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CRITICAL, ETHICAL AND LEGAL DILEMMA WITH COMBINED / TWIN PACK LABELING OF FORMULATIONS

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ABSTRACT

Label of a formulation provides its identification and the product details. A label should provide scientifically accurate and clear instruction to health care practitioners for prescription drugs and to consumers for over-the-counter drugs and supplements. Security of pharmaceutical products is particularly important as it ensures that medications are not tampered with before they reach customers. However, we find that there are many lacunae between the way of labeling and regulatory aspects related to that. Many pharmaceutical manufacturers take the opportunity skillfully to avoid essential information on labels. Labeling of combined/ twin packs is one such critical area to demonstrate. Here some interesting findings related to twin-packs are highlighted with their possible consequences.

INTRODUCTION

Drug labeling refers to all of the printed information that accompanies a drug, including the label, the wrapping and the package insert. The term labeling means all the labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package [1]. The label must be scientifically accurate and provide clear instruction to health care practitioners for prescription drugs and to consumers for over-the-counter drugs and supplements [2]. Labeling/packaging is one area that has been strongly neglected by Indian pharmaceutical industry for years. Labeling of pharmaceutical products is a great challenge to pharmaceutical industries unlike those encountered in other industries because of the stringent regulations in place to ensure their accuracy. Overall usefulness of information on a formulation label accompanies the drug, namely, the name of the medicine along with any critical warnings, uses of the medicine along with conditions under which the medicine should not be used, directions for contraindications with any related precautions, symptoms of any adverse reactions to the drug, any risk of drug tolerance or dependency while taking the drug, storage instructions, warning of the danger of giving the drug to someone other than the patients, along with the other necessary legal information, etc. [3]. Further, security of pharmaceutical products is of paramount importance to ensure that medications are not tampered with before they reach patients [4]. Indeed there are lacunae between a label and its legal aspects. In many cases, inadequate regulatory aspects extend the hands of pharmaceutical manufacturers to by-pass essential information on label and this may have some serious consequences. Combined/ twin pack is one such area where many pharmaceutical manufacturers are opportunists to by-pass regulatory aspects. Some cases it is done unknowingly too.

In the present study, we have reported here findings related to twin-pack and highlighted some consequences.

Several licensed manufacturers market their products (such as injectable in powder form) in combined/ twin pack, without mentioning important particulars such as name of manufacturer, manufacturing license no. (M.L.No.), batch/ lot no, manufacturing date, expiry date etc) (Fig. 1) of

additional diluents/ solvents [mainly sterile water for injection (S.W.F.I.), in some cases even products such as sterile normal saline (S.N.S.) provided for re-constitution] on outer carton (Fig. 1). The carton contains the active drug and diluents/solvent. But it is only normally indicated on the carton that it contains one ampoule/ vial of S.W.F.I. / S.N.S. Some examples are given in Table 1.

Figure 1: Combined / twin pack without mentioning details of solvent/diluents

Again, three leading Rabies vaccine namely "Rabipur" Manufacturer CHIRON BEHRING VACCINES Pvt. LTD., 3502, G.I.D.C. Estate, Anklshwar-393 002 and marketed by Novartis Healthcare Pvt. Ltd., Sandoz House, Dr. Annie Besant Road, Worli, Mumbai- 400 018], "Verorab" [Fig. 2] [Manufacturer: SANOFI PASTEUR SA, France, Assembled and Marketed by RANBAXY Laboratories Ltd. 1st Floor HMTD Textile Pvt. Ltd., J Ari Mari, Kurla - Andheri Road, Mumbai - 400 072], and "Vaxirab" [Fig. 3] [Manufacturer:Cadila Healthcare Ltd., Sarkhej – Bavla, N. H. No. 8, Moraiya, Tal: Sanand, Dist: Ahmedabad – 382 210,Marketed by : Zydus Alidac] are being marketed as composite pack consisting of one vial of lyophilized vaccine powder, one ampoule of diluents and one 2 ml syringe.

Table 1: Few examples of combined/ twin packs of injectables, which do not disclose the particulars of S.W.F.I./ S.N.S., supplied inside the pack.

