– Report 2 –

Product Testing Requirements Connected to Good Manufacturing Practices for Natural Health Products

Report of the Natural Health Products Program Advisory Committee
to the Natural Health Products Program

January 26, 2010

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Foreword

The Natural Health Products Program Advisory Committee (NHP-PAC) is an expert advisory committee formed to provide Health Canada's Natural Health Products Program with timely advice and recommendations on issues under federal responsibility for assuring the safety, quality and efficacy of natural health products for sale in Canada. Collectively, the Committee members provide regulatory and related expertise and advice pertaining to risk/benefit assessments of natural health products, to assist the Natural Health Products Program with making appropriate risk management decisions. The decision-making responsibility remains with the Natural Health Products Program.

Report 2: Product Testing Requirements Connected to Good Manufacturing Practices for Natural Health Products was presented to Ms. Michelle Boudreau, Director General, Natural Health Products Directorate (NHPD) on January 26, 2010 (Meeting #3, Agenda Item #3) by the NHP-PAC in follow-up to a commitment made by the Committee at its September 14-15, 2009 meeting to submit a report containing recommendations on issues of interest related to Product Testing Requirements Connected to Good Manufacturing Practices for Natural Health Products, as identified by the NHPD.

A draft of this Report was presented to the Committee for deliberation at its December 2009 meeting (Agenda Item #3) by the Committee's Working Group #2 on Product Testing Requirements Connected to Good Manufacturing Practices for Natural Health Products: Ms. P. Brown, Chair (British Columbia Institute of Technology), Mr. C. Carter (Canadian Health Food Association), Mr. J. Chan (Bayer Inc., Consumer Care), Mr. L. Cheng (Chamber of Chinese Herbal Medicine of Canada), Dr. S. Dentali (American Herbal Products Association), Ms. S. Gaudette (Canadian Homeopathic Pharmaceuