Association for Responsible Health Information and Advertising (ARHIA)

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1. The Director General
Department of Health;
2. The Registrar
Medicines Control Council;
Private Bag X828
PRETORIA
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23 October 2011

Dear Madame Director General,
Dear Mrs Hela,

Complementary Medicines: Regulations and Guidelines

I am writing on behalf of the Association for Responsible Health Information and Advertising (ARHIA) to submit comments on both the amended General Medicines Regulations (Notice No R. 587, 22 July 2011) and the accompanying "Complementary Medicines – Quality, Safety and Efficacy" Guidelines (published by the Medicines Control Council (MCC) ("Council"), dated August 2011 with a deadline for comment of 22 September 2011). These both relate to the Medicines and Related Substances Act, 1965 (Act 101 of 1965) – the "Medicines Act".

ARHIA is a voluntary association and has as its main objective the protection of South African consumers from health products and services that are in any way misrepresented in terms of efficacy, safety or quality. These are useful descriptors of information and advertising as well as medicines! ARHIA has a series of secondary objectives which would include commenting on proposed regulations related to health products and services.

We found it somewhat puzzling that the comments on the regulations deadline was a whole month after that for the guidelines – particularly as the guidelines document refers to information from the proposed regulations. On behalf of ARHIA, I applied for an extension to the deadline for the guidelines and received a response stating that the request (similar to that received from other parties as well) would be put to a Council meeting on 30 September, 2011. Unfortunately it was not confirmed whether an extension had been granted or not, and we therefore assumed that it was granted.

The three month comment period on the gazetted draft regulations expired on 22 October 2011, and we would request condonation for being one day late. This is partly because as we have considered

the draft regulations in the context of the present regulations and the Medicines Act we have found anomalies that we felt needed additional comment. See Annexure A. This submission also includes our comments on the MCC's document on quality safety and efficacy of complementary medicines guidelines as Annexure B.

ARHIA welcomes the revised draft Regulations, noting that previous versions of draft regulations were gazetted (to the best of our knowledge) in 2001, 2004 and 2008. We particularly welcome the inclusion of an explicit role for the Allied Health Professions Council (AHPCSA) and the professions regulated by it.

As is stated in the Medicines Act, Section 3, the Council shall have regard only to the safety, quality and therapeutic efficacy of any medicine when determining whether or not such medicine's registration or availability is in the public interest. We would submit that to date, and mainly as a consequence of the 2002 Complementary Medicines "call up" – the public interest has not been served and that many medicines are presently available (155,000 according to the Minister of Health one year ago) for which the MCC has paid no regard to safety, quality or therapeutic efficacy. As a result the complementary medicines industry's interest has been served and not the public interest. We believe therefore that the public interest, safety, quality and therapeutic efficacy must now take precedence over industry interest. This is in line with the National Department of Health's strategic plan 2009/10 – 2011/12 which explicitly stated that unregulated complementary medicines pose a public health risk. We agree with this consequence of unregulated complementary medicines and urge that the opportunity be taken to finally take full charge of the regulation of these medicines in order to reduce or even eradicate such public health risk. Please see Annexure C for some remaining concerns.

The revision of the Regulations provides the Council with an opportunity to revert to its statutory mandate, and this opportunity should be taken without prevarication by Council in insisting on the highest standards possible. It is also an opportunity for Council to exert its authority and indeed, if Council is sufficiently courageous and motivated, to become a world leader in this contested arena.

We note with appreciation the move away from lingering suggestions of a "listing" system as previously proposed as this would not have met the combined criteria of safety, quality and efficacy needed and mandated.

In terms of the "general" regulations, we would recommend to the MCC that serious consideration be given to formally incorporating all or most of its "guidelines" into the Regulations to the Act, so that guidelines become required rather than optional and/or negotiable. Perhaps the most pragmatic way of doing this might be to include a definition of "guideline" in the definitions to the Regulations which states that all guidelines published by the MCC, unless specifically excluded, shall be adhered to as if they were themselves Regulations. We would urge the Council to consider this suggestion or an alternative approach which would hold up if challenged legally to enforcing guidelines.