Sl.No.	Name of Manufacturer	Product(Brand Name)	Accompanied by	M.L. No.
1	Alembic limited, Baddi	Cepime 1, 0.1, 0.25	S.W.F.I.	L/06/238/MB
2	Venus Remedies Ltd. Baddi	Ceftichek, Kefbactum, Formic, Keftragard, Primegard, CA007	S.W.F.I.	MB/05/204
3	Integrated Laboratories Pvt. Ltd., Simour, H.P.	Zoomax, Dicef, Machozone-S	S.W.F.I.	MB/06/397
4	Systacare Remedies, Amritsar	Sazid	S.W.F.I.	1789-B
5	Zee Laboratories, Pontasahib, H.P.	Pepzone-S	S.W.F.I.	MNB/05/115, MB/05/116
6	Odin Healthcare Pvt. Ltd, Sapron, H.P.	Cafzone-S, Machocef-S 1.5, Ceftrix-1	S.W.F.I.	MB/05-163
7	Alkem Laboratories Ltd., Thana, Baddi(for Galpha Laboratories)	Odicef lg, Odicef 125, Odicef 500, Odicef-S 750, Odicef-S375	S.W.F.I.	L/05/169 MB
8	Aristo Laboratories Pvt. Ltd., Daman	Monocef 250, 500, Maxicef, Montaz	S.W.F.I.	DD/217
9	IPCA Laboratories Ltd., Mumbai	Sulax 0.75, Lactagard 1500, Gardcef 1500	S.W.F.I.	KD-845-A
10	Iskon Remedies, Sirmour, HP	Ceeta-SB,Zidden-250, Machozid- 1000	S.W.F.I.	MB/06/288
11	Health Biotech Ltd, Baddi, HP	Prexon-S 1.5	S.W.F.I.	MB/05-158, MNB/06/445
12	Scott-Edil Pharmacia Ltd., Jhamraji, HP	Notax-SB, XL One 1.5g, ZOOM-1, *Pantakind, Suncefop-SB	S.W.F.I., *S.N.S.	Mb/05-139
13	Orbit Life Science Pvt. Ltd., Pondichery	Dibact 1000, Cefoprox XP	S.W.F.I.	06 23 1664
14	Parental Drugs(India) Ltd. Solan, HP	Maxopime 500, Tazomax 4.5	S.W.F.I.	MB/06/369
15	Aqua Vitoe Laboratories, Baddi, HP	Avsul-lg, Cefosum-S, Cefmag-TZ, Cefmag-SB, Cefocom-SB	S.W.F.I.	MB/07/536
16	Shreya Life Science Ltd.,	XTUM	S.W.F.I.	137/UA/SC/P-

The lyophilized powder required to be stored between 2°C to 8°C preferably 2°C to 4°C [as per Schedule F**], whereas the diluents and the syringe need not be stored in cold condition.

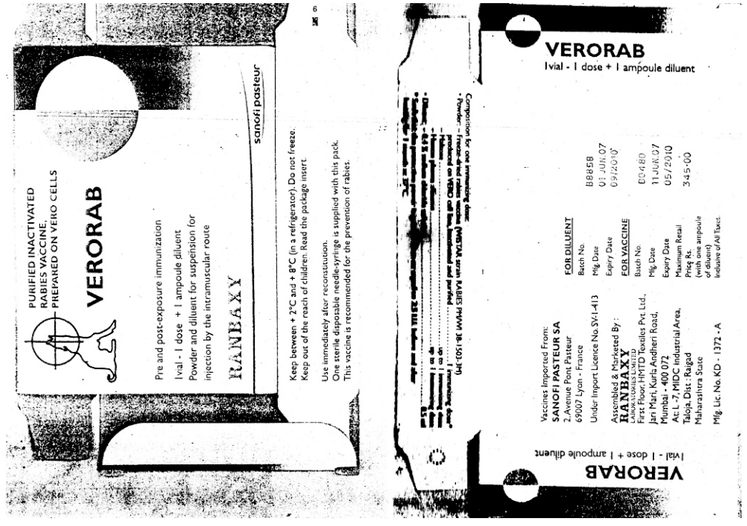

Figure 2: Composite pack of one vial and one ampoule of diluents and syringe

A composite pack not only increases the pack size (volume) but also requires more time to reach storage condition (cold). The another point to mention is that almost in all cases, marketing organizations are not mentioning the manufacturer as well as batch details of the "syringes" (disposable syringe is also a drug as per Drugs and Cosmetics Act 1940) provided inside the composite pack, [Fig. 4A, 4B, 4C] thus violating Rule 96 of Drugs and Cosmetics Rule 1945 and rendering the product to treated as "Misbranded Drugs" u/s 17(b) of Drugs and Cosmetics Act. Being vaccines, if any preventive measure taken in the market, a crisis may take place. Thus we believe that it is essential for the authority to communicate concern licensing authority to ask the manufacturer to take corrective measure.

Figure 3: Composite pack of one vial, one ampoule and one 2ml syringe

From a regulatory point of view, the movement/ distribution/ sell of syringe provided in composite pack remain untraced. In most of the cases, the manufacturer of the syringes is rarely known. It is also not known whether the manufacturer are permitted to undertake free distribution/ sell of the syringe, as saleable unit of such syringes never traced in the market. There are several vaccines available in the market without accompanying syringe. Moreover there is no report of any problem due to non-availability of syringe in the market to administer the vaccine.

Figure 4: Combined pack of drugs with diluents; A: Pantocid; B: Lycortin – S ; C: Oframax

CONSEQUENCES AND RECOMMENDATIONS

The possible consequences of which could be as described below along with some recommendations in some cases:

- The consigning and forwarding agents/ stockiest/ distributor are not maintaining any record the diluents/ solvent accompanying the active drugs. For the same reason the buyer/ customer/ patient party is not getting any written document (i.e. cash memo/ credit memo) in support of procurement of such diluents/ solvents.
- The pack can be tempered with, by replacing the original diluents/ solvent/ syringe provided by the manufacturer by cheaper and sub-standard diluents/ solvent, at any stage of marketing.

- If those diluents/ solvent are proved to be/ declared spurious or sub-standard by government analyst (if rule 23 followed), legal steps cannot be initiated since the original supplier can not be traced. The manufacturer of active drugs may refuse to take responsibility for the particular batch of S.W.F.I. sighting that particular batch was not supplied by them. The manufacturer of S.W.F.I. / S.N.S. cannot be charged as nowhere it was recorded that the particular manufacturer has supplied those product.
- The patients are helpless since they are completely unaware of the fact but they may receive the diluents/ solvent (may be spurious), and they are not in a position to check/ verify the batch No.
- If a particular batch/ lot of diluents/ solvent found contaminated or adulterated, it is difficult to trace the rest part in the market. It is also difficult to recall the diluents/ solvent/ syringe from the market. Usually batch size of S.W.F.I. is much more than batch size of active drugs.
- There is no provision of combined pack in D and C rule (Rule 96, Manner of Labeling Subject to the other provisions of these Rules, the following particulars shall be printed or written in indelible ink and shall appear in a conspicuous manner on the label of the innermost container as well as successive packs. If combined/ twin packs are approved, Rule 96 needs to be strictly followed.
- It appears to be re-packed S.W.F.I. / S.N.S. (manufactured by other manufacturer) by manufacturer of active drugs along with vial of active drug. As per rule 70 re-packing is not applicable for schedule C and C (1) drugs. In all the cases only M.L.No. has to be printed on the carton. (It is not yet confirmed, whether such combined/ twin packs are approved by concerned state Drugs Control Authority).
- **Problem of Sampling and testing**: The quantity required for complete testing of powder injectable is 25 vials, whereas for S.W.F.I. the required quantity is 1500 ml (i.e. 300 X 5ml or 150 X 10ml) (As per Central Drug Laboratory) and 60 ampoules (as per authorized laboratory). So, if 25 combined packs are sampled S.W.F.I can not be completely tested due to insufficient quantity. If 60 combined packs are sampled just to complete analysis of S.W.F.I, huge amount of Government money will be wasted (If price of combined pack and price of S.W.F.I. taken in consideration). The rest i.e. (60-25) =35 vial of injectable are to be drawn in excess.
- **Presently** more than 90% manufacturers' sale combined packs with S.W.F.I; hence S.W.F.I. is going beyond scope of regulation.
- **Generally found** S.W.F.I. are manufactured by Vifor(Mumbai), Mark (Gujarat), Aisharya (Baddi) and Nirma.
- **In 99.5%** cases powder and S.W.F.I./ S.N.S. are manufactured by two different manufacturers.

The predominant issue arises here is to take up the challenges how such combined/ twin pack should be stopped from marketing.

CONCLUSIONS

In conclusion, twin pack labeling is a serious issue in terms of security of medicine as it can directly affect the health of the patients. Drug Regulatory Authority must understand the importance of it to find out the short-comings to overcome the loopholes and strengthen the regulatory aspects more stringent. Last but not the least, Drug Regulatory Authority help the Pharmaceutical manufacturers adopt proper labeling procedure to comply with the regulation as may be designed by the Drug Regulatory Authority in an obligatory way.

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