Review Article

Available online through
www.ijrap.net

IJRAP
ISSN 2229-3566

WHO GUIDELINES ON QUALITY CONTROL OF HERBAL MEDICINES

Patel Parthik*, Patel N. M., Patel P. M.
Department of quality assurance, BMCPER, Modasa, India

Received on: 11/06/2011 Revised on: 19/07/2011 Accepted on: 30/07/2011

ABSTRACT

This WHO guidelines present general consideration on potentially hazardous contaminants and residues in herbal medicines and include guiding principles of assessing quality of herbal medicines in terms of major contaminants and residues. It also recommends analytical methods for qualitative and quantitative determination of such contaminants and residues.

Within overall context of quality assurance these guidelines intended to provide general technical guidance to Member state in assessing quality relating to safety of herbal materials and products classified as medicines with regards to major and common contaminants and residues.

The objectives of these guidelines are to provide:

- Guiding principle for assessing the quality in relation to the safety of herbal medicines with specific reference to contaminants and residues
- Model criteria for use in identifying possible contaminants and residues
- Example of methods and techniques and
- Example of practical procedures for controlling the quality of finished herbal products.

The scope of these guidelines does not cover issues of adulteration of herbal medicines and/or counterfeit products.

The annexes to these guidelines present several example of suitable methodologies found in national or regional pharmacopoeias and WHO documents it should be noted that these methods need to be validated for the material that is to be tested and also for each type of instruments.

KEYWORDS: Herbal medicines, WHO guidelines, contamination, residues

***Author for Correspondence**

Patel Parthik Jitubhai, M.Pharm student, Department of quality assurance, BMCPER, Modasa, India
Email: parthik.pharmacist.patel@gmail.com

INTRODUCTION

Because of the increase use of herbal medicine worldwide and herbal products make the global market for their use globally, the safety and quality of medicinal plants and finished herbal products have become a major concern for health authorities, pharmaceuticals and the public.

National regulation and registration of herbal medicines varies from country to country. Where herbal medicines are regulated, they are categorized either as prescription or non prescription medicines. Herbal products categorized other than as medicines and foods, are become increasingly popular and there potential for adverse events due to lack of regulation.

The international conference of Drug Regulatory Authorities (ICDRA) at its 9th, 10th and 11th meetings of the national centers participating in the WHO Drug Monitoring Programme requested WHO to develop and constantly update the technical guidelines on quality safety and efficacy of herbal medicines.[1]

The participants at the WHO informal meeting on methodologies for quality control of finished herbal products, held in Ottawa, Canada, 20-21 july 2001, also reviewed the entire production process of herbal medicines, from raw materials to distribution and supply of finished herbal products. Recommendation from these meetings led to the development of these general guidelines addressing the important issues of safety and quality of herbal medicines with special reference to contaminants and residues.

Objectives

Within the overall context of quality assurance, these guidelines are primarily intended to provide general technical guidance to Member State in the assessment of

quality related to safety of herbal medicines with regard to both major and common contaminants and residues. These guidelines may need to be adjusted according to each country's situation

The objectives of these guidelines are to provide:

- Guiding principle for assessing the quality in relation to the safety of herbal medicines with specific reference to contaminants and residues
- Model criteria for use in identifying possible contaminants and residues
- Example of methods and techniques and
- Example of practical procedures for controlling the quality of finished herbal products.

In the pursuit of the above-mentioned objectives, these guidelines should be read together with the other WHO documents and publications (including future versions) relating to the quality assurance of herbal medicines with regard to safety, for example (for details see reference list):

- ✓ Quality control methods for medicinal plant material.[2]
- ✓ Good agricultural and collection practices (GACP) for medicinal plants.[3]
- ✓ International pharmacopoeia, 4th ed.[4,5]
- ✓ Good manufacturing practices: main principles for pharmaceutical products.[6]
- ✓ Good manufacturing practices: supplementary guidelines for the manufacture of herbal medicinal products.[7]
- ✓ Guide to good storage practices for pharmaceuticals.[8]
- ✓ Good trade and distribution practices (GTDP) for pharmaceutical starting materials.9
- ✓ General guidelines for methodologies on research and evaluation of traditional medicine.[10]
- ✓ Guidelines for assessment of herbal medicines.[11]
- ✓ WHO monographs on selected medicinal plants.[12,13]
- ✓ Codex Alimentarius code of practice, general principles of food hygiene.[14]
- ✓ Codex Alimentarius guidelines for the production, processing, labeling and marketing of organically produced foods.[15]
- ✓ Codex Alimentarius code of practice for spices and dried aromatic plants.[16]

