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Drug Regulating Mechanisms in Indian Scenario Related to *Ayurvedic* Drug Industry: A Quick Look

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ABSTRACT

Quality and safety are the two most essential aspects for the acceptance of drugs. The drug, which is going to be administered in to the human body, should be standard and should not produce any kind of untoward effects after its administration. A drug fulfilling the criterion of a standard drug will always become panacea provided, if it is used properly. On the other hand, a poorly prepared or manufactured drug however used skillfully, will always prove to be a poison. Seers of *Ayurveda* considered these aspects and stressed their significance in respective classics. In due course of time, considering the enormous growth of pharmaceutical sector; Governments established different Drug Regulating Mechanisms to regulate entering of spurious drugs in to the market. The Drugs & Cosmetics Act & Rules governs the Drug Regulating Mechanisms to maximum extent in India. Considering the need of the industry, the rules will be amended at regular intervals. Here an attempt has been made to compile certain important amendments took place in recent past.

Keywords: Ayurveda; Drugs & Cosmetics Act; Drug Regulating Mechanism.

INTRODUCTION

If one goes through the history of drug legislations of various countries, it can be learnt that the legislations were enacted essentially to stop the distribution of deteriorated or adulterated drugs in the market. The oldest drug legislation is 'Drug Legislation of the United States of America', which was approved during 1848. Followed by approval of food and drug laws (in 1906) under Federal Food and Drug Act (FDA), the recognition of National Formulary (NF) and the United States Pharmacopoeia (USP) as the official standards for drugs has taken place. Many amendments were made in FDA, and in 1963 the first GMPs were published. The drugs further being manufactured were required to meet the standards set out therein. Most of the drug legislations of different countries followed this approach.

Indian Scenario

Quality, safety and efficacy of drugs have always been a matter of concern for public even in India. During the first quarter of 1900s, an agitation towards substandard medicines was raised by the medical professionals of those days, who brought the issue to the notice of 'Council of States' in 1927. Consecutive to this, the Government appointed a 'Drug Enquiry Committee' under the Chairmanship of Lt. Col. RN Chopra in 1930, which recommended the formation of a 'Central Legislation' for setting up of suitable standards. Based on these recommendations, Government introduced 'Import of Drugs Bill' in Legislative Assembly in August 1937. This

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bill was presented in Legislative Assembly on 15th March 1940. This was later discussed and passed on 5th April 1940. Further, the same was discussed in the Council of States and ultimately passed on 10th April, 1940 under the name of 'Drugs Act'. This legislation gave powers to the Government to make rules to regulate import, manufacture, sale and distribution of drugs in the country. Consecutive to this, rules were framed during 1945. Later, the scope of the Drugs Act was extended to cosmetics in 1962 and the title of the act was changed to 'Drugs & Cosmetics Act'. The drugs belonging to the Ayurveda, Siddha and Unani (ASU) Systems were brought within the purview of the D & C Act in 1964.

In the current scenario, the following Acts and Rules are regulating the manufacture, export and clinical research of drugs & cosmetics in India.

- Drugs and Cosmetics Act, 1940
- Drugs and Cosmetics Rules, 1945
- Pharmacy Act, 1948
- Drugs and Magic Remedies Act, 1954
- Medicinal and Toilet Preparations Act, 1955
- Narcotic Drugs and Psychotropic Substances Act, 1985

In addition to these,; there are some other laws which have a bearing on manufacture, distribution and sale of drugs & cosmetics in India. The important ones are:

- Factories Act, 1948
- Industries Act, 1951
- Trade and Merchandise Marks Act, 1958
- Indian Patents and Design Act, 1970

Relevant Parts of D & C Act & Rules Related to Ayurveda

Below is a brief on the important parts of Drugs & Cosmetics Acts & Rules with special reference to *Ayurveda* has been placed at Table 1.