We note with concern that again no proposed regulations have been published relating to Section 18C of the Medicines Act, which states that the "Minister shall . . . make regulations relating to the

marketing of medicines and such regulations shall also provide for an enforceable Code of Practice". (emphasis added) This has not yet happened despite this Section of the Act first being published in 2003 (i.e. eight years ago). The Medicines Act further provides in Section 35.1 subclauses (vii), (x), (xxvii) and (xxxiv), for the making of Regulations under which medicines may be sold (which by definition in the Act includes "advertise") and advertised. We therefore believe it is time for the MCC to exert its authority in regulating the advertising and marketing of medicines, especially considering that Section 39 of the Medicines Act specifies that the Act "binds the State".

We would further point out that Sections 3.1, 3.2, 3.6, 7.2 and 7.7 of the National Drug Policy 1996 (NDP) also directly and indirectly mandate an oversight role for the MCC in marketing practice.

We would urge the Minister of Health and the Council to address this omission in adherence to the Act (and neglect of the NDP) as soon as possible.

Yours sincerely,

M. R. JOBSON
on behalf of the Association for Responsible Health Information and Advertising

Annexure A. Comments on the proposed draft Regulations of 22 July 2011.

Amendment of Regulation 1:

The component of the proposed definition of a complementary medicine that refers to "assisting the innate healing power of the human being or animal" cannot be accepted. Every healing modality ultimately does this and it is not a "special", "unique", or "defining" feature of complementary medicines. We suggest that the definition of a complementary medicine be:

"complementary medicine" means a medicine that -

(a) meets the definition of a medicine as defined in Section 1 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965); and

(b) is used in accordance with the practice of the professions regulated under the Allied Health Professions Act, 1982 (Act No. 63 of 1982).

We also recommend that, similarly to the concept of a "new chemical entity" (NCE), a definition for a "new complementary medicine" (NCM) be developed. This definition should include, for example, products where combinations of complementary medicines and/or herbal ingredients and/or other substances previously not recorded, have been formulated, e.g. a complex formulation of several herbal ingredients (including herbal blends), vitamins and minerals. The definition of a new complementary medicine should also include previously used combinations of ingredients but with different strengths and dosages. As with NCEs the requirements for registration of these "new complementary medicines" must be at a higher standard than single component or previously widely used multi-component complementary medicines.

Amendment of Regulation 2:

The proposed definition of "pharmaceutical alternative" and reason for including it is unclear. The heading of Regulation 2 is "Requirements for Therapeutic Equivalence". The definition of an interchangeable multisource medicine (IMM) in the Medicines Act states that an "IMM" must comply with the requirements for therapeutic equivalence as prescribed. The definition of an "IMM" also states that an IMM contains the same active substances which are identical in strength or concentration, dosage form and route of administration and meet the same or comparable standards. The proposed definition of pharmaceutical alternative seems to be in conflict with this as it does not require the identical dosage form or strength! If the definition of pharmaceutical alternative is accepted, then subclause 2.2 must be amended to exclude in vitro studies and must use the originator medicine as a comparator e.g: "2.2 Therapeutic equivalence is determined from comparative bioavailability, pharmacodynamic, or clinical ~~or in vitro~~ studies using the originator medicine, which meet the requirements and accepted criteria for bioequivalence as determined by the Council." It is not acceptable to use "in vitro" studies for purposes of therapeutic equivalence if a pharmaceutical alternative is being used. As Section 22F(1)(b) of the Medicines Act states that a pharmacist or other licenced dispenser shall dispense an IMM (unless the prescriber has stated that no substitution may occur, or a patient refuses), the Act puts all dispensers at risk if the IMM has

been shown to be "therapeutically equivalent" on the basis of a "pharmaceutical alternative" using in vitro studies only. The patient would also not adequately be protected. The present opportunity to make the registration requirements appropriately more stringent should be taken. This would be in line with Section 35.1(xi) of the Medicines Act.