Important terms

Relating to the herbal medicines

The terms and their definitions have been selected and adopted from other WHO documents and guidelines that are widely used by WHO Member States. Definitions of the terms may differ from those adopted in regulations and/or in common usage in some Member States. However, one of the purposes of these definitions is to provide consistency in terminology with other relevant WHO documents in this field, such as the WHO General guidelines for methodologies on research and evaluation *of* traditional medicine and WHO Good manufacturing practices. It should also be noted that these definitions have been developed to meet the demand for the establishment of standard, internationally acceptable definitions to be used in the evaluation and research of herbal medicines.[10]

Herbal medicines: These include herbs, herbal materials, herbal preparations and finished herbal products.[10]

Herbs: Herbs include crude plant material such as leaves, flowers, fruit, seeds, stems, wood, bark, roots, rhizomes or other plant parts, which may be entire, fragmented or powdered.[10]

Herbal materials: Herbal materials are either whole plants or parts of medicinal plants in the crude state. They include herbs, fresh juices, gums, fixed oils, essential oils, resins and dry powders of herbs. In some countries, these materials may be processed by various local procedures, such as steaming, roasting, or stir baking with honey, alcoholic beverages or other materials.[10]

Herbal preparations: Herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils, expressed juices and processed exudates of herbal materials. They are produced with the aid of extraction, distillation, expression, fractionation, purification, concentration, fermentation or other physical or biological processes. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials.[10]

Finished herbal products: Medicinal products containing as active substances exclusively herbal drugs or herbal drug preparations. They may consist of herbal preparations made from one or more herbs. If more than one herb is used, the term mixed herbal product can also be used. They may contain excipients in addition to the active ingredients. In some countries herbal medicines may contain, by tradition, natural organic or inorganic active ingredients, which are not of plant origin (e.g. animal materials and mineral materials). Generally however, finished products or mixed products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal.[10]

Medicinal plants: A plant, either growing wild or cultivated, used for its medicinal purposes.[7]

Relating to the contaminants and residues in herbal medicines:

In general the following terms and their explanations as they relate to contaminants and residues in herbal medicines have been adopted verbatim or where necessary adapted from the definitions for pesticide residues in foods, developed by the Codex Alimentarius Commissio and the Joint FAO/WHO Meeting on Pesticide Residues. Thus when Member States consider the terms relevant to their individual needs, these documents should be consulted. The reason for this suggestion is that in future the Joint FAO/WHO Meetings on Pesticide Residues(JMPR) will probably continue as the group mandated to evaluate the safety of pesticides and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) for contaminants in herbal medicines and in foods.

Contamination: The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a starting material, intermediate product or
Finished herbal product during production, sampling, packaging or repackaging,
Storage or transport.[6]

Cross-contamination: The contamination of a starting material, intermediate product or finished product with another starting material or product during production.[6]

Foreign matter: Material consisting of any or all of the following:

- parts of the medicinal plant material or materials other than those named with the limits specified for the plant material concerned;
- any organism, part or product of an organism, other than that named in the and description of the plant material concerned;
- mineral admixtures such as soil, stones, sand, and dust; and glass, metal and plastics or any other extraneous materials. These may be loose or adhering to these medicinal plant material.[2]

Acceptable daily intake (ADI) of a chemical: A daily intake, which, during an entire lifetime, appears to be without appreciable risk to the health of the consumer, on the basis of all the known facts at the time of the evaluation of the chemical by the Joint FAO/WHO Meeting on Pesticide Residues. It is expressed in milligrams of the chemical per kilogram of body weight.[21]

Acceptable residual level (ARL): The ARL is given in mg of pesticide per kg of medicinal plant material and can be calculated from the maximum acceptable daily intake (ADI) of the pesticide for humans, as recommended by FAO and WHO, and the mean daily intake (MDI) of
the medicinal plant material.[21]

