NHPD Monograph Consultation: Traditional Chinese Medicine Ingredients

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NHPD Consultation Submission on

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Bad Science Watch

Bad Science Watch is an independent Canadian consumer protection organization dedicated to promoting good science in public policy.

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Overview

This is a submission as part of the public comment process for the monograph entitled "Traditional Chinese Medicine Ingredients (TCMI)". We have serious concerns about this monograph and would suggest that Health Canada re-evaluate its approach to the licensure of TCMIs.

Overall, the approach of including close to 400 ingredients in this list is confusing and flawed. Given the great variety in the safety and quality of evidence and risk assessment of the individual ingredients, they each deserve their own monograph. As noted below, there are a number of inherent weaknesses in the monograph, thus it is unclear how this monograph would help any manufacturer prepare a Product License Application (PLA) for evaluation by Health Canada. Each individual ingredient will require its own treatment concerning evidence for efficacy and risk assessment. Finally, given the well documented problem of serious adulterations, contaminations and misidentification of TCMIs, we feel it is irresponsible for Health Canada to fast track any evaluation of TCMIs for market and there needs to be a standardized quality control process to ensure that these products are pure and do not constitute a risk to the Canadian consumer. It is unclear if this document is meant to fast track these items, therefore this needs to be clarified in the document.

It cannot be stressed enough that the one-month window for public consultation was far too brief for a list as comprehensive as that provided in tables 1 through 4. This suggests either an attempt by Health Canada to willfully mislead the public by making it impossible to evaluate every ingredient on the list, or that Health Canada is seeking to abrogate its responsibility to properly evaluate the risks and benefits as set out in the mandate of the Natural Health Products Directorate. Either way, this process is seriously flawed.

General Problems with TCM: Adulterations, Contaminations, Mistaken Identity

Health Canada, in the production of this monograph, has ignored known problems with the general safety and quality of TCM products. This constitutes a danger to the public if left unaddressed. We have summarized these problems below:

- There has been an ongoing problem with adulterants, contaminants, and misidentified ingredients in TCMIs:
    - Eighteen case reports, two case series, and four analytical reviews found evidence of adulterations. The list of adulterants identified included many with serious adverse effects and several instances in which patients were seriously harmed (Ernst, E., 2002)
    - A report from Taiwan suggests 24% of samples were contaminated with at least one conventional pharmaceutical (Huang et al. , 1997)
    - Haneef et al. (2013) highlights the new analytical tools needed to evaluate TCMs due to the high rates of contaminations, including undeclared drugs.
    - Coghlan et al. (2012), found evidence of adulteration with synthetic drugs and the presence of endangered animals in TCMIs. Ellis (2005) in his book “Tiger Bone and Rhino Horn” lays out the evidence for the trade in endangered species and its connection to TCMIs.
    - Misidentification and substitution are a serious concern, according to Wu et al. (2007)
    - Toxic heavy metals were found in some Asian medicinal preps (Ernst, 2002)
    - Posadzki , Watson , and Ernst (2013) concluded that based on an overview of 26 systematic reviews there was evidence of serious adverse health effects and reason for concern over the quality of these remedies.

The technology exists for standardized testing of TCMIs for adulterations and contaminants (Chen et al. , 2009, Haneef et al. 2013, Li and Reich, 2009, Lui et al. , 2001). Additionally, there is evidence that TCMIs are associated with higher rates of cancer (Chen et al. , 2012) and that TCMIs alter drug-metabolizing enzymes in the liver (Nose et al. , 2003). This evidence suggests that Health Canada should demand a more rigorous risk evaluation as a part of the PLA application process. TCMIs are neither benign nor inherently safe.

Recommendation:

As a requirement for licensure and to protect the public, Health Canada should mandate all TCMIs undergo standardized quality control testing and show definitive evidence for the purity of the products.

Individual Problems With Monograph

We found a number of problems in the monograph that must be addressed:

1. **"This monograph is intended to serve as a guide to industry for the preparation of Product License Applications (PLAs) and labels for natural health product market authorization. It is not intended to be a comprehensive review of the medicinal ingredient."**

This statement demonstrates that this monograph is in fact overly general in its treatment of TCMIs. Each single entity or blended product should have a comprehensive monograph that is truly useful for consumers, healthcare providers and their patients. The absurdity of this monograph can be easily illustrated with an analogy to pharmaceuticals. This analogy would have all of the prescription drugs used in mainstream medicine have the indication "to be used in the framework of orthodox medicine". This would obviously be seen as woefully inadequate to help with the approval of any pharmaceutical. While we understand that this monograph does not replace the PLA process, it seems to give some botanicals an easier ride on the path to licensure than others.