Amendment of Regulation 6

The proposed additions of subclauses (i) and (j) do not make sense because Regulation 6 applies to the gazetting of applications for registration and the date of registration and conditions of registration would not yet have been determined by Council. Subclauses (i) and (j) can therefore not apply to new applications. It seems, to the best of our knowledge that the Council has anyway failed to gazette the 155,000+ "applications" received in terms of the Complementary Medicines Call-up, unless not gazetting them is a tacit acknowledgment that the application itself is not yet complete.

Amendment of Regulation 8

The proposed substitution for Regulation 8.1(c) cannot be implemented because it would seemingly contradict Regulation 8.1(p). The latter implies that the medicine has already been registered as it requires that the name of the "holder of the certificate of registration" must appear. This precludes the use of an application number on the label as contemplated in the amended regulation. We would argue that medicines for which new applications are made should in any case not be sold until they are registered. Medicines which are already being sold (Section 14(2)(b) and Section 14(3) of the Medicines Act) would on a "use", "diagnosis" or "systems" basis most likely already have been called up, and would therefore have, in effect been sold illegally. It is important to note that with a few exceptions, the call up notices were not substance, ingredient or "discipline"-based. We would recommend that an additional regulation be incorporated under Regulation 8 which would state that any medicine for which an application has been made but which was already "available for sale", may no longer be sold until the medicine has been registered unless the applicant can show that the medicine had not already been called up on a "use", "diagnosis" or "systems" basis. The Minister of Health stated in a written reply to a parliamentary question (No 3059, 29 October 2010, Internal Question Paper No 34) that no grandfather clause would be introduced with regard to the registration of any medicine. We regard this as binding.

Amendment of Regulations 9 and 10

How can a dispenser of a discipline-specific complementary medicine, not necessarily trained in that discipline, ensure that the person to whom the medicine is dispensed will understand and use the medicine according to the principles of the discipline? How does a consumer of a discipline-specific complementary medicine bought over the counter know how to use that medicine according to the principles of the discipline? The phrase "use according to the principles of the discipline" needs to be re-evaluated and contextualized.

Regulation 14

Subregulation (11) – perhaps this should be re-worded as it presently seems to imply that a scheduled substance or medicine may be administered by a veterinarian outside of a hospital setting for the purposes of the satisfaction or relief of a habit or craving. It is not clear how this applies to animals.

Amendment of Regulation 18

This amendment now seemingly excludes practitioners registered under the Allied Health Professions Act. Is this the intention of the amendment?

Regulation 21

Regulation 21(2) requires that an appeal "shall" be sent by "registered mail". It seems pragmatic today to include alternative means of communication of an appeal which can be tracked – including facsimile and email. Consideration should be given to a subregulation that only a decision that has been officially and correctly communicated to the stakeholder(s) or has been accepted in the Council Minutes as a correct reflection of a Council resolution, may be appealed.

Amendment of Regulation 22

Regulation 22(4) seems unrealistic. Is it necessary to have all details in subregulation (3) in another language as well as English? Surely it is only the label which is needed to be in English and one official language?

Amendment of Regulation 25

If for subsections (2) and (3) the exact pharmacological class cannot be determined for a complementary medicine (in category D) how will this be catered for? Complementary medicines should not simply by default be categorised as "other" in the different classes. The applicant must indicate which class a complementary medicine is contained in or justify with adequate reasons why the medicine should be classed as "other".

It is noted that there is inconsistency in the pharmacological classes – for example Class 1.6 states "Other central nervous system stimulants"; and Class 3.5 states only "Others" rather than "Other connective tissue medicines". Wherever an unqualified "others" is listed, we recommend that the heading of that class be added as in the example of class 1.6.