The list of books [The first schedule of the drugs & cosmetics Act 1940]. This schedule holds a list of 98 books of different systems of medicines as mentioned below:

The list of scheduled books under Ayurvedic system of medicine holds 54 books. In addition to this, 54-A, B & C have also been added in

	System of Medicine	Number of Books
1	Ayurveda	54
2	Siddha	30
3	Unani	14

consecutive amendments, which include Ayurvedic Formulary of India (AFI), *Ayurveda Sara Sangraha* and Ayurvedic Pharmacopoeia of India (API) respectively. All successive volumes / parts being published under AFI and API will become a part of Schedule - I automatically. This amendment is even applicable to other systems of medicines (Siddha and Unani) too.

Shelf life of ASU drugs [Part XVII - Rule 161-B]

Shelf life is the length of time that a substance can be considered as suitable for sale or consumption. Information pertaining to shelf life of different formulations does exist in classics of *Ayurveda*, which is scattered. This information has been gathered and explained under the umbrella of "*Saviryata Avadhi*" by *Acharya Sharangadhara* (I-1/51-3) for the first time. According to him the shelf life of different dosage forms is as under:

	Shelf life	Dosage Forms
1	2 Months	*Churna*
2	12 Months	Raw Material
3		*Gutika, Avaleha*
4	16 Months	*Sneha Kalpana*
5	Infinite Period	*Sandhana Kalpana, Rasa Yoga*

Though the classical concepts are time tested and scientifically proven at many instances; are not pharmaceutical friendly which has led to draft certain amendments. Initial official gazette on shelf life was released during November 2005. Certain modifications have

Table 1: Relevant parts of D&C Act & Rules related to Ayurveda

Part of Act / Rule	Chapter / Part	Nature of Activity
Drugs & Cosmetics Act 1940	Chapter IV-A (section 33-B to 33-N)	Provides provisions related to *Ayurveda, Siddha* and *Unani* Drugs
Drugs & Cosmetics Act 1940 - Schedules	The First Schedule	List of scheduled books
	The Second Schedule	Standards to be complied with by imported drugs and by drugs manufactured for Sale, Stocked or Exhibited for Sale or Distributed
Drugs & Cosmetics Rules 1945	Part XVI (Rule 151-160)	Manufacture for sale of *Ayurvedic* (including *Siddha*) or *Unani* Drugs
	Part XVI-A (Rule 160 A - 160 J)	Approval of institutions for carrying out tests on ASU Drugs and Raw material used in their manufacture
	Part XVII (Rule 161)	Labeling, Packing and Limit of Alcohol in ASU Drugs
	Part XVII (Rule 161-B)	Shelf life or date of expiry for ASU Medicines
	Part XVIII (Rule 162-167)	Government analysts and Inspectors for ASU Drugs
	Part XIX (Rule 168-170)	Standards of ASU Drugs
Drugs & Cosmetics Rules 1945 - Schedules	Schedule A	Different types of forms, particularly 24D, 24E, 25D, 25E, 26D, 26E, 26E-1, 47, 48, 49
	Schedule B-1	Fees for the test or analysis by Pharmacopoeial Laboratory for Indian Medicine or the Govt. Analyst
	Schedule E-1	List of poisonous substances under ASU Systems of Medicine
	Schedule FF	Standards for Ophthalmic Preparations
	Schedule T	Good Manufacturing Practices for ASU Medicines
	Schedule Y	Requirements and Guidelines for permission to import and / or manufacture of new drugs for sale or to undertake clinical trials
	(Proposed) Schedule Z	Requirements and Guidelines for permission to manufacture of ASU drugs for sale or to undertake clinical trials

been made in this rule and a revised gazette has been released during October 2009 by the Government of India, where the life span of different Ayurvedic dosage forms is mentioned. This is covered under Rule 161 - B of Drugs & Cosmetics Rules 1945 and came into force since 1st April 2010. Brief information on the revised Gazette is placed at Table 2.

• It has been clearly mentioned that the date of expiry of ASU medicines shall be conspicuously displayed on the label of the container or package of the medicine and after the said date of expiry, these medicines shall not be in circulation.

• A separate list depicting the shelf life of Siddha and Unani medicines is also provided in the same rule.

Poisonous substances under ASU systems of medicine [Schedule-E(1)]

Few substances being used in the preparation of formulations under ASU systems have been identified as poisonous and been categorized under Schedule E (1). An amendment in this regard has been released during August 2010, making certain changes in the list. A comparative list of such substances and changes made subsequently with reference to *Ayurvedic* system of medicine is placed at Table 3.