Acute reference dose (ARD): ARD is the amount of pesticide to which a person is exposed, usually, at one day's regimen of herbal medicines and which results in acute effects on the human body. ARD estimations include a safety factor to ensure that the elderly, infants, children and those whose systems are under stress because of illness, are protected.[21]

Extraneous maximum residue limits (EMRL): Apesticide residue or a contaminant arising from environmental sources (including former agricultural uses) other than the use of a pesticide or contaminant substance directly or indirectly on the herbal medicine. The concentration is expressed in milligrams of pesticide residue or contaminant per kilogram of the herbal medicine.[21]

Maximum Residual limit (MRL): The MRL is the maximum concentration of a pesticide residue (expressed as mg/ kg) recommended by the Codex Alimentarius Commission to be legally permitted (in food commodities and animal feeds). MRLs are based on good agricultural practices (GAP) data established for foods, and foods derived from commodities that comply with the respective MRLs are intended to be toxicologically acceptable.[21]

Permitted daily exposure: The term "permitted daily exposure" (PDE) is defined, in the ICH guidelines, as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing ADIs for the same substance.[22]

Pesticides: For the purpose of these guidelines, pesticides are defined as any substance intended for preventing, destroying, attracting, repelling, or controlling any pest including unwanted species of plants or animals during production, storage, transport, distribution and processing. The term includes substances intended for use as a plant-growth regulator, defoliant, desiccant, fruit thinning agent, or sprouting inhibitor and substances applied to crops either before or after harvest to protect the commodity from deterioration during storage and transport. The term normally excludes fertilizers and plant nutrients.[21]

Pesticides residue: Pesticide residues are any specified substance in food, agricultural commodities or animal feed resulting from the use of a pesticide. The term includes any derivatives of a pesticide, such as conversion products, metabolites, reaction products and impurities considered to be of toxicological significance.[21]

Persistent organic pollutants (POPs): Persistent organic pollutants (POPs) are chemical substances that persist in the environment, bioaccumulate through the food web and pose a risk of causing adverse effects to human health and the environment. With the evidence of long- range transport of these substances to regions where they have never been used or produced and the consequent threats they pose to the environment of the whole globe, the international community has, on several occasions, called for urgent global action to reduce and eliminate releases of these chemicals.

Tolerable intake: Tolerable intake is defined as an estimate of the intake of a substance over a lifetime that is considered to be without appreciable health risk.[23]

Residue solvents: These are residues of organic solvents that are used or produced in the manufacture of and processing of herbal preparations/products. Solvents are classified by the ICH (CPMP/ICH 283/95) according to their potential risk into:

- class 1 (solvents to be avoided such as benzene);
- class 2 (limited toxic potential such as methanol or hexane); and
- class 3 (low toxic potential such as ethanol).

Guidelines for assessing safety of herbal medicines with reference to contaminants and residue

Determination of arsenic and toxic metals

In general, quantitative tests and limit tests accurately determine the concentrations of toxic metals in the form of impurities and contaminants. The latter are unavoidably present in the samples being tested i.e. herbal medicines and their herbal products.[34] See Table no. 2

In general, if the heavy metals burden of the herbal material is unknown, it is suggested that it be determined qualitatively and quantitatively on several batches preferably collected over several years. These data should be used to establish acceptance limits that should be checked by appropriate limit tests.[32]

Determination of radioactive contaminants

Method of measurement

Following a severe nuclear accident, the environment may be contaminated with airborne radioactive materials. These may deposit on the plants. Their activity concentration and the type of radioactive contamination can Leaves of medicinal plants. Their activity concentration and the type of radioactive contamination can be measured by the radiation monitoring laboratories of most of the WHO Member States. The activity concentration of radioisotopes in herbs should be assessed by The competent national radio hygiene laboratories taking into account the relevant International Atomic Energy Agency (IAEA), FAO and WHO. Since radionuclide's from accidental discharges vary with the type of facility involved, a generalized method of measurement is not yet available. However, should such contamination be a concern, suspect samples can be analysed by a competent laboratory. Details of laboratory techniques are available from the IAEA.[32]

Determination of aflatoxins

Determination of aflatoxins should take place after using a suitable clean-up procedure, during which great care should be taken not to become exposed or to expose the working or general environment to these dangerous and toxic substances. Thus Member States should adapt their good practices for national pharmaceutical control laboratories and GMP accordingly. Only products that have a history of aflatoxin contamination need to be tested.