Recommendations:

1.1 The monograph should clearly state that a TCMI must provide a comprehensive review of efficacy for specific indications and report all known or perceived risks, as a minimum standard for licensure.

2. **Tables 1-4 in Appendix 1**

While there are risks with individual products (see below), risk can increase with multi blended products, in which case more risk evaluation is required. This is not clearly stated in the document.

We have found evidence that Table 4 is incomplete (see individual ingredient assessments in the following section). As well, as it is unclear exactly what Table 4 means, we offer new language that should be included in the preamble to Table 4.

Recommendations:

2.1 Require additional risk assessments for blended products that include testing of the combined ingredients, not just assessments for the individual ingredients.

2.2 A more comprehensive risk review must take place to ensure a complete list of high-risk products in Table 4.

2.3 New language should be included in Table 4, such as the following: “the following medicinal ingredients have been evaluated and are excluded from this monograph. The absence of a substance or ingredient from this list does not automatically allow for its licensure or consideration of a submission.”

3. **Proper name(s) and Common name(s)**

There is no explicit requirement that Latin binomial names are to be used to identify ingredients. Due to the risk for misidentification and mischaracterization of common names, the omission of Latin binomial names could cause confusion.

Recommendations:

3.1 The monograph should explicitly require the use of Latin binomials to identify the botanical ingredients in TCMIs.

4. **“Unacceptable Combinations: Ingredients from Table 2 (Appendix I) with stimulant laxative properties may not be combined with the medicinal ingredient Gan cao (/Glycyrrhiza glabra, G. inflata, G. uralensis/).”**

There is no reasoning provided for this. One possible reason for the exclusion of the combination of the Glycyrrhiza species with other stimulant laxatives is that these botanicals have been linked to inhibitory action towards the cytochrome P450 family of isozymes. If this is indeed the rationale, there are many other botanicals that need to be considered for inclusion on this list. The lack of detailed information in this section, as well as the omission of other botanicals that also present significant risks to human health, demonstrates the inadequacy of the risk review undertaken by Health Canada.

Recommendations:

4.1 The inclusion criteria and rationale for unacceptable combinations must be included in the monograph.

4.2 A comprehensive review of multi-ingredient products needs to be undertaken to have a complete list of unacceptable combinations.

5. "**Ingredients indicated as mutually incompatible or antagonistic in the referenced texts should not be combined."**

This is far too general a statement for a monograph of this kind and does not go far enough to ensure that antagonistic combinations should be avoided.

Recommendations:

5.1 The monograph should fully recognize and identify the current published literature on known or suspected interactions with any drug, other natural health products, food or lab tests, and its effects on diseases and conditions.

6. "**When the reference dosage is for a powder, the ingredient may be present as a powder or the dose must be extrapolated for a hydroethanolic extract."**

If hydroethanolic extraction is not a traditional method of preparation, the extrapolation may be unwarranted and present a risk not previously associated with the traditional preparation.

Recommendations:

6.1 Hydroethanolic extraction should not be included as a traditional method of preparation and should be subject to specific product testing for efficacy and harm.

7. **Recommended conditions of use**

Given that the list comprised almost 400 different ingredients, this section is far too brief. By deferring to the TCM texts in the reference section, Health Canada is abrogating its responsibility to ensure that the information they provide is accurate and up to date and that all of the information is backed by rigorous scientific studies. This would only be possible by having monographs for each individual ingredient. As well, to ensure that the monograph accurately and impartially reflects the current state of scientific evidence for each ingredient there must be a section that details what clinical trials have been done to establish safety and efficacy, the populations (age, gender, ethnicity etc.) studied, the number of subjects, the length of study, and any negative findings.

Recommendations:

7.1 Each ingredient on this list should have its own monograph that reflects the assessment done by Health Canada, not possibly biased textbook authors.

7.2 Each monograph should have scientific evidence for the approved conditions of use.

8. **"For prolonged use, consult a healthcare practitioner"**

There is no definition of "prolonged-use" in this section.

Recommendations:

8.1 The monograph must have a definition of prolonged use.

9. **"If you are taking prescription medications consult a healthcare practitioner before use"**

This statement does not adequately reflect the fact that dangerous interactions are known to occur between different natural health products as well as with prescription drugs.

