of the total IAS. The situation was broadly similar across various therapeutic segments, with the exception of PIs of monoclonal antibodies which were more complete.

Information related to pediatric and geriatric population was present in 81.48% of our PIs which is good considering the fact that 56% of ADR related hospital admissions occurred in patients over 60 years age in a study from North India.[17] While inadequate information in pharmaceutical and miscellaneous items may not seriously jeopardize the clinical utility of the PIs, on occasions they may be a hindrance such as when cross-checking incompatibility or shelf life of injections. Pharmaceutical excipients occasionally cause allergies and other drug-related problems,[18] and lack of excipients information may hinder exploration of suspected ADRs.

It is expected that a uniform PI format will enhance rapid access to important pharmacologic information and improve patient safety by decreasing medication errors.[8] In our blinded comparison of information adequacy of PIs from Indian and multinational pharmaceutical manufacturers, those from multinational companies fared better, primarily because they provided more complete pharmaceutical information. This gap can be easily breached by Indian manufacturers if they pay a little more attention to details while designing their prescribing information and PIs.

Our study also has its share of limitations. We could not cover all therapeutic segments, and even among segments that we covered, there was a wide disparity in numbers precluding formal intersegment statistical comparisons. Profusion of brands is a known feature of the Indian pharmaceutical market, and although we evaluated some PIs of different brands of the same product, this was based on purposive rather than random sampling. The possibility of biased selection of PIs therefore remains.

CONCLUSIONS

We can conclude that our survey of PIs in the Indian market, assuming them to be intended for health professionals, suggests that while they do provide clinically useful information, there is scope for considerable improvement. The ideal PI must provide complete information on all expected heads, and this requires greater effort on the part of manufacturers and also greater regulatory vigil. It would be worthwhile to explore the expectations regarding and actual utility of PIs to physicians and other health-care professionals in the Indian context.

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Conflicts of interest
There are no conflicts of interest.

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