There are specific sampling problems especially of aflatoxins due to the way in which contamination spreads, as described for some food commodities, such as nuts and corn. This may need to be taken into consideration when sampling, for example in terms of sample selection and sample size, and when the analysis is made.

Tests for aflatoxins are designed to detect the possible presence of aflatoxins B , B , G and G , which are highly toxic contaminants in any material of plant origin.

Some examples of proposed national limits for aflatoxin in various types of herbal products are presented in Box 1 below. Country figures are based on information provided by national health authorities.[33]

Determination of microbiological contaminants

Microbial contamination limits in herbal materials, preparation and finished products

Differential limits are set according to the intended use of herbal material and the medicines themselves. Some example are given here.[34]

Raw medicinal plant and herbal materials intended for further processing

For contamination of raw medicinal plant, and herbal materials intended for further processing (including additional decontamination by a physical or chemical process) the limits, adapted from the provisional guidelines established by an international consultative group (35), are given for untreated herbal material harvested under acceptable hygienic conditions:

- Escherichia coli, maximum 10^4 per gram
- mould propagules, maximum 10^5 per gram
- shigella, absence per gram or ml.

Herbal materials that have been pretreated

For herbal materials that have been pretreated (e.g. with

boiling water as used for herbal teas and infusions) or that are used as topical dosage forms, the limits are:

- aerobic bacteria, maximum 10^7 per gram
- yeasts and moulds, maximum 10^4 per gram
- Escherichia coli, maximum 10^2 per gram
- other enterobacteria, maximum 10^4 per gram
- clostridia, absence per 1 gram
- salmonellae, absence per 1 gram
- shigella, absence per 1 gram.

Other herbal materials for internal use

For other herbal materials for internal use, the limits are:

- aerobic bacteria, maximum 10^5 per gram
- yeasts and moulds, maximum 10^3 per gram
- Escherichia coli, maximum 10 per gram
- other enterobacteria, maximum 10^3 per gram
- clostridia, absence per 1 gram
- salmonellae, absence per 1 gram
- shigella, absence per 1 gram.

Herbal medicines to which boiling water is added before use

For herbal medicines to which boiling water is added before use, the limits are:

- aerobic bacteria, maximum 10^7 per gram
- yeasts and moulds, maximum 10^4 per gram
- Escherichia coli, maximum 10 per gram
- other enterobacteria, maximum 10^3 per gram
- clostridia, absence per 1 gram
- salmonellae, absence per 1 gram
- shigella, absence per 1 gram.

Other herbal medicines

For other herbal medicines, the limits are:

- aerobic bacteria, maximum 10^5 per gram
- yeasts and moulds, maximum 10^3 per gram
- Escherichia coli, absence per 1 gram
- other enterobacteria, maximum 10^3 per gram
- clostridia, absence per 1 gram[34]

