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QUALITY CONTROL IN HOMOEOPATHIC PHARMACEUTICAL INDUSTRY

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ABSTRACT

Availability of standard quality medicine is of utmost importance to human kind and for that stringent quality control in manufacturing pharmaceutical products is necessary. For manufacture of quality medicine proper testing of both the raw material used and of the finished preparation is required. Homoeopathic Pharmacopoeia of India has set standards for raw materials to be used in the preparation of Homoeopathic medicines but only those standards are not enough to establish proper identity or quality of raw materials especially in the case of botanical drugs. A few more parameters like 'Ash content', Assay of Principle Active Constituents' etc. are required to be incorporated there. Where T.L.C. standards have been recommended 'rf' values of a few chemical constituents have been given, but since 'rf' values differ considerably depending upon condition at which TLC is being done, even for a genuine drug they may not match exactly with the given data; it is therefore advisable to do co - TLC with a standard reference substance and relative 'rf' value be given.

Apart from these for finished preparations color of mother tinctures may be incorporated to discourage unscrupulous manufacturers from adding colouring matter. Measurement of viscosity of some mother tinctures may also be of importance to establish genuineness.

In no Homoeopathic Pharmacopoeia standard of containers to be used for storage and dispensing of medicines have been set. Selection of proper material for the manufacture of containers to be used in Homoeopathic industry is also of much importance. Comparative study shows superiority of glass over polymers used in the manufacture of containers used.

We know that availability of standard quality medicine is of utmost importance to mankind for keeping them in good health and for that stringent quality control in manufacturing pharmaceutical products is essential. Homoeopathic profession at large is plagued with this problem particularly because of lack of protocols for standardizing finished medicines particularly in dilution above 6 potencies. It is therefore essential to put much importance on selecting proper raw materials for preparation of medicines and not the least to have strict control over the process of preparation of medicines.

Homoeopathic Pharmacopoeia of India (HPI) has set standards for materials to be used in the preparation of homoeopathic medicines but the standards set are in many cases insufficient or even defective. Let us think of a good manufacturer who wants to prepare good quality medicine. He collects a botanical drug, identifies the same as per standards given in HPI, prepares mother tincture from the drug as per method prescribed but ultimately finds that the preparation does not conform to the standards set forth for the mother tincture in HPI for no fault on his part; then where lies the defect? Let me try to pin point the problem.

(1) Nowhere in the HPI, limit for the presence of foreign matter (both organic as well as inorganic) has been set. During collection of botanical drugs contamination of earth, sand etc. is unavoidable. Now if a drug material contains much amount of these contaminants, the mother tincture produced from it must be of inferior quality. Let us take the example of *Asafoetida*. The very collection procedure of this drug, which is incidentally a gum-resin obtained from the roots of *Furela asafoetida* Linn. suggests that contamination is unavoidable and in the market so many qualities of *Asafoetida* with wide variation in the quantity of the contaminants are available. So mother tinctures produced from these drugs should also vary widely in quality as will be evident from the solid matter content of the mother tinctures as enumerated in Table 1.

Now if a standard of alcohol insoluble substance be set for the drug in question we may get a more or less standard mother tincture in this respect.

Determination of *Ash Content* is also a good procedure for determination of inorganic contaminants for both vegetable as well as animal products.

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Table 1

Estimation of Solid Matter Content In *Asafoetida mother* tinctures

Sample	Solid Matter per 100ml of Mother Tincture
1	2.1540 g
2	0.4120 g
3	0.4693 g
4	1.8160 g
5	0.3261 g
H.P.I. recommendation	0.3000 g

Inference from the above table : Wide variation in solid matter content due to lack of adequate standard in Raw Material monograph

(2) We know that botanical drugs must be collected at a particular season from well developed plants. *Belladonna* is a very common medicine in use by the profession. Dried *Belladonna* herb is available in abundance in the market but only a few are of proper maturity. From the standards set in the HPI one cannot ascertain whether the drug has been collected at proper time or if it is immature. For that, estimation of total alkaloid or for atropine, which is the main active ingredient present in *Belladonna* should be given.

