Original Article

Are we providing complete drug information to its users? Status of information adequacy of package insert in India

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Abstract

Background: Package inserts (PIs) serve detailed information on drug products to the users and primary care physicians, so information should be accurate, reliable, and as per the regulatory guidelines. The study aims to analyze the information adequacy of the PIs available in the Indian market as per Drug and Cosmetic Rule 1945 and US Food and Drug Administration criteria. **Materials and Methods:** A cross-sectional study was conducted on PIs collected from accessible pharmacy stores. Information provided was recorded as per criteria, and total information adequacy score (IAS) and information deficiency (IDS) score were calculated. The association of factors like single-drug/FDCs, a company of origin Indian/multinational, and route of administration (ROA) with IDS was statistically analyzed. **Results:** Of 120 PIs, 60%, 86.66%, and 73% were single-drug, prescription-drug, and drugs by Indian manufacturers, respectively. Most PIs provided generic names, ROA, and indications for use. 85%, 12%, 29.16%, and 3.33% provided information on PIs on the ability to drive, drug–food interactions, drug–drug interactions, and addiction potential, respectively. Lacking area was information on use in pediatrics–geriatrics (30%), excipients (28.3%), preclinical (15.83%), post-surveillance data (18.33%), and approval date (2.5%). There was a statistically significant difference between pharmaceutical score (3.22 vs 4.12), therapeutic score (11.5 vs 13.18), and total IAS (14.78 ± 3.39 vs 17.31 ± 2.33) of Indian and multinational companies. IDS was statistically significantly different in both pharmaceutical and therapeutic categories for single-drug vs FDCs ($P = 0.00001$), OTC vs prescription drugs ($P < 0.05$), and Indian vs multinational companies' PIs ($P = 0.00001$). **Conclusion:** Numerous facets of information are lacking in PIs, and they do not impart whole information, especially of Indian origin, as per objective IDS.

Keywords: Information adequacy, information adequacy score, information deficiency score, package inserts

Introduction

A piece of precise and authentic information on drug products is crucial for rational, effective, and safe medication use. Unreliable and incomplete drug information can lead to irrational drug use and undesirable and severe patient consequences. The package insert (PI) in a drug has all the information on the drugs in detail, compiled and distributed by the manufacturers, and synthesis begins early during the development phase of a drug and continues to the later phases with more detailed information on the pharmacological and clinical profile.[1] This information in the PI is aimed primarily at the prescribing physicians, and primary care providers and is intended to provide information for effective and safe therapy use.[2] As per "Food and Drug Administration" (FDA), the PIs are also synonymously addressed as prescribing information, professional labeling, package circular, or prescription drug label, and the information provided in these PI varies across countries, and depends on the amount or type of information needed by the prescribers and sometimes the primary users.'[2-4] This prescribing information is prepared by a detailed analysis of the new drug application submitted by the applicant.[4]

In a country like India, where the number of prescribing physicians are comparatively lower compared to the population

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considered, providing strict and to-the-point drug use communication by the doctors to the patients is virtually impossible and cumbersome.[5] The gap in communication regarding drug use can lead to adverse consequences among patients. Therefore, patient-centric drug information is crucial, which can partly resolve the issue.[6,7] To overcome this issue, patient-directed drug information is already included by the European Union, and they are called "patient information leaflets." The prime purpose is to inform the patients about the drug regarding its use, precautions, and adverse effects.[6,8] Further, as per the Article 11 of Directive 2001/83/EC passed by the European Parliament, these patient information leaflets should provide unbiased, evidence-based, clear, comprehendible, and readable information suited for the normal public.[6,9] The patient information leaflet is a brief synopsis of the exhaustive information provided in the "full prescribing information" or "summary of product characteristics."[3,10]

As per the 1945 Rules of Drugs and Cosmetics, as per the Drugs and Cosmetics Act of 1940, the Schedule D (II) of section "6" lays downs the information regarding the labeling and packaging of drugs.[11] Section 6.2 states that the information must be in the language—English and must also include data like administration method and posology, special warnings, contraindications, special precautions during pregnancy, other drugs and interactions with other drugs, effects on driving abilities and machine usage, the overdosing antidote, and in section 6.3 of the above document lays down details of all the for pharmaceutical data like incompatibilities, list of excipients, the shelf life of the product at various stages from sale to use, special storage precautions, specification and nature of container and usage instruction.[1,11]

Primary care physicians and healthcare providers use PIs and other data as the source of approved prescription information; hence, the PIs must provide thorough and unbiased information to facilitate the rational use of therapy. Evidence shows that the PIs in India are not up to the mark and supply inadequate information compared to the minimum requirement laid by regulatory authorities.[12-15] PIs uniformity with optimal information level is desirable, and its absence might result in errors in medication and prescription. This observational analysis aims to estimate the adequacy of information on the package insert available in the market.