REFERENCES

1. WHO Traditional Medicine Strategy: 2002–2005. Geneva, World Health Organization, 2002 (WHO/EDM/TRM/2002.1).
2. Quality control methods for medicinal plant materials. Geneva, World Health Organization, 1998.
3. WHO guidelines on good agricultural and field collection practices (GACP) for medicinal plants. Geneva, World Health Organization, 2003.
4. International pharmacopoeia, 4th ed., Vol. 1. Geneva, World Health Organization, 2006.
5. International pharmacopoeia, 4th ed., Vol. 2. Geneva, World Health Organization, 2006.
6. Good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908) Annex 4. (These guidelines are also included in Quality assurance of pharmaceuticals: a compendium of guidelines and related materials, Vol. 2, 2nd updated ed.: good manufacturing practices and inspection. Geneva, World Health Organization, 2007.) (These guidelines are also extracted and published as: WHO guidelines for Good Manufacturing Practices (GMP) for herbal medicines. Geneva, World Health Organization, 2007.)
7. Good manufacturing practices: updated supplementary guidelines for manufacture of herbal medicines. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937) Annex 3. (These guidelines are also included in Quality assurance of pharmaceuticals: a compendium of guidelines and related materials, Vol. 2, 2nd updated ed.: good manufacturing practices and inspection. Geneva, World Health Organization, 2007.) (These guidelines are also extracted and published as: WHO guidelines for Good Manufacturing Practices (GMP) for herbal medicines. Geneva, World Health Organization, 2007.)
8. Guide to good storage practices for pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-seventh report. Geneva, World Health Organization, 2003 (WHO Technical Report Series, No. 908) Annex 9.
9. Good trade and distribution practices for pharmaceutical starting materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 917) Annex 2.
10. General guidelines for methodologies on research and evaluation of traditional medicine. Geneva, World Health Organization, 2000 (WHO/EDM/TRM/2000.1).
11. Guidelines for assessment of herbal medicines. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-fourth report. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 863) Annex 11. (These guidelines are also included in Quality assurance of pharmaceuticals: a compendium of guidelines and related materials, Vol. 1. Geneva, World Health Organization, 1997.)
12. WHO monographs on selected medicinal plants, Vol. 1. Geneva, World Health Organization, 1999.
13. WHO monographs on selected medicinal plants, Vol. 2. Geneva, World Health Organization, 2002.
14. Codex Alimentarius Code of Practice, general principles of food hygiene, 2nd ed. Rome, Joint FAO/WHO Food Standards Programme, 2001 (document Codex Alimentarius GL 33).
15. Codex Alimentarius Guidelines for the production, processing, labelling and marketing of organically produced food. Rome, Joint FAO/WHO Food Standards Programme, 2001 (Codex Alimentarius GL 32, Rev. 1).
16. Codex Alimentarius Code for hygienic practice for spices and dried aromatic plants. Rome, Joint FAO/WHO Food Standards Programme, 1995 (Codex Alimentarius CAC/RCP 42).
17. Control and safe trade of starting materials for pharmaceutical products. Geneva, World Health Organization (http://www.who.int/medicines/publications/

qa_starter/en/index.html).
18. WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-eighth report. Geneva, World Health Organization, 2004(WHO Technical Report Series, No. 917) Annex 3.
19. Good distribution practices for pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937) Annex 5.
20. WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation. Report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations. Geneva, World Health Organization, 2004 (WHO Technical Report Series, No. 917 (http://www.who.int/medicines/areas/quality_safety/regulation_legislation/certification/en/index.html).
21. Pesticide residues in food – methods of analysis and sampling. Codex Alimentarius. Vol. 2A, Part 1, 2nd ed. Rome, Joint FAO/WHO Food Standards Programme, 2000.
22. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized TripartiteGuideline, Impurities: Guidelines for Residual Solvents (Q3C (R3)) (http://www.ich.org/cache/compo/363-272-1.html#Q3C).
23. International Programme on Chemical Safety. Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits. Geneva, World Health Organization, 1994. (Environmental Health Criteria 170.)
24. Facts about low-level radiation. Vienna, International Atomic Energy Agency, 1986.
25. Derived intervention levels for radionuclides in food. Guidelines for application after widespread radioactive contamination resulting from a major radiation accident. Geneva, World Health Organization, 1988.
26. Codex Alimentarius Commission. Guide. Codex maximum limits for pesticide residues, Part 2, April 1992. Rome, Food and Agriculture Organization of the United Nations, 1992 (unpublished FAO document CX/PR2-1992; available in hard copy and electronic format from FAO).
27. IARC Working Group, International Agency for Research on Cancer (IARC). Some naturally occurring substances: food items and constituents. IARC monographs on the evaluation of carcinogenic risk to humans. Vol. 56, Lyon, France, World Health Organization, 1993.
28. Public health impact of pesticides used in agriculture. Geneva, World Health Organization, 1990.
29. Official herbicide recommendations for vegetable crops, herbs and medicinal plants. The Hague, International Society for Horticultural Science, 1981.
30. Good practices for national pharmaceutical control laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902).
31. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902). Commission, 28th Session, July, 2005. Rome, Food and Agriculture Organization of the United Nations, 2005 (http://www.codexalimentarius.net/download/report/644/al28_41e.pdf).
32. NIS International Draft Standard (Draft Standard NSF 173-2001). Ann Arbor, Michigan, National Sanitation Foundation International, 2001.
33. Sampling plans for aflatoxin analysis in peanuts and corn. Rome, Food and Agriculture Organization of the United Nations, 1993 (FAO Food and Nutrition Paper 55).
34. Commission Directive 98/53/EC of 16 July 1998, European Commission, 1998 .