Table 2

Estimation of Total Alkaloid Content In *Belladonna* mother tinctures

Sample	Per cent of Total alkaloid Estimated as Hyoscyamine in Mother Tincture
1	0.2988
2	0.1840
3	0.3369
4	0.0987
I.P. '96 recommendation	0.3000 g min.

Inference : Sample Nos. 2 & 4 are definitely substandard

The same is the case for *Cinchona*. The bark of *Cinchona officinalis* collected from the Nilgiris vary in content of quinine or other cinchona alkaloids from those collected from the mature plants of Darjeeling District of West Bengal and therefore quantitative estimation and setting of minimum limit of presence of these compounds must be given to ascertain proper quality of finished product.

Table 3

Estimation of Total Alkaloid Content In *Cinchona officinalis* mother tinctures

Sample	Per cent of Total alkaoid in Mother Tincture
1	6.9163
2	6.0281
3	3.1647
4	7.8241
I.P. recommendation	6.0000 min.

Inference : Sample No. 3 is definitely substandard

(3) Homoeopathic Pharmacopoiea of India has prescribed TLC standards for a number of mother tinctures produced from botanical drugs. But while setting the standard of raw materials used for preparation of these mother tinctures, Thin Layer Chromatographic standards have not been prescribed. Now through Thin Layer Chromatography we get an idea about the chemical constituents present in a given drug. As referred earlier, the chemical composition of a botanical drug varies with maturity of the botanical species and even with ecological or climatic variations. A botanical sample may be devoid of some chemical compound though it is from a correct species and if somebody depending only on the botanical identification of the drug prepares a tincture, the same may fail in the TLC standard set forth for the finished preparation for no fault of the manufacturer. It is therefore essential to prescribe TLC standards of the botanical raw materials also.

(4) While giving TLC standards HPI has prescribed Rf values only of a few ingredients present in the drug. But we know Rf value of a compound is influenced by a number of factors like layer thickness of the adsorbent, percentage of moisture that may be present in the adsorbent layer and in the mobile phase, the temperature at which the TLC is being done, the rate of evaporation of the solvent system etc. which are all difficult to reproduce. The age of the solvent mixture can also have a significant influence. Comparison of migration distance is especially difficult when the work is being carried out in different chambers.

It is therefore always preferred to have some reference standard compound for co-TLC with the experimental sample. The Rf value for the reference standard will often help to calculate the correct Rf values of the spots obtained from the test sample.

Table 4

Comparative figures of Rf values obtained by T.L.C. of *Atista indica* Q using Silica Gel as adsorbent and 4% ethanolic chloroform as developer at different seasons of the year

Month (Season)	Rf values
May (Summer)	0.12, 0.39, 0.59, 0.86
August (Rainy season)	0.14, 0.41, 0.66, 0.89
December (Winter)	0.12, 0.36, 0.52, 0.83

Comparative figures of Rf values obtained by T.L.C. of *Chelidonium majus* Q using Silica Gel as adsorbent and 10% ethanolic chloroform as developer at different seasons of the year

Month (Season)	Rf values
April (Summer)	0.10, 0.24, 0.53, 0.88
August (Rainy season)	0.20, 0.38, 0.79, 0.96
November (Winter)	0.12, 0.28, 0.57, 0.92

The allopathic pharmacopoeias or formularies always recommend a reference standard for co-TLC with the test sample Let me give a reference from the National Formulary (N.F.)

Thin Layer Chromatography

As per N.F. XIV

"The Rf values obtained by T.L.C. are less reproducible than those obtained by Paper Chromatography.For this reason it is always necessary to prepare chromatograms of authentic specimens or reference standards, preferably in varied quantities, alongside the chromatogram of the sample."

Comparison of Rf and Rst

Rf =distance of spot center from starting point/ ÷distance of solvent front from starting point

Rst =distance of sample spot from starting point X 100/÷distance of reference material spot from starting point

We may add here that instead of giving the Rf values it is often better to give Rf values by comparing migration of the substance concerned with that of a simultaneously chromatographed reference substance; this last named material should belong to a same or similar compound class as far as possible.

Apart from the so far discussed problems associated with stardardisation of botanical raw materials a few anomalies have also crept in the HPI which causes concern, for example the synonyms for *Cinchona officinalis* has been stated to be *C. calisaya* or *C. succirubra*. But all these are different species of *Cinchona* and are not synonyms of *Cinchona officinalis*.