Insertion of Regulation 25A

A subregulation needs to be considered which states that if special complementary medicine discipline criteria are needed to assess a complementary medicine's efficacy, such criteria should be determined in consultation with the Allied Health Professions Council. For example, if a complementary medicine claims to have an effect on a person's "qi" or "prana", an acceptable

validated mechanism for i) measuring such "qi" or "prana" must be included in the application; and ii) if the medicine is taken orally, it must be shown that such medicine's purported ability to affect the "qi" or "prana" following ingestion remains intact and is not destroyed by stomach acid or other physiological processes in the pharmacokinetics/pharmacodynamics of such a medicine.

Regulation 27

The possibility of adding Regulation 27(1)(d) should be considered to include the destruction of S0 medicines – especially those complementary medicines which are registered as Schedule 0 medicines. This is particularly important as the shelf life of many complementary medicines is likely to be relatively short and unused medicines will have to be disposed of and destroyed.

Amendment of Regulation 28

Regulation 28(1)(g) needs to be amended to include instructions, in the prescription, for the use of the medicine according to the principles of the discipline of a specified complementary medicines. Regulation 28(5) may need a qualifier if the diagnosis is a diagnosis specific to an allied health profession registered with the AHPCSA. For example – if a diagnosis of "too much dampness in the body" is stated on the prescription, it must also state "according to the principles of Traditional Chinese Medicine.

Regulation 34

Regulation 34(2)(e) should be amended to state "clearance by any ethics committee accredited by the National Health Research Ethics Council or otherwise recognised by the Council." We suggest the substitution of the word "clearance" for "endorsement".

Regulation 37

Regulation 37(1) should be expanded with the following statement or something similar: "Where the adverse reaction is "lack of efficacy" (as per the definition in Regulation 1) the report must include what the diagnosis was and whether or not the condition has remained the same or worsened, with details of how these were measured. If the diagnosis is specific to a registered allied health profession, full details of the alternative diagnosis, the expected effect of the medicine and the measurement of no effect or the worsening of the patient, must be reported.

Amendment of Regulation 40

Regulation 40(1)(q)(ii) should be changed to read: "<u>administer</u> according to the principles of the discipline" as this subregulation refers to veterinary complementary medicines.

Regulation 41

This regulation needs to be updated completely in terms of current practice and the recommendation that only combination products for prevention be used (with the exception of doxycycline).

Regulation 44

We recommend that Council include a definition of "biological medicine" in Regulation 1; that Council make clear in this regulation or another that biological medicines do not have "generic equivalents" or "interchangeable multisource medicines" equivalents, and similar biological medicines (or "biosimilar medicines") meet the criteria as outlined in the Council's "Biosimilar Medicines Guideline".

Regulation 45

Regulation 45(2)(c) should have added to it a statement similar to: "Care must be taken when graphically depicting medicines' containers or packs that no medicinal claims are visible to the public."

Regulation 45(4)(c)(ii) is anomalous as medicines for which applications for registration have been submitted but are not yet registered should not be being advertised for sale anyway. This is the same as our argument relating to Regulation 8 above.

Regulation 45(4)(c)(v) refers only to homoeopathic medicines. This is anomalous in the context of the proposed new definition of complementary medicines. Consideration to changing this to a statement similar to: "of a complementary medicine, an indication that the medicine must be used in accordance with the principles of the specific profession registered with the AHPCSA".

Regulation 46

We recommend that this Regulation should be re-written to make the process simpler without losing any essential elements. Consideration of the inclusion of references to the Promotion of Access to Information and the Promotion of Administrative Justice Acts should be given. Based on the writer's personal experience, consideration should be given to formalising the acceptance of documentation provided only at that meeting and that the full reasons for such acceptance or not, must be minuted. It is noted that representatives of the pharmaceutical industry have on occasion put inordinate pressure on members of the secretariat to make documentation available at a meeting and not prior to it within the time periods usually adhered to for Council and committee meetings. This has the potential to undermine the credibility and the authority of the Council. Consideration should also be given to the most severe of penalties should any member of the secretariat be found to have collaborated (or more seriously "colluded") in manipulating a Council agenda or the documentation presented at a Council meeting.