Materials and Methods

Study setting

This study was conducted in the Department of Pharmacology, AIIMS, Rajkot, Gujarat, to determine the content adequacy of package inserts available in the Indian market.

Study design

This was a cross-sectional observational study.

Study duration

PIs of different drugs were collected randomly from various accessible pharmacy stores over three months, from May 2022 to July 2022.

Sample size

Considering the information inadequacy in PIs of the Indian market 76.86% as per a previous study by Ramdas *et al.*,[14] the sample size at 95% CI and ± 7% margin of error was calculated as 140. Considering around 10% of the dropout/duplicate samples, the final sample of 158 PIs was collected.

Data collection

Two investigators approached pharmacies with the request to provide PIs from packaging, which is to be discarded. PIs include leaflets of an injectable, oral, topical preparation, or inhaled prescription and over counter (OTC) drugs. PIs of ayurvedic and other indigenous food supplements and medicine systems were not included in the study. PIs that were written other than in the English language were also not included in the research.

Data analysis

Once PIs are collected, they are screened, and duplicates were excluded from the study. A number is given to each PI and then categorized of them into therapeutic segments. The information contained in each PI was analyzed per the Drug and Cosmetic Rule 1945 and US Food and Drug Administration (FDA) criteria.[2,11] Drug and Cosmetic Rule 1945 divides the whole PIs information into two broad categories: therapeutic and pharmaceutical information. The therapeutic information section has 15 subcategories, while the pharmaceutical section has seven subcategories. If the information related to a particular subcategory is mentioned in PI, then a score of "1" is given, and if it is absent, then "0" is given, and hence, a maximum Information Adequacy Score (IAS) of 22 (7 for pharmaceutical information and 15 for therapeutic information) was assigned to each PIs which was analyzed by Drug and Cosmetic Rule 1945. FDA divides the PIs information into three broad categories, including therapeutic information, pharmaceutical information, and one additional miscellaneous information, a category which is not mentioned in Drug and Cosmetic Rule 1945. The therapeutic information section of the FDA has 15 subcategories, while the pharmaceutical and miscellaneous sections have three and five subcategories, respectively. Scoring was carried out in the same way as explained above, and hence, a maximum IAS of 23 (3 for pharmaceutical information, 15 for therapeutic information, and 5 for miscellaneous information) was assigned to each PI which was analyzed by FDA criteria. Information deficiency score (IDS) was also calculated by subtracting IAS obtained by each PI from the maximum IAS.

In addition, the package insert was also evaluated with regard to the origin of the manufacturer company (Indian Versus Multinational), prescription drugs versus nonprescription

drugs, single versus fixed-dose combination, and route of administration. Data were extracted twice to minimize the chances of missing any information.

Statistical analysis

Information from the proforma was coded and entered into Microsoft Excel 365 and analyzed by using descriptive and analytical statistics. The normality of numerical factors is assessed by the Shapiro–Wilk test and was concluded to be skewed. The Mann–Whitney U test was used to compare total IAS and the IAS for two sections between the received PIs from both multinational and Indian pharmaceutical manufacturers. Subgroup comparison of total IDS and IDS for the two sections as per DCA and FDA criteria between PIs of single vs FDC, OTC vs prescription drug were done. The "*P*-value" will be determined to evaluate the significance levels. Statistical significance is proved on $P < 0.05$.

Ethical issues

The study protocol was approved by the Institutional Ethics Committee of AIIMS, Rajkot (O.W.No/AIIMS.Rajkot/IEC/06/2022).

Results

A total of 158 package inserts were collected, out of which 38 were excluded due to duplication of package inserts. Hence, 120 package inserts were analyzed for this research. The maximum number of package inserts was from the endocrinology therapeutic segment, followed by the antimicrobial and cardiovascular systems [Table 1]. The majority of PIs (60%) dealt with FDCs while the remaining dealt with single drug [Figure 1]. Among the 120 PIs, 104 (86.66%) PIs were prescription drugs, while 16 were OTC drugs [Figure 1]. Further, out of the total 120 PIs studied, 82 were oral preparation, 29 were parenteral preparation, and 9 were topical preparation [Table 2]. Nearly 73% of PIs were marketed by Indian manufacturers, while 26.6% were marketed by multinational companies [Figure 1].