Omission

• The seeds of two herbal sources (*Ahiphena* and *Bhanga*) have not been considered as poisonous.

Table 2: Brief Information on Shelf Life of Ayurvedic Compound Formulations

Shelf life	Dosage Forms
Infinite Period	*Rasaushadhies, Parpati, Pisti, Bhasma of Swarna, Rajata, Lauha, Mandura, Abhraka, Godanti & Sankha, Kupipakva Rasayana, Asava, Arista Kalpanas*
1 Year	*Arka* and *Netra Bindu*
2 Years	*Churna, Kwatha Churna, Ghrita Kalpana, Danta Manjana Powder / Paste, Varti, Sveta Parpati, Karna & Nasa Bindu, Dhoopana Dravya*
3 Years	*Gutika of Kastha Aushadhi, Ghana Vati, Avaleha Kalpana, Taila Kalpana, Lepa Churna, Lepa Guti, Malahara (*Ointment / Liniment etc), Capsules of Soft Gelatin, *Khanda /* Granules / *Paka,* Syrups & Liquid Orals, *Pravahi Kwatha* (with preservatives)
5 Years	*Gutika of Rasa Aushadhi (Kharaliya Rasayana), Guggulu, Dravaka, Lavana, Ksara, Bhasmas of Naga, Vanga and Tamra,* Capsules of Hard Gelatin
10 Years	*Mandura* and *Lauha Kalpana*

• One herbal source, i.e. *Snuhi,* has been omitted from the list.

• Two minerals, i.e. *Sindura* and *Girisindura,* have been omitted from the list.

Other Amendments

• Only the seeds of *Gunja* and *Jayapala* have been considered as poisonous.

• *Vatsanabha* and *Shringivisha* both have been grouped under one.

• The chemical composition of *Haratala* and *Manahshila* has been specified clearly.

• The botanical identity of *Parasika Yavani* has been changed from *Hyoscyamus inibar* Linn to *Hyoscyamus niger* Linn

• Other substances have been retained as such.

The number of substances under individual groups is as under.

	Category	1970	2010
1	Herbal	15	13
2	Animal	01	01
3	Mineral	09	07
Total		25	21

Permissible excipients for manufacturing of ASU formulations [Rule-169]

A gazette has been notified during July 2001 permitting preservatives, excipients etc. for Patent and Proprietary ASU Formulations. Additionally, it has been mentioned that no patent or proprietary ASU formulation should contain preservatives, excipients, coloring and flavoring agents other than the specified ones in the gazette.

This list includes

	Category	Number
1	Class I Preservatives	08
2	Class II Preservatives	11
3	Anti-oxidants	09
4	Sequestering and Buffering Agents	07
5	Natural Coloring Agents	11
6	Flavoring Agents	32
	For Tablet Manufacturing	
1	Diluants	07
2	Binders	11
3	Lubricants	08
4	Disintegrators	08
5	Additives	14
	For Eye Drops	
1	Preservative	01

Further, the list of excipients for ASU drug manufacturing has been updated and a gazette has been released during May 2005. The list has been prepared considering the reference standards / grades under Indian Pharmacopoeia (IP), British Pharmacopoeia (BP), United States National Formulary

Table 3: A comparative list of substances under Schedule E-1 under *Ayurvedic* system of medicine.