Recommendations:

9.1 This section should read "if you are taking prescription medications *or other natural health products,* consult a healthcare practitioner before use"

10. **Contraindications: "If you are pregnant or breastfeeding, do not use this product."**

Given that the list includes almost 400 ingredients, this section is woefully inadequate. Health Canada admits that combination products have a known risk. It is therefore possible for a user to be taking more than one individual product, or have the products combined at a traditional dispensary. It is therefore necessary to have per-ingredient evaluations of specific contraindications.

Recommendations:

10.1 All ingredients should have their own monograph with specific contraindications listed.

11. **Referenced Texts**

The referenced texts are publications that have no obligation to provide balanced and impartial information, and therefore may not reflect the current evidence for efficacy and risks associated with

TCM medications. There are no scientific publications listed and the monograph could be read to imply that that only these references are required; this may miss important risk or efficacy information in the scientific literature. As well, the absence of scientific evidence should not be interpreted as meaning the botanical is “safe”.

Recommendations:

11.1 Individual monographs are necessary to fully and impartially convey essential information about the individual ingredients.

11.2 The monograph must include the scientific evidence for the choices of categorization of the individual ingredients into tables 1 through 4. Their risks should be included as well.

12. **Appendix I**

This appendix gives an incomplete picture of the risks of TCM botanicals. Some of these botanical species or closely related species present inherent risks or, when combined with a drug, could render them unsafe for use.

Recommendations:

12.1 All health products subject to Health Canada review should meet the same standard of acceptable risk, and those that do not should not be approved for market authorization

Specific Problems with Ingredient Lists

The very short time frame provided for public comments on the 400 products in this list has prevented us from performing more than a cursory review. Nonetheless, even a brief check of the literature for known problems with hepatotoxicity identified and matched products that the NHPD had included here as low risk. Health Canada must provide a more critical appraisal of these products as the current approach is clearly inadequate.

While we mainly investigated hepatotoxicity, there may well be other risks imposed by individual or combined ingredients as suggested by Bagnis et al. (2004). This list below is a sample only.

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Recommendations:

13.1 The four tables of ingredients must undergo much greater scrutiny by Health Canada before inclusion in this or any monograph.

Table 1: General Medicinal Ingredients

The following ingredients' inclusion in Table 1 should be reconsidered due to evidence of hepatotoxicity risk (citation at end of ingredient name) or for the reasons noted below:

***Angelica dahurica* - Bai zhi - Radix Angelicae Dahuricae**
***Angelica pubescens* - Du huo - Radix Angelicae Pubescentis**
***Angelica sinensis* - Dang gui - Radix Angelicae Sinensis**
A. dahurica can be a source of furanocoumarin derivatives (Saruwatari et al., 2014)

***Areca catechu* - Da fu pi - Pericarpium Arecae**
Listed as Bing Lang in the restricted list in the Association of Traditional Chinese Medicine (ATCM) as being too toxic for oral ingestion. Should be in Table 4. (ATCM, 2010)

***Bupleurum chinese* - Chai hu- Radix Bupleuri (Lv et al., 2009)**
***Bupleurum scorzonerifolium* - Chai hu -Radix Bupleuri**
These species can cause changes in the metabolism of certain drugs (Nose et al., 2003). The first botanical has saponins that are associated with hepatotoxicity, and it is therefore likely that the second related species is also associated with hepatotoxicity (Huang et al., 2010).

***Citrus aurantium* - Zhi shi - Fructus Aurantii Immaturus**
***Citrus aurantium* - Zhi qiao - Zhi ke - Fructus Aurantii** (Teschke et al., 2012)

***Gardenia jasminoides*- Zhi zi- Fructus Gardeniae** (Ding et al. 2012)

***Dioscorea oppositifolia* - Shan yao - Rhizoma Dioscoreae** (Xu et al., 2011)
This species can be confused/substituted for D. Bulbifera which has been associated with hepatotoxicity (Wang J et al., 2010).

***Lycopodium japonicum* - Shen jin cao - Herba Lycopodii**
This species can be confused/substituted with *L. serratum* which has been associated with hepatotoxicity (Teschke et al., 2012).

***Melia azedarach* - Ku lian p i- Cortex Meliae**
This species can be confused/substituted with *M. toosendon* that has been associated with

hepatotoxicity (Teschke et al., 2012).

***Morinda officinalis*- Ba ji tian- Radix Morindae Officinalis**
This species can be confused/substituted with *M. citrifolium* that has been associated with hepatotoxicity (Teschke et al., 2012)

***Paris polyphylla* - Chong lou - Rhizoma Paridis**
Considered toxic or slightly toxic by the Association of Traditional Chinese Medicine (ATCM, 2010) and should be in table 3.