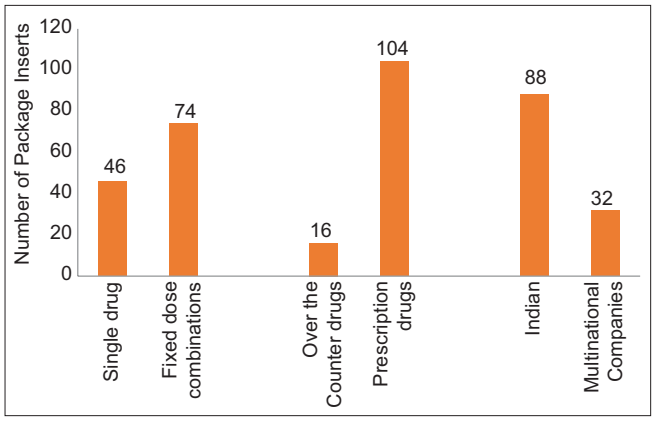

Figure 1: Distribution of package inserts based on single-drug vs fixed-dose combinations (FDCs), OTC vs prescription drug and India vs multinational manufacturer origin

The PIs were evaluated in accordance with the Drug and Cosmetics Rules 1945 and the US FDA criteria for their adequacy of information [Table 3]. All collected PIs listed the dosage form and strength of medicines. The majority (99.16%) of the PIs also listed the dose, method of administration, indication, and uses of the drug. The use of medicine in pediatric and geriatric patients was discussed by only 73% and 69% of PIs, respectively. Eighty-five percent of PIs gave information regarding the interaction of drugs with other drugs. Only 12% of PIs brought up the topic of drug–food interactions. A very less number (35, 29.16%) of PIs included information on the effect of drugs on the ability to drive. There were only four (3.33%) PIs that discussed the abuse and dependence properties of drugs. A list of excipients was provided by 34 (28.33%) PIs, while 50 (41.66%) PIs instructed the patient regarding the use and handling of drugs. Preclinical and post-surveillance data were provided by 15.83% and 18.33% of PIs, respectively. Only three (2.5%) PIs mentioned the date of approval.

Table 1: Analysis of package inserts based on therapeutic drug class (*n*=120)

Drug class	Number of package insert *n* (%)
Antimicrobial	18 (15)
Analgesic	5 (4.16)
Anti-allergic	2 (1.66)
Blood	8 (6.66)
Cardiovascular system	17 (14.16)
Central nervous system	10 (8.33)
Dermatology	4 (3.33)
Endocrinology	28 (23.33)
Gastrointestinal tract	10 (8.33)
Immunosuppressant	1 (0.83)
Nutritional supplement	5 (4.16)
Ophthalmology	4 (3.33)
Respiratory	8 (6.66)
Total	120 (100)

Table 2: Distribution of package insert based on the route of administration and dosage formulations (*n*=120)

Route of administration and dosage formulation	Number of package inserts, *n* (%)
Oral	82
Tablets	64 (78.04)
Capsules	13 (15.85)
Powder	02 (2.43)
Solution	02 (2.43)
Suspension	01 (1.21)
Parenteral	29
Injection	25 (86.20)
Respules	02 (6.89)
Inhaler	01 (3.44)
Vaginal capsules	01 (3.44)
Topical	9
Eye drops	5 (55.55)
Cream	2 (22.22)
Gel	1 (11.11)
Roll on emulsion	1 (11.11)

Table 3: Comparison of frequency distribution of items as per drug and cosmetic act (DCA) and United States Food and Drug Administration (US FDA) criteria