Category		Drug	1970	2010
Herbal	1	*Ahiphena*	*Papaver somniferum* Linn	Seeds have been exempted
	2	*Arka*	*Calotropis gigantea (linn.)*R. Br. ex. Ait.	Same
	3	*Bhallataka*	*Semecarpus anacardium* Linn. F	Same
	4	*Bhanga*	*Cannabia sativa* Linn.	Seeds have been exempted
	5	*Danti*	*Baliospermum monatanum* Mull. Arg	Same
	6	*Dhattura*	*Datura metal* Linn	Same
	7	*Gunja*	*Abrus precatirius* Linn	Seeds have been identified as poisonous
	8	*Jayapala*	*Croton tiglium* Linn	
	9	*Karaveera*	*Rerium indicum* Mill	Same
	10	*Langali*	*Gloriosa superba* Linn	Same
	11	*Parasika Yavani*	*Hyoscyamus inibar* Linn	*Hyoscyamus niger* Linn
	12	*Snuhi*	*Euphorbia neriifolia* Linn	Omitted
	13	*Vatsanabha*	*Acontium chasmanthum* Stapfex Holm	*Acontium ferox* Wall. Ex Ser / *chasmanthum* Stapf. ex Holm
	14	*Vishamushti*	*Strychnox nuxvomica* Linn.	Same
	15	*Shringivisha*	*Acontium chasmanthum* Stapfex Holm.	Considered under *Vatsanabha*
Animal	1	*Sarpa Visha*	Snake Poison	Same
Mineral	1	*Gauripashana*	Arsenic	Same
	2	*Haratala*	Arseno sulphide	Arsenic trisulphide
	3	*Manahshila*	Arseno sulphide	Arsenic disulphide
	4	*Parada*	Mercury	Same
	5	*Rasa Karpura*	Hydrargyri subchloridum	Same
	6	*Tuttha*	Copper sulphate	Same
	7	*Hingula*	Cinnabar	Same
	8	*Sindura*	Red oxide of lead	Omitted
	9	*Girisindura*	Red oxide of mercury	

(USNF), Fruits Product Act (FPO) and Prevention of Food Adulteration (PFA). This list contains:

	Category	Number
1	Additives	87
2	Preservatives	14
3	Anti-oxidants	06
4	Coloring Agents	16
5	Flavoring Agents	As permitted under PFA
6	Alternate Sweeteners	As permitted under FPO

In continuation to these the gazette released during October 2008 states that the "Excipients along with their standards, i.e. additives, preservatives, antioxidants, flavoring agents, chelating agents etc., permitted in the Indian Pharmacopoeia (IP), Prevention of Food Adulteration (PFA), Bureau of Indian Standards (BIS) are permitted for use in ASU Drug Manufacturing with following few conditions."

- The excipients shall comply respective quality standards and be used in the permissible limits as prescribed in the respective pharmacopoeias / acts.
- Additives, preservatives and coloring agents shall be mentioned clearly on the label and the record of the same shall be maintained.
- Manufacturers shall be responsible to ensure rationality, safety and quantity of various excipients used in the formulation.
- If any excipient referred in IP or PFA or FPO or BIS is deleted at a particular point of

time, this will also be deleted simultaneously for the ASU drugs.

In addition, this gazette has defined Acceptable Daily Intake (ADI) of artificial sweeteners in proprietary ASU formulations, which is as follows:

	Artificial Sweetener	ADI
1	Sucralose	1.7 mg/kg body weight
2	Aspartame	13.3 mg/kg body weight
3	Saccharin	1.7 mg/kg body weight
4	Acesulfame K	5 mg/kg body weight

Guidelines for evaluation of ASU drugs & other traditional medicines of India [RULE-170]

With an objective of developing methodologies for records and evaluation; improving quality, value of research, providing appropriate evaluation methods to facilitate the development of regulation and registration in ASU and other traditional medicines in a phased manner; and also to facilitate and to promote health understanding of these drugs, particularly in Indian scenario, recently in December 2008, Govt. of India released a gazette notification entitled "Guidelines for evaluation of ASU Drugs & Other Traditional Medicines of India", which will be covered under Rule - 170 of Drugs & Cosmetics Rules 1945.

These guidelines are intended to serve as a reference source for research scientists, registered medical functionary, ASU drug manufacturers and Health authorities. The ASU and other traditional medicines have been categorized into the following four categories:

i. ASU Drugs.

ii. Patent or Proprietary ASU Drugs.

iii. Indian Ethno medicine based drugs not covered under I & II

iv. Medicines based on Extracts of Medicinal Plants of India.