Another component which needs to be written into the regulations for the conduct of business of the Council and its committees is that, in the unlikely event of an applicant being appointed as a member of a committee or of Council (which would anyway conflict with Section 6(1)(d) of the Medicines Act), that person will not be given access to any information which may have been submitted by a competitor or a potential competitor.

Amendment of Regulation 48

Regulation 48(1)(c) should not include reference to medicines which are not registered but for which applications for registration have been accepted. This is in conflict with subregulation 48(1)(o). See also our similar comments for Regulation 8. Such unregistered medicines should in any case not be sold. See also our comments on Regulations 8 and 25 in this latter respect.

Regulation 48(1)(w)(ii) – As with the suggested amendment of Regulation 40, the wording for a veterinary complementary medicine should state "administer" rather than "use".

Regulations 48(2)(ii), (iii), (iv), (v) – are all in apparent conflict with subregulation 48(1)(o) in Regulation 48(1)(c).

Insertion of Regulation 48B

Regulation 48B should not include the phrase "or the public" unless it is specified that the medicine or scheduled substance is either a S0 or a S1 medicine. This new regulation needs to be rewritten so that it accords with Regulation 45.

Annexure B. Comments on the proposed Guidelines of August 2011.

Section 1: Introduction

The statement "Before submitting an application for registration of a complementary medicine, it is first necessary to establish that the product contains substances that are, in fact, complementary medicine substances" is incomplete. It needs to be supplemented with the phrase "and not medicines, substances or scheduled substances which have already been defined in or registered according to the Medicines Act".

The phrase "tradition of use" needs to be qualified with the word validated, or verified.

It would be appropriate to insert here, if it is accepted by the MCC, the definition of "new complementary medicine" as suggested in Annexure A. A statement that new complementary medicines are by definition excluded from claiming to have an established identity and tradition of use, despite one (or more) ingredients having such an established identity and tradition of use.

For data on quality aspects of complementary medicines, we would recommend that it be more explicit that any manufacturing facilities have a current GMP licence and where possible evidence that the facility has recently been inspected. Any laboratory facilities should be accredited laboratories and meet required standards.

Section 3 refers to general principles related to safety and efficacy. We would recommend some additional resources for the safety and efficacy aspects of complementary medicines:
Cochrane reviews
Natural Medicines Comprehensive Database

We would also recommend that use is made of the Consolidated Standards of Reporting Trials (CONSORT) framework by applicants (and reviewers) of applications in consideration of safety and efficacy components of clinical trials of complementary medicines. See: http://www.consort-statement.org/home/ and in particular the CONSORT statement: http://www.consort-statement.org/consort-statement/overview0/. It should be noted that herbal medicines are a particular "extension" of the CONSORT framework.

Section 4 Safety is divided into the following subsections:
4.1 Criteria for determining the safety of indications and health claims.
4.2 Documenting Safety
4.2.1 The safety section should include the following
4.2.2 Overview of Safety
4.3 Post Marketing Data

We believe this is incorrectly presented because the first priority is not the "safety of indications or health claims" but the "safety of the medicines / substances" themselves.

We would therefore recommend re-structuring this section as follows:

4.1 Overview of Safety
This should include mention of laboratory (in vitro) data and animal (in vivo) studies where applicable and available, as well as all relevant human studies.
4.2 Post Marketing Data
4.3 Safety of indications and health claims
4.3.1 Defining indications and health claims in terms of safety
4.3.2 Determining risk related to indications and health claims

We do not believe there should be a "medium risk" category. There should be only high risk and low risk categories. A medium risk category merely confuses the picture and too easily allows for it to become a "throw away" category when it cannot be decided whether a medicine (for a health claim) is high or low risk.