Information category	As per drug and cosmetic act (DCA) criteria (*n*=120) (%)	As per US Food and Drug Administration (FDA) criteria (*n*=120) (%)
Therapeutic information		
Dosage Form and Strength (Posology)	120 (100)	120 (100)
Dose and method of administration	119 (99.16)	119 (99.16)
Indication and uses	119 (99.16)	119 (99.16)
Pharmacodynamic properties	112 (93.33)	112 (93.33)
Pharmacokinetic properties	108 (90.00)	108 (90.00)
Contraindications	112 (93.33)	112 (93.33)
Use in pregnancy and lactation	106 (88.33)	106 (88.33)
Use in pediatric population	88 (73.33)	88 (73.33)
Use in geriatric population	83 (69.16)	83 (69.16)
Special warning and precautions for use	110 (91.66)	110 (91.66)
Interactions with other drugs	103 (85.83)	103 (85.83)
Interactions with food/other substances	15 (12.50)	15 (12.50)
Undesirable effects/SE/ADR	112 (93.33)	112 (93.33)
Effect on ability to drive/machines	35 (29.16)	NA
Abuse/dependence property	NA	04 (3.33)
Overdosage and antidotes	97 (80.83)	97 (80.83)
Pharmaceutical information		
Generic name	119 (99.16)	119 (99.16)
List of excipients	34 (28.33)	NA
Incompatibilities	40 (33.33)	NA
Shelf life	60 (50.0)	NA
Special precaution for storage	109 (90.83)	NA
Nature and specification of the container	54 (45.0)	54 (45.0)
Instruction for use and handling/patient counseling information	50 (41.66)	50 (41.66)
Miscellaneous information		
Preclinical study data	NA	19 (15.83)
Post-marketing surveillance data	NA	22 (18.33)
References made	NA	09 (7.50)
Recent major changes	NA	07 (5.83)
Date of approval	NA	03 (2.50)

An information adequacy score (IAS) was also determined by comparing the information provided by the PIs of Indian origin with that of the multinational companies as per Drug and Cosmetics Rules 1945. In relation to pharmaceutical information, the majority of PIs of Indian origin (59.09%) fall in the range of 0–3 of IAS, while PIs which were marketed by multinational companies fall in the range of 4–7. The mean pharmaceutical category IAS was 3.22 for Indian companies and 4.12 for multinational companies. Different was proved on $P < 0.05$ to be statistically significant. In the same manner, a statistically significant difference was detected between the mean therapeutic category IAS for Indian companies (11.55) and for multinational companies (13.18) [Table 4].

As shown in Table 5, IDS was also calculated and compared to the IDS of PIs as per Drug and Cosmetics Rules 1945 and FDA criteria in relation to different parameters. When single-drug formulation PIs were compared to FDC formulation PIs, IDS was shown to be statistically significant in both pharmaceutical and therapeutic categories ($P = 0.00001$). The results were also statistically significant for OTC vs prescription drugs and Indian-origin PIs vs multinational companies' PIs ($P = 0.00001$). Information deficiency score of PIs as per route of administration for the formulation oral vs parenteral vs topical or others also showed significant difference ($P < 0.05$).

Discussion

Pharmaceutical businesses and authorities are accountable for making sure that correct and current product information is supplied while keeping in mind the safety of people utilizing medication goods. The increasing number complexity of medicines day by day, including contemporary medicines, which imply that today's need for quick access to medication information is greater than ever. The information presented within the PIs is critical for both the prescribers and patients. This study has analyzed the adequacy of the information provided in the PIs as per the criteria laid down by the USFDA and DCA.

This study shows that the majority of PIs showed dosage form and strength of medicines. The majority (99.16%) of the PIs also listed the dose, method of administration, indication, and

uses of the drug. The finding of this study suggests that PIs are lacking in medicinal information like shelf life, excipients lists and instructions for use and handling, and patient counselling information. These put certain people at risk for allergic responses, poisoning, adverse drug reactions, the development of drug resistance, and treatment failure due to exposure to toxic degradation products, medications with poorer quality ingredients, and undesired excipients. Moreover, consistent deficiencies were seen in areas including handling and disposal of unneeded medications, information on excipients, shelf-life, and compatibilities. A medicine's shelf-life information is crucial because, although it may still be safe to consume a drug beyond its expiration date, its quality cannot be assured. Diabetes and hypertension may be poorly managed as a result. Excipient safety was first disregarded, and often no in-depth safety assessments were out. The connection between efficacy and toxicity may have evolved throughout time, but it is now generally acknowledged that the excipient's toxicity is not insignificant due to the possibility of direct interactions with the active pharmaceutical component or with other excipients.[16,17] The famous sulfonamide elixir disaster was a key incident in the development of regulations pertaining to the proof of the safety of active pharmaceutical ingredients as well as before the release of any new drug. Elixir sulfanilamide, a liquid preparation of sulfanilamide, was created using diethylene glycol as the diluent,

Table 4: Information adequacy score (IAS) among Indian and multinational company package insert as per DCA criteria