Under each category, certain subdivisions were also made for convenience and proper evaluation. It also recommended pre-clinical safety evaluation of ASU and other traditional medicines in India. Details on sub-chronic toxicity tests and recovery from toxicity have been mentioned exclusively. Information on genotoxicity studies (Based on Schedule – Y on a case-to-case basis) has also been available in these rules. The last part of this draft Gazette deals with "data required to be submitted with application for permission to conduct clinical trials on ASU and other traditional medicines in India."

The guidelines for clinical evaluation of ASU drugs and other traditional medicines in India are placed at Table 4.

In addition to this, the gazette also holds information on the required data to be submitted while conducting clinical trials with ASU medicines. The below data needs to be provided:

- Introduction
- Information on the formulation
- Experimental Pharmacology (if required)
- Safety Data
- Investigator Brochure
- Protocol
- Case Report Form
- Patient Information Sheet
- Informed Consent Form (in English & Local Language)

Requirements and guidelines for permission to manufacture of ASU drugs for sale or to undertake clinical trials [(Proposed) schedule Z]

Dept. of AYUSH, Ministry of Health & Family Welfare, Govt. of India has drafted guidelines on Good Clinical Practices (GCPs) for clinical trials on Ayurveda, Siddha, Unani (ASU) Medicines, which have been circulated very recently in November 2011.

Good Clinical Practice (GCP) is a set of guidelines which encompasses the design, conduct, termination, audit, analysis, reporting and documentation of the studies involving human subjects. The fundamental tenet of GCP is that in research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the study subject. It aims to

Table 4: Guidelines for clinical evaluation of ASU drugs and other traditional medicines in India

Guidelines for Clinical Evaluation of ASU drugs and other Traditional Medicines in India							
Category		Ingredients	Indications	Safety Data	Experience / Evidence of Efficacy		
					Published Literature	Pharmacological Profile	Clinical Evaluation
I. ASU Drugs							
I.A	In accordance with Classics	As per text	As per text	NR*$	R	NR	NR
I.B	For New Indication	As per text	As per text	NR*$	R	IR	NR
II. Patent or Proprietary Drugs							
II.A	Drugs with the ingredients of formulations as defined under proprietary medicine	As per text	Textual rationale	NR*$	Ingredients Based	IR	R
II.B	With ingredients of Schedule E(1)	As per text	New	R	Ingredients Based	R	R
II.C	Change in composition / Dosage Form / Route of administration	As per text	New	R	Ingredients Based	R	R
III. Indian Ethno-medicines based drugs not covered under I & II							
		As per practices	As per usage	R	If available	R	R
IV. Medicines based on extracts of Medicinal Plants of India							
A	Aqueous	As per text	As per text	NR*$	R	IR	IR
A1	Aqueous	As per text	New	NR*$	R	R	R
B	Hydro-Ethnolic	As Specified	As Specified	R	R	R	R
Other than A, A1 & B		As Specified	As Specified	R	R	R	R

IR : If Required, R : Required, NR : Not Required

* Required if intended human use is more than three months or there are reports suggesting toxicity or when larger multicentric Phase III trials is sub-sequentially planned based on the results of Phase II study.

$ Required if the formulation contains any of the ingredients of schedule E(1)

ensure that the studies are scientifically and ethically sound and that the clinical properties of the ASU medicine under investigation are properly documented. The guidelines seek to establish two cardinal principles: protection of the rights of human subjects and authenticity of ASU medicine clinical trial data generated. These guidelines should be followed for carrying out all ASU medicines research in India at all stages of drug development, whether prior or subsequent to product registration in India.

In brief, these guidelines consists of information on the protocol, ethical issues, Safety considerations, Informed consent process, Responsibilities of the involved personnel in research, Record keeping, Data management, Quality assurance, Statistics and areas of special concern like studies with contraceptives, surgical procedures, *Panchakarma*, Medical devices etc.

Draft of this schedule is under consideration and within few months it may come in to force.

In addition to these, there are a few more amendments released by the authorities:

like Categorization of Ayurvedic products under three categories, viz. Ayurvedic supplements, Ayurvedic cosmetics and Ayurvedic extracts under Rule 158-B' etc.

The information on this subject is enormous and cannot be covered in a single attempt. Complete details can be obtained after referring the respective gazettes.

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