***Scutellaria baicalensi* - Huang qin - Radix Scutellariae** (Yang et al., 2012)

***Coptis chinensis*- Huang lian- Rhizoma Coptidis**
***Coptis deltoidea*- Huang lian- Rhizoma Coptidis**
***Coptis teeta*- Huang lian- Rhizoma Coptidis**
Reported hERG inhibition leading to QTc prolongation (Schramm et al., 2011)

***Pinellia ternata* - Fa ban xia; Zhi ban xia - Rhizoma Pinelliae Preparatum**
***Pinellia ternata* - Qing ban xia - Rhizoma Pinelliae Preparatum cum Alumine**
***Pinellia ternata* - Jiang ban xia - Rhizoma Pinelliae Preparatum cum Zingibere et Alumina**
Extracts may have cardiac toxicity in rats (Zhang et al., 2013). Considered toxic or slightly toxic by the ATCM (ATCM, 2010) and should be in Table 3.

Table 2: Medicinal Ingredients with diuretic or stimulant laxative Properties.

The following ingredients' inclusion in Table 2 should be reconsidered due to evidence of hepatotoxicity risk (citation at end of ingredient name) or for the reasons noted below:

***Polygonum aviculare* - Bian xu - Herba Polygoni Avicularis**
P. multiforum has been associated with hepatotoxicity (Dong et al., 2014). This species may be confused/substituted for the above species. Its use is more common than the above species.

***Sophora flavescens* - Ku shen - Radix Sophorae Flavescentis**
This species be confused/substituted for *S. Tonkinensis* which has been associated with hepatotoxicity (Li et al., 2011).
Prenylflavanones in this botanical associated with hepatotoxicity (Yu et al., 2013)

***Stephania tetrandra*- Fang ji Radix- Stephaniae Tetrandrae**
This species be confused/substituted with *S. sinica* which has been associated with hepatotoxicity (Teschke et al., 2012).

***Aloe vera*- Lu hui- Aloe** (Teschke et al., 2012)
Aloe ferox- Lu hui- Aloe (Teschke et al., 2012)

Table 3: Medicinal Ingredients that are only allowable when prepared according to the specifications outlined in the NHPID.

The following ingredients' inclusion in Table 3 should be reconsidered due to suspected or confirmed toxicity as noted below by species**.**

***Aconitum carmichaeli* - Chuan wu - Radix Aconiti**
Overdose of powdered Aconiti is common and can have serious cardiac side-effects (Chan, 2012)

***Xanthium sibiricum* - Shen qu - Massa Medicata Fermentata**
***Xanthium sibiricum* - Cang er z i-Fructus Xanthii**
Studies associate *X. strumarium* with hepatotoxicity which is a danger due to mistaken substitution (Xue et al., 2014) and (Wang Y et al., 2011).

***Monascus purpurea* - fermented /Oryza sativa - Hong qu - Red Yeast Rice**
Therapeutic Products Directorate Health Hazard Evaluation determined that this botanical may contain lovastatin, and other secondary metabolites which may be carcinogenic and/or teratogenic. This product has serious risks that are greater than any benefit. Hence this entity should be listed in table 4, particularly if the US FDA has not revised their ban on this material (FDA, 2007).

Table 4: The following medicinal ingredients have been evaluated and are excluded from this monograph.

The list of ingredients in Table 4 is far too short. It should include the following ingredients which are inherently toxic and known to have been found in TCM preparations:

Zhu Sha - Mercuric sulphur - Cinnabar
Qing Fen - Mercuric chloride - Calomel
Hong Fen - Mercuric oxide - Realgar
Bai Fan - Aluminium silicon oxide - Alum
Hei Xi - Lead
As per ATCM (2009).

Tripterygium wilfordii
Studies show associated hepatotoxicity (Zhuang, 2013); others have reported heart problems (Chen, 2001).

Wenxin Keli
Studies show dose related QTc prologation (Xue, X et al., 2013).

***Monascus purpurea* - Oryza sativa - Hong qu - fermented Red Yeast Rice (as above)**

Aristolochia
Aristolochia species should be included in Table 4 along with herbs that can be confused with *Aristolochia*, including but not limited to *Clematis armandii* and *Stephania tetrandra* which are currently listed in Table 1 (Kim et al, 2013).

Citations

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