Parameters	Indian origin *n*=88 (%)	Multinational *n*=3 2 (%)	*P*
Pharmaceutical Information score			
0–3	52 (59.09)	09 (25.71)	
4–7	36 (40.90)	23 (71.87)	
Mean	3.22	4.12	0.04
Median	3	4	
Mode	3	4	
Therapeutic information score			
1–4	03 (3.40)	00 (00)	
5–8	09 (10.22)	00 (00)	
9–12	33 (37.50)	07 (21.87)	
13–16	43 (48.86)	25 (78.12)	
Mean	11.55	13.18	<0.05
Median	12	13	
Mode	13	13	
Miscellaneous information	NA	NA	
Total information adequacy score	14.78±3.39	17.31±2.33	<0.05

Table 5: Comparison of information deficiency scores (IDS) in package inserts and its association with different parameters

Parameter	Deficiencies in the information score (IDS)						
	Measure (Mean/SD)	Ph score DCA	Ph score FDA	Ther Score DCA	Ther Score FDA	Total score DCA	Total score FDA
Type of formulation as single-drug vs. fixed-dose combination (FDC)							
Single-drug formulation	Mean	3.4730	2.0135	2.7027	3.0000	6.1757	8.0000
	SD	1.3771	0.1162	2.3038	2.2269	3.2324	2.8381
FDC	Mean	3.6304	2.0000	3.5000	3.6957	7.1304	8.9348
	SD	1.1027	0.0000	2.8186	2.6822	3.4487	2.9844
P		0.00001		0.04871		0.00001	
Availability as OTC drug Vs. Schedule H drug							
OTC	Mean	2.0625	5.6250	5.7500	9.6250	10.5000	2.0625
	SD	0.2500	3.3441	3.2558	4.031	4.2269	0.2500
Schedule H	Mean	3.4615	2.0000	2.6058	2.8846	6.0673	8.0288
	SD	1.2612	0.0000	2.1335	2.0352	2.9072	2.5331
P		0.00001		0.00001		0.00001	
Manufactured by Indian Company Vs. Multinational company							
Indian	Mean	3.7727	2.0114	3.4432	3.6591	7.2159	8.8977
	SD	1.1216	0.1066	2.7286	2.6125	3.3986	2.8569
Multinational	Mean	2.8750	2.0000	1.8125	2.1875	4.6875	6.8750
	SD	1.4536	0.0000	1.3060	1.3305	2.3340	2.5872
P		0.00001		0.00006		0.00001	
Route of administration for the formulation oral vs. parenteral vs. topical or others							
Oral	Mean	3.5556	2.0000	2.6420	2.8889	6.1975	8.0864
	SD	1.2247	0.0000	2.1349	2.0248	2.8785	2.6655
Parenteral	Mean	3.1667	2.0000	2.5833	2.7917	5.7500	7.6667
	SD	1.4039	0.0000	1.6659	1.5874	2.4891	2.2968
Topical	Mean	3.5000	2.1000	4.9000	5.4000	8.4000	10.0000
	SD	0.9718	0.3162	3.4785	3.0984	4.3256	3.6209
other	Mean	5.000	2.000	7.200	7.400	12.200	12.800
	SD	1.2247	0.0000	4.6583	4.4497	5.7184	3.9623
P		0.0001		0.0005		0.0001	

Ph score=Pharmaceutical information deficiency score, Ther Score=Therapeutic information deficiency score, Total score=Total information deficiency score

which resulted in the deaths of 105 individuals. Premarketing toxicity testing was not necessary at the time due to the drug rules in place. The 1938 Federal Food, Medicine, and Cosmetic Act, which demanded safety testing before the distribution of a new drug, was a response to this catastrophe. The 1938 statute transformed the "Food and Drug Administration's" (FDA) emphasis on medications from that of a regulatory body more engaged with monitoring the assessment of new drugs to that of a regulatory agency increasingly involved with overseeing the seizure of contaminated drugs.[18,19]

The findings of this study indicate that the package inserts under analysis did not consistently provide information pertinent to the effective and safe use of medications. It was identified that PIs lacked proper therapeutic instructions on use in the pediatric population, use in the geriatric population, interactions with food/other substances, and effect on the ability to drive/machines. Pediatric and geriatric populations are the most vulnerable. Use of leftover OTC or schedule H drugs is very common in Indian consumers without consulting doctors. So, proper and detailed therapeutic information related to use in the pediatric and geriatric populations can prevent unfortunate events from occurring.[3] Also, it is necessary to give thorough therapeutic information on PI about drug interactions with food/other substances and their effect on the ability to drive/machines, so the unforeseen or any deleterious effect of drugs can be prevented.[3,7]

Miscellaneous information like preclinical study data, post-marketing surveillance data, date of approval, and other information was lacking on the majority of PIs in this study. Such information improves knowledge and helps to gain the confidence of prescribing doctors. For the implementation of display of such info, we need to impart rigorous regulation execution and supervision.

