Review Article

Quality and safety of traditional medicines: Current regulatory scenario in India

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ABSTRACT

Traditional medicines (TMs) play an important role in maintaining public health, especially for those living in remote and rural areas. It is reported that 80% of the Indian population living in the rural sector depend primarily on the TMs. A well-structured regulatory control mechanism yet to be implemented in most of the developing countries. In India, the authority has given special attention to the safe use of TMs and to sustain its quality as well as safety among users. The Drugs and Cosmetics Act 1940 and Rules, 1945, is the law that regulates the TMs in India and is being amended many times. The act speaks the provisions related to the regulation pertaining to the manufacture and other activities such as manufacturing, packaging, labeling, standards, and sale of TMs. To manufacture good quality indigenous medicines in India, good manufacturing practices have been made mandatory by incorporation of revised Schedule T in the act. The present review highlights the current regulatory situation of TMs in India and the various approaches adopted in Indian regulation to ensure its quality and safety among the users.

KEY WORDS: D and C act, Provisions, Quality, Safety, Traditional medicines

INTRODUCTION

Traditional medicines (TMs) play a significant role in maintaining the public health of the population in developing countries.[1] The countries using the TMs are very much aware of the need for its regulation for maintaining its safety and quality.[2] The World Health Organization advices each country to frame regulations to govern the rational use of TMs.[3] To ensure the acceptable quality, safety and efficacy of the TMs used in India have always required a clear regulatory mechanism.[4] In India, traditional herbal medicines include Ayurveda, Siddha, and Unani (ASU) systems of medicines. These are regulated in India under the Drugs and Cosmetics Act 1940 and Rules 1945, where regulatory provisions are clearly laid down.[5] In India, the department of AYUSH concentrates on the overall governance, regulation, growth, and advancement of TMs inside and outside the country.[6]

LEGAL CLASSIFICATION FOR INDIAN TMs

Section 3(a) of Chapter I of the act provides a specific definition for the regulated TMs in India, commonly known as classical medicines. It includes the medicines for both the purposes of internal and external use. According to the definition, all TMs must be indicated either for the diagnosis or treatment or mitigation or prevention of any disease or disorder both in human beings and animals. The products are allowed to manufacture only as in the formulae specified in the authoritative books of ASU Tibb systems of medicine. These formulae specifications are clearly stated in the texts of First Schedule of the Act. The first schedule contains only the notified authoritative books for each system of medicines. There are 58 books for Ayurvedic systems, 31 books for Siddha Systems, and 14 books for Unani Tibb Systems listed in the schedule.

Whereas Section 3(h)(i) in the act provides the definition for patent and proprietary medicines that are manufactured in India. It includes the products formulated exclusively with the ingredients as specified in the formulae of the texts in the First Schedule of the Act. Most importantly, these products should not be used for parenteral administration and it should not be formulated with the formulae described under any texts of Schedule I. No manufacturers are permitted to manufacture a formulation for sale in the country with an ingredient which is not a part of any formulations described in the books of Schedule I.[7]

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PROHIBITORY AND PENAL PROVISIONS OF INDIAN LAW

Drugs and Cosmetics Act contains Chapter IV-A which describes the provisions relating to the TMs in detail. Section 33-EEB of this chapter reminds us that the manufacturing of TMs is only performed in accordance with the standards as specified in relation to that drug in the act.

The act contains some prohibiting provisions also to maintain product quality and to check the chances of counterfeit drugs in the market. Manufacturing as well as the distribution of any ASU drugs which are either misbranded or adulterated or spurious, prohibited in the country as per Section 33-EEC of the act. The criteria to declare a medicine in the above category are also defined separately in the chapter. These regulatory provisions help to maintain the quality of TMs among users and to prevent the chances of occurrence of counterfeit drugs in the market.

Section 33E of the act gives definition for misbranded drug. As per the definition, a drug can be classified as misbranded (a) if the medicines are colored or coated or powdered or polished to conceal its exact damage, or if it is made to appear of better therapeutic value than it really is; (b) if it is not labeled in the prescribed manner (c) if the label or accompanying materials such as inserts attached with the drug bears any misleading or false claim.

In the country, a drug is deemed to be adulterated if it contains in whole or partly filthy/putrid/decomposed substances, or if it contaminated with filth as it prepared or packed or stored under unsanitary conditions or any toxic substance which is detrimental to health, or if the container is made up of any toxic substance, or it contains an un-prescribed color or if mixed therewith that causing its quality reduction. It is defined under Section 33EE of the act.

A drug is assumed to be declared as a spurious drug if it matches the definition as described under the Section 33-EEA of the act. If the ASU drugs are sold or exhibited for sale, under a name but it contains a different drug; or if it either resemble or substitute for another drug or appears like another drug in a falsified manner, or carry the name of another drug, unless it is plainly and conspicuously marked so as to reveal its normal character or the label contains the name of mythical company or, if it substituted with any other drug or if it purports to be the product of another manufacturer.

There may be instances involving risk to the health of the users, or the drug may not have any claimed therapeutic value on its administration. In such cases, if clear evidence is available, there is an empowering section to the Central Government to prohibit the manufacture, sale as well as the distribution of the drugs by special notification through Official Gazette for the public interest.

If any offenses are being conducted or if found any provisions are being violated, the act empowers the specially designated inspectors to institute prosecution action to present the accused before the court of law Table 1.[8]

LEGAL REQUIREMENTS FOR MANUFACTURING OF TMs

The manufacturing of traditional drugs such as Ayurvedic, Siddha, and Unani systems is strictly regulated in India for ensuring its quality. The rule contains Part XVI that details the manufacturing provisions of these systems of drugs. In India, the manufacturing of such drugs is permitted in licensed premises only. However, licenses are not required for sale of TMs in Indian market. Each State Government is required to appoint Licensing Authority (LA) by notification in the Official Gazette for executing Part XVI of the Act. Licensing procedures and the conditions to be satisfied for the manufacturing of regulated TMs in India are clearly laid down in the rules.

Table 1: Penal provisions under the drugs and cosmetic act

Section in the act and punishable offense	Punishable section	Punishment
S.33E. Manufacturing of misbranded drug	33-I (1)(a)(i)	Imprisonment up to 1 year and fine which shall not be <Rs. 20,000/-
S.33EE. Manufacturing of adulterated drug	33-I (1)(a)(ii)	Imprisonment up to 1 year and fine which shall not be <Rs. 20,000/-
S.33EEC (c). Manufacturing of a drug without valid licence	33-I (1)(a)(iii)	Imprisonment up to 1 year and fine which shall not be <Rs. 20,000/-
S.33EEA. Manufacturing of spurious drug	33-I (1)(b)	Imprisonment of 1–3 year and fine which shall be minimum of Rs. 50,000/-
Contravene any of the provisions of any notifications issued under Section 33-EED	33-I (1)(c)	Imprisonment up to 3 years and with fine which may extend to 50,000/-
Contravene any other provisionary part or section 24 as applied by Section 33H or any other rule	33-I (2)	Imprisonment up to 6 months and with fine which shall not be <10,000 rupees.

LICENSING PROCEDURE FOR MANUFACTURING OF TMs IN INDIA

An application in form 24-D is required to be submitted before the LA, along with the required fee for the manufacturing of approved TMs in India. The Manufacturing License in "Form 25-D" is issued to the applicant only if the conditions are found satisfied after site inspection. It should be granted within 3 months which is calculated from the date on which the application is received. The license is granted by the LA after consultation with such experts, approved by the State Government. It is the responsibility of the license holder to get it renewed the license in Form 26-D before its expiry.

Loan license is another facility provided in the act to promote the production of TMs and its circulation across the country. A loan is issued by the Stale Licensing Authority, where the applicant does not have their own manufacturing facilities but take advantage of the facilities of a manufacturer holding a license in "Form 25-D." The applicant is required to submit the application in "Form 24-E" to the Licensing Authority along with the required fee. A loan licence for manufacturing any ASU drugs is issued in the statutory Form of "25E." The loan licence is also granted by the LA after consulting with the experts. It is granted by the authority, only if satisfied that the manufacturing unit is well equipped with adequate staff and has the capacity for manufacturing, testing etc. The loan license is also required to be renewed before the validity expires and issued in "Form 26-E."

CONDITIONS FOR GRANT OR RENEWAL OF DRUGS LICENSES OF TMs IN INDIA

The manufacture of ASU drugs is required to follow "Good Manufacturing Practices" (GMP) specified in "Schedule T" of the act. GMP Certificate in "Form 26 E-I" is also granted along with the license in Form 25D after verifying the compliance of Schedule T by the Licensing Authority. The manufacturers are not permitted to use any prefix or suffix with the name of any ASU drug which belongs to classical medicines as given under Section 3(a) of the Act, except as described in the authoritative books specified in the First Schedule to the Act. The name of any TMs falling under Section 3(a) of the Act should not be used for naming any approved patent or proprietary medicine. The manufacturing plant shall be run under the supervision and in charge of a technically competent staff only. This technically competent person is required to have adequate qualifications in their respective systems of medicines, and the mandatory qualifications are also clearly laid down in the act.

GMP FOR REGULATED TMS IN INDIA

"Schedule T" of the Act describes in detail the GMP of ASU drugs. The law mandates that the raw materials for the manufacturing purposes should be authentic and of prescribed quality. Furthermore, it must be free from any contamination. The process of manufacturing has been prescribed in detail in the schedule to uphold the standards of each drug. Apart from this, it is the duty of the manufacturer to take proper measures for quality control and it should be ensured that the products are of acceptable quality before releasing to market. Each manufacturer must evolve an appropriate methodology which is to be followed during the manufacturing process. This should be documented as a manual and must be kept ready for reference and inspection. The important specifications of manufacturing plant and factory building are clearly provided in the schedule. Special attention must be given for the quality of water used and its control during the manufacturing process. There shall be adequate arrangements separated from the manufacturing operations for cleansing, washing, and drying of containers. Handling of raw materials and its storage and tests during the manufacturing process are also given special importance in GMP. It is also very important to keep the records of the receipt, testing, and approval or rejection and use of raw material in the plant. Personnel cleanliness and periodic check-up are also a major concern during manufacturing under GMP. Suitable equipment either manually operated or operated semi-automatically which is electrical or steam-based or fully automatic machinery shall be made available depending on the size of operation and nature of the products manufactured. A list of equipment and machinery recommended for manufacturing are also given in Part II-A of the Act. Proper Standard Operating Procedures for the processes such as cleaning, maintaining, and performance of all machines must be described in the factory premises.

Most importantly, a quality control section shall be maintained in the manufacturing premise or the product is getting tested with Government Approved Testing Laboratory. It shall be carried out only in compliance with the pharmacopeia standard prescribed for ASU drugs. If no specific tests are available, it should be tested in accordance with the specifications of the manufacturer or any other information available. It is the duty of the quality control team to verify the authenticity of the raw materials used and also, responsible for monitoring in-process quality control checks of the finished products before releasing to finished goods store or warehouse.

GUIDLINES TO ISSUE LICENSE FOR MANUFACTURING OF TMs IN INDIA[9]

Many guidelines are inserted in the act by the Government of India vide Official Gazette No.G.S.R.663(E) to issue licenses to the regulated TMs in the country. The conditions relating to "safety study and the experience or evidence of effectiveness" shall be specified in the application for every TM defined in Section 3(a) or 3(h) Tables 2 and 3. The guidelines are framed separately under Rule 158(B) for each class of patent or proprietary medicines such as Positive Health Promoter Formulations or Soudarya Prasadak or Aushadh Ghana. Positive Health promoter is a formulation recommended for promotional and preventive Health and is also termed as Balya/Poshak/Unavuporutkal in the act. The formulation Saudarya Prasadak is intended and recommended for caring for the parts of oral, skin, hair, and body and is also termed as Husaneafza/ Azhagh Sadhan Formulation. Aushadh Ghana is another formulation which is wet or dry medicinal plant extract including aqueous or hydro-alcohol in nature.

Application for the license to manufacture a formulation of Positive Health promoter and Saudarya Prasadak must be accompanied with a photocopy of the textual reference of ingredients used in the formulation as mentioned in the book of first schedule and safety study data of the products, if contains any ingredients specified in the Schedule E(1). For textual indications, there is no need to submit data of safety and effectiveness study.

REGULATIONS RELATED TO LABELING OF TMs

A separate provision of Rule 161 has been provided in the Act with regard to labeling and packing of ASU drugs. The list of all ingredients must be displayed in the label with the quantity used thereof. The textual reference for the preparation shall also be mentioned in the label of the product. If the label is not able to accompany the list of ingredients, it shall be printed separately and enclosed with the product. The words "Caution: to be taken under medical supervision" both in Hindi and English Languages have to be printed on the label if it contains any poisonous substance specified in Schedule E1 of the act. The name of the drug, name, and address of the manufacturer of the drug, Manufacturing License Number, Batch No, Manufacturing Date and Expiry dates are also required to be printed on the label in indelible ink. The label of the products intended for external applications shall bear the said purpose on it. The rule also specifies to mention the type of traditional system such as "Ayurvedic Medicine" or "Siddha Medicine" or "Unani Medicine" on the label. The products for export purposes are exempted from the labeling requirements mentioned in Rule 161. Such products shall comply with the specific requirements of that country concerned. The word "Export" shall also be mentioned in the label.[10]