Table 6

Standards given in HPI vis-a-vis in other Literatures

Item	HPI	Other literature
Cinchona officinalis	Synonym: *C.calisaya, C.succirubra*	*C. calisaya* & *C. succirubra* are different species Chopra's Glossary of Indian Medicinal Plants, Trease & Evans' Pharmacognosy
Ocimum sanctum	Glandular hair on the leaves are stalkless	Glandular hair are both stalked as well as stalkless Trease & Evans' Pharmacognosy
Rauvolfia serpentina	Length of xylem vessel is 350μ	Length of xylem vessel is about 57μ Trease & Evans' Pharmacognosy
Damiana	Leaf surface is smooth	Leaf surface is pubescent T.E. Wallis' Pharmacognosy
Jaborandi	Leaves contain hair of various nature	Leaves do not have any hair Trease & Evans' Pharmacognosy T.E.Wallis's Pharmacognosy

For identification of *Ocimum sanctum* HPI states that the glandular hair present on the leaves are *stalkless* but actually both *stalked* as well *stalkless* hair are found on the leaves. In the case of *Rauvolfia serpentina* the length of xylem vessels has been stated to be 350 μ but actually those are found to be around 57 μ which corroborates with the figure given in the Textbook of Pharmacognosy by Trease and Evans. For *Damiana* leaves the surface is actually pubescent (i.e. rough and containing hair) but HPI has stated those to be smooth (T.E.Wallis) *Jaborandi* leaves have been stated to contain hair of various nature but actually there is complete absence of hair as per books by T.E. Wallis and by Trease and Evans.

Let us now shift our attention to the chemical compounds to be used as raw material in preparing homoeopathic medicines. Apart from the apparent printing errors a few serious conceptual error has crept in the HPI., e.g. in the Assay for *Arsenicum sulphuratum flavum* or for *Arsenicum sulphuratum rubrum* it has been directed to dissolve the sample in $NaHCO_3$ but neither As_2S_3 nor AS_2S_2 are soluble in $NaHCO_3$ solution and so how the Assay is to be done?

Assay of *Arsenicum sulphuratum flavum* (AS_2S_3)as per H.P.I. Vol.I

Dissolve about 0.5g accurately weighed in 50ml of water to which is added about 2g of sodium bicarbonate. Titrate with.....

Assay of *Arsenicum sulphuratum rubrum* (AS_2S_2)as per H.P.I. Vol. I

Dissolve about 0.5g accurately weighed in 50ml of water to which is added about 2g of sodium bicarbonate. Titrate with.....

Assay of *Antimonium arsenicium* ($SbAsO_4$) as per H.P.I. Vol. I

About 0.5g accurately weighed, is dissolved in 20ml of concentrated nitric acid and an slight excess of an accurately measured volume of neutral *silver nitrate* solution is vigorously stirred in and the precipitate of silver arsenate is allowed to settle in the dark.......

Similarly in the case of *Antimonium arsenicum* ($SbAsO_4$) it has been directed to dissolve the material in concentrated HNO_3 and then to add slight excess of neutral silver nitrate solution to precipitate silver arsenate. But will silver arsenate be precipitated from an acid solution? Or the solution is to be neutralized to get the precipitate. We know that *quinine hydrochloride* is a laevo-rotatory compound, the specific rotation being about - 245° but in HPI Volume 3 it has been described as "dextro-rotatory".

So far we were dealing with the problems of quality control of raw materials to be used for manufacturing homoeopathic preparations but how to establish standards of finished medicines? It is a matter of regret that we are yet to find any method for establishing quality of a potentised preparation above 12 potencies in decimal or so to say 6 potencies in the centesimal scale and that too can be done with mass spectrometric analysis to a limited extent. There are some records of differentiating higher potencies by NMR spectrophotometry but our effort to replicate those experiments failed as no reproducible results were obtained. Very recently two papers appeared in the British Homoeopathic Journal, Vol 90, No. 1, p.5 and p.14 (2001). They also came to the same conclusion that of ours. However the experiment made by W. Boyd may be tried again to find if any clue surfaces by that.