Overall adequacy of information on the PI of multinational companies was found generally to be higher than the Indian-origin counterparts. In a general comparison of the inclusiveness of Indian and multinational company PI's, it becomes determined that multinational company PIs are imparting, particularly additional records and attained better total scores. Their earlier evaluation and approval in nations with strict regulatory criteria for the regulation of drugs have contributed to this adherence.[20] Based on this finding, there is a need for improvement in PI of Indian companies with the inclusion of more extensive details. These can be done by stringent regulation implementation and supervision.

Pharmaceutical deficiency score is appreciably higher in fixed-dose combinations in comparison to single-drug formulations. At the same time, there is no enormous distinction in therapeutic deficiency scores among fixed-dose combinations and single-drug formulations. There are always some demerits along with fixed-dose combinations, like dose adjustment of one drug is impossible without altering the other drug. Also, a simple logic by giving a fixed-dose combination increases the chances of drug interaction and adverse effects.[21]

Pharmaceutical deficiency score and therapeutic deficiency score are appreciably better among schedule H drugs as compared to OTC pills, respectively. In countries like India, patients use schedule H drugs without a prescription; in that case, significant pharmaceutical information has to be there on the PI. Same way, therapeutic information has to be there on the PI for all OTC drugs, like its effect on the ability to drive/machine, interactions with food/other substances, and so on. It has been observed use of OTC medication in 18.72% of the consumers in India.[22]

Strengths and limitations

Overall, this study has highlighted the information adequacy of the package inserts in the Indian market by objective criteria and highlighted their key deficiencies in them. IDS was calculated and compared for different parameters. As per our literature search, this study is the first attempt to calculate and compare IDS for PIs.

A few limitations of the research were the single center and small sample size, which may have led to data collection bias from one region only.

Future implications

This study has shown that there are numerous facets of information which is lacking in PIs as per the objective information adequacy and deficiency scores, and PIs are no longer imparting whole information. This can be attributed to the informal attitude of pharmaceutical corporations due to laxity in guideline implementation. Superlative guidelines are certainly important; however, their reinforcement is similarly critical too. If the limitations of therapy like unfavorable effects, contraindications, or drug interactions are not presented adequately, then it can adversely affect the safe and rational use of drugs in the community. Considering the vast amount of information to be memorized by the primary healthcare provider to serve the community, it is practically a humungous task to memorize and keep a track of all the information pertinent to drugs to be used. To overcome this issue, the adequate concise information provided in the PIs can serve as a huge help for primary care physicians to emend their knowledge regarding the existing drugs and also regarding novel drugs.

Conclusion

PIs available in the Indian market are lacking in many important aspects of information like ADRs, use in pediatric and geriatric populations, drug–drug interactions, drug–food interactions, ability to drive, addiction potential, list of excipients, preclinical data, post-marketing surveillance data, date of approval, etc. IDS was significantly higher with FDCs, OTC drugs, and PIs of Indian manufacturer companies, which can attribute to many drug-related problems in India. Therefore, there is a need for

joining hands by practitioners, pharmaceutical companies, and government agencies to improve the information adequacy of package inserts for better patient care.

Key points

- A piece of precise and authentic information on drug products is crucial for rational, effective, and safe medication use.
- Package inserts available in the Indian market are lacking in many important aspects of information like ADRs, use in pediatric and geriatric populations, drug–drug interactions, drug–food interactions, ability to drive, etc.
- Information deficiency score was significantly higher with FDCs, OTC drugs, and PIs of Indian manufacturer companies, which can attribute to many drug-related problems in India.
- There is a need for joining hands by practitioners, pharmaceutical companies, and government agencies to improve the information adequacy of package inserts for better patient care.

Take home message

There is a need for joining hands by practitioners, pharmaceutical companies, and government agencies to improve the information adequacy of package inserts for promoting better patient care and rational prescribing.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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