STANDARDS OF REGULATED TMS

The traditional drugs manufactured in the country must comply with the standards for its identity, purity,

Table 2: Requirements of safety study and experience/evidence of effectiveness to issue a license for drugs described under Section 3(a)

Category	Ingredient (s)	Indication (s)	Safety study data	Experience/Evidence of effectiveness data	
				Published literature	Proof of effectiveness
ASU drugs, given in 158 B as referred in 3(a)	Textual	Textual	N	Y	N
Any change in dosage form of ASU drugs, as described in section 3 (a)	Textual	Textual	N	Y	N
ASU drugs, referred in 3(a) to be used for the new indication	Textual	New	N	If necessary	Y

ASU: Ayurveda, Siddha, and Unani, N: Not required, Y: Required

Table 3: Requirements of "safety study and experience/evidence of effectiveness" to issue a license with respect to P&P medicine

Category	Ingredient (s)	Indication (s)	Safety study data	Experience/Evidence of effectiveness data	
				Published literature	Proof of effectiveness
Patent or proprietary medicine	Textual	Textual rationale	N	Of ingredients	Pilot study to be done with the relevant protocol
ASU drugs with any of the ingredients of Schedule E (1)	Textual	Existing	Y	Y	Y

ASU: Ayurveda, Siddha, and Unani, N: Not required, Y: Required

and strength as given in the Ayurvedic Pharmacopoeia of India. The self-generated alcohol content in the preparations such as Asavas and Aristas are restricted to 12% only. The raw materials used in the preparations should be identified and tested for its genuineness and such records required to be maintained by the manufacturer.[10]

MAINTANANCE OF RECORDS OF RAW MATERIALS[11]

The manufacturers are required to maintain a record of all used raw materials in the preceding year for the manufacture of TMs. It should be maintained in a statutory proforma as provided in "Schedule T-A" of the act. It should be required to submit by the June 30 of the succeeding financial year to the State Drug Licensing Authority and the National Medicinal Plants Board or any agency nominated by the National Medicinal Plant Board for this purpose. The annual utilization of the raw material during the manufacture of these drugs shall be analyzed from the data submitted. Schedule TA includes the particulars such as the name and address of the manufacturing units with its license number, contact details, and Quantity of Medicinal Plants/Extracts/Essential Oils used in the preceding year. Sources of supply and the parts used by the manufacturers are also be recorded in Schedule TA.

ISSUANCE OF FREE SALE CERTIFICATE AND NON-CONVICTION CERTIFICATE

The quality and safety of TMs used in India are the major concerns when exporting to another country. In India, a separate statutory provision of Rule 158C has been inserted vide Gazette Notification No.G.S.R.153(E) in the Act to issue Free Sale Certificate and Non-Conviction Certificate to the manufacturers who intend to export the TMs that are approved in India. Free sale certificate is a document required in certain countries, certifying that the imported medicines are normally and freely sold in the exporting countries open market and approved for export. The Non-Conviction Certificate in Form 26E2-II is also issued to the manufacturers to prove that the firm has not been convicted in any court of law. It enables to maintain the belief among other countries about the quality of traditional products which are being exported. Free Sale Certificate in "Form 26 E2-I" will be issued by the State Drugs Controller or Licensing Authority within 15 days on verifying the request application of the manufacturers.

CONCLUSION

The demand for TMs in India has been increased continuously and recognized around the world in spite of many hurdles. Although the Act cater a number of provisions to ensure the quality and safety of TMs in India, a combined effort of public as well as government is also indispensable. Manufacturing of the patent and proprietary medicines using ingredients of the formulations mentioned in the texts of Schedule I and formulations presented in classical texts are meant to ensure the quality and safety of TMs. The prohibitory and penal sections provided in the act are also intended to monitor, control, and prevent the floating of counterfeit drugs in the market. The stringent licensing procedures, GMP, and the guidelines to be followed during manufacturing are helpful to maintain the quality of regulated TMs in India. To compete with marketed products of the modern world, the need for conducting clinical trials is very significant that enables the society to understand the safety and efficacy of these drugs before their entry in global market. The provision for issuing of free sale certificate and Non-Conviction Certificate to the manufacturers enables to maintain the belief for other countries about the quality and safety of TMs which is being exported.

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