High risk categories must include the seriousness of the disease as well as potential toxicity of the complementary medicine. Clinical trials need to be conducted for all high risk categories. Every "new complementary medicine" as defined above (as recommended for inclusion in the Regulations) is automatically high risk and requires a clinical trial (or trials) to be conducted using the medicine as a whole. Safety cannot be extrapolated from studies of individual ingredients. Low risk categories would require evidence for safety as indicated in the "medium risk" category proposed in the guideline.

Section 5 Efficacy

Efficacy of medicines as a whole and not of individual ingredients alone, is required. We would recommend the inclusion of systematic reviews with meta-analyses from recognised databases such as the "Cochrane Collaboration"; the relevant components of the CONSORT framework; and natural medicines evidence-based databases such as the Natural Medicines Comprehensive Database and the Natural Standards Database. Every new complementary medicine should have clinical trials for efficacy conducted with careful attention to the appropriateness and validity of study design and analysis of results. Where the complementary medicine claims to affect "qi" or "prana", etc., the criteria and methodology for the measurement of these aspects of the medicine's effect (before and after) with appropriate controls must be used or must be developed if no suitable criteria are already in use. All clinical trials must be conducted in accordance with the South African Good Clinical Practice (GCP) Guidelines 2006 or equivalent.

Quality of Life (QoL) instruments (e.g. Short Form 36 or SF 36 questionnaires) may be used to provide supportive evidence of efficacy only and not as primary evidence. Such QoL instruments must have been validated for the intended users of the medicine(s) in South Africa.

It is suggested the Subsection 3.3 be moved and placed after Section 6 (Scheduling) as a new Section 7 with the heading: "Conclusion: Harms-Benefits Profiles of Complementary Medicines". This section should clearly summarise the data and unequivocally demonstrate that the benefits outweigh any potential harms.

Annexure C: Aspects not addressed by the draft complementary medicines Regulations and guidelines

In a written response to a parliamentary question last year, the Minister of Health stated that approximately 155 000 submissions for complementary medicines have been received since the publication of the call up notice of February 2002 and that none of them had been evaluated for safety, quality and efficacy. The medicines referred to fell into the following categories:
Anthroposophical medicines
Aromatherapeutic medicines
Ayurvedic medicines
Chinese traditional medicines
Energy substances
Homeopathic medicines
Nutritional substances that purports (sic) to have therapeutic or medicinal effects
Western herbal medicines
Unani-Tibb medicines
Combination Homoeopathic / Flower essence
Combination Complementary Medicines

The Minister also stated that the safety, efficacy and quality of these products will begin to be evaluated when "enabling amendments to the Medicines and Related Substances Act, 1965, Regulations and Guidelines have been finalized". (Question no 3057, date of publication in internal question paper: 29 October 2010, internal question paper no 34.)

The welcome and rational definition of a complementary medicine in terms of professions registered with the Allied Health Professions Council means that (at this time) only medicines used in the following professions/disciplines will be covered:
Ayurveda,
Chinese medicine and acupuncture,
Chiropractic,
Homeopathy,
Naturopathy,
Osteopathy,
Phytotherapy,
Therapeutic aromatherapy,
Therapeutic massage therapy
Therapeutic reflexology
Unani-Tibb medicines

There is therefore no accommodation for "Anthroposophical medicines", "energy substances", "nutritional substances that purport to have therapeutic or medicinal effects", "Western herbal medicines" (unless it is considered that "phytotherapy" incorporates this – but phytotherapists may add vitamins and minerals to the herbs), "combination Homoeopathic / flower essence medicines" and "combination complementary medicines" in the proposed regulations and/or guidelines.

As the “nutritional substances that purport to have therapeutic or medicinal effects” and the “combined complementary medicines” categories are likely to be amongst the most numerous to date of all the submissions in terms of the 2002 complementary medicines call up, we would recommend that the MCC as a priority calls up these categories in terms of Section 14 of the Medicines Act for full registration as soon as the regulations are finalised.