1) Research with modern instruments for the evaluation of Homoeopathic Drug Structure.. R.B. Smith & M.T. Boericke. *J. Am. Inst. Hom.,* 60, 260 (1967)

2) Changes caused by succession on bradykinin triacetate (BKTA) on NMR pattern and bio-assay of BKTA...... G.Boericke & R.B. Smith..... *J. Am. Inst. Hom.*, 61, 197 (1968)

3) Modification of 4MHz NMR Water proton relaxation times in highly diluted aqueous solutions... J.L. Demangeat et.al *Brit. J.Hom.*, 84, 169 (1995)

4) On the investigation of homoeopathic potencies using low resolution NMR T2 relaxation times. L.R. Milgrom et.al *Brit.J.Hom.*, 90, 5 (2001)

5) Nuclear magnetic resonance studies of homoeopathic solutions.... S. Abel et.al..... *Brit. J. Hom.*, 90, 14 (2001)

6) Biochemical & Biological of the activity of high potencies W.E. Boyd.... *Brit. J.Hom.*, 44, 6 (1954)

It is therefore of immense importance that strict control over the process of manufacture of homoeopathic potencies be kept to ensure proper quality.

Though we cannot test higher potencies we definitely can standardise the mother tinctures and low attenuations. In fact HPI has prescribed some standard for mother tinctures and potencies up to 3x. Apart from the standards set by HPI, of which TLC is one major parameter, and I expressed my views over it earlier, I would like to focus attention of the audience on the colour factor especially for the mother tinctures. In many market samples we find that colouring matters have been added to impart darker colour. But addition of any artificial colouring matter is forbidden in Homoeopathy. It is therefore advisable to put a standard on colour of the mother tinctures. Analysis for colour can be done in a very simple way as given in United States Pharmacopoeia 1973. The latest edition of Indian Pharmacopoeia has also adopted similar technique. Here different shades of colours are prepared by mixing solutions of *copper chloride, cobalt chloride* & *ferric chloride*. The test sample is diluted to match any of the shade and shade of the colour thus obtained as well as the dilution required becomes the standard of the colour for the medicine.

For a few mother tinctures like *Symphytum* viscosity of the medicine may also be of importance as standard because of their peculiar nature.

Packing Material

Packaging of homoeopathic medicines is of no less importance in keeping proper standards of medicines. Packing material is here of utmost importance. In no Homoeopathic Pharmacopoeia standard of containers to be used for storage and dispensing of medicines has been given. Selection of proper material for the manufacture of containers to be used in homoeopathic industry is also a critical matter. I show here a comparative study of glass with different polymers which are in use for making containers. Comparative study shows superiority of glass over polymers used.

Table 9

Suitability Experiment for use as Container material

Material	90% Ethanol 50°C, 6 months	50% Ethanol + 10% Oil 50°C, 6 months	50% Ethanol packed in powdered Camphor Below 30°C, 6 months
Glass	No loss	No loss	No presence of Camphor
Polystyrene	2% loss	6% loss	Presence of Camphor
Polyethylene	1% loss	2% loss, material becomes soft	Slight presence of Camphor
Polypropylene	1% loss	2% loss	Slight presence of Camphor
PVC	1% loss	Diffused Vinyl chloride found in the liquid	

Table 10

Materials suitable for Packing & Dispensing Homoeopathic medicines

Glass	Non toxic, inert to most of the chemicals, insoluble in oils & solvents, non porous, easy to clean, sterilisable by heat
Polyvinylchloride (PVC)	Toxic, more soluble in alcohol than other plastics especially in presence of essential oils
Polystyrene	Brittle, porous to some extent, Cracks in presence of oils
Polyethylene(H.D. or L.D.)	Somewhat porous towards oils, attracts dust, very difficult to clean thoroughly
Polypropylene	Slightly better than polyethylene in above respects
PET & Polycarbonate	Not yet tested extensively, small bottles not available commercially

Plasticisers and hardeners are used extensively in the preparation of these Polymers which affect the content of the vessel in many cases. They cannot be sterilised by application of heat as they are very low melting. Almost all plastics attract dust from the atmosphere.

Glass is the most preferred material for packing of medicines in liquid form.

Polyethylenes may be used for packing of medicines in solid form only; but they must be of proper grade which is suitable for food or medicine.