Table:1 Contaminants and residue in herbal in medicine

Contaminents:					
General classification	**Group**	**Sub group**	**Specific example**	**Possible sources**	**Stages of production at which detectable***
Chemical contaminants:	Toxic and hazardous materials:	Toxic metals & non metals	Lead, cadmium, mercury, chromium	Polluted soil & water during cultivation growth, mfg process	1,2,3,4
		Persistent org.pollutants	Dioxin aldrin, chlordane	Polluted air soil and water	1,2,3,4
		Radionuclide	Cs-134, Cs-137	Air, soil, water during cultivation	1,2,3,4
		Biological toxins	Mycotoxins	harvest process transportation & storage	2,3,4
			Bacterial endotoxins	"	1,2,3,4
Biological contaminants:	Micro-organism	Becteria	S.aureous P.aeruginosa E.coli Shigella & salmonella sp.	Soil, post harvest process transportation & storage	1,2,3,4
		Fungi	Yeast, moulds	"	1,2,3,4
	Animals	Parasites	Protozoa, amoebae, helminthes	Soil, excreta; organic farming; / cultivation mfg process	1,3,4
		Insects	Cockroach & its part	post harvest process transportation & storage	1,2,4
		Other	Mouse excreta earthworms, acarus	"	1,2,4
Solvents:		Org. solvents	Acetone, methanol, ethanol, butanol	Soil & water during cultivation / growth mfg process	1,2,3,4

Residues:					
General classification	**Group**	**Subgroup**	**Specific example**	**Possible source**	**Stages of production at which detectable***
Agrochemical residues	Pesticides	Insecticides	Carbamate, chlorinated, hydrocarbon, organophosphorous	Air, soil, water during cultivation/ growth post harvest process	1,2,3,4
		Herbicides	2,4-D, 2,4,5-T	Air, soil, water during cultivation/ growth post harvest process	1,2,3,4
		Fungicides	dithiocarbamate	Air, soil, water during cultivation/ growth	1,2,3,4
	Fumigants	Chemical agents	Ethylene oxide, phosphine, methyl bromide, sulfur dioxide	Post harvest process	2,3,4
	Disease control agents	Antiviral agents	Thiamethoxam	During cultivation	1,2,3,4
Residual solvents		Org. solvents	Acetone, methanol, ethanol, butanol	Mfg process	3,4

*Stages of production at which detectable: 1- medicinal plants; 2- herbal plants; 3-finished herbal products.[3]

Table:2 example of national limits for arsenic and toxic metals in herbal medicines and products

		Arsenic (As)	**Lead (Pb)**	**Cadmium (Cd)**	**Chromium (Cr)**	**Mercury (Hg)**	**Copper (cu)**	**Total toxic metals as lead**
For herbal medicines:								
Canada	Herbal material	5 ppm	10 ppm	0.3 ppm	2 ppm	0.2 ppm		
	Finished products	0.01 mg/day	0.02 mg/day	0.06 mg/day	0.02 mg/day	0.02 mg/day		
China	Herbal materials	2 ppm	10 ppm	1 ppm		0.5 ppm		20 ppm
Malaysia	Finished herbal products	5 mg/kg	10 mg/kg			0.5 mg/kg		
Thailand	Herbal material	4 ppm	10 ppm	0.3 ppm				
WHO recommendation			10mg/kg	0.3 mg/kg				
For other herbal products:								
National Sanitation Foundation Draft Proposal(raw dietary supplements)		5 ppm	10 ppm	0.3 ppm	2 ppm			
National Sanitation Foundation Draft Proposal(finished dietary splmnts)		0.01 mg/daily	0.02 mg/day	0.006 mg/day	0.03 mg/day	0.02 mg/day		

Source of support: Nil, Conflict of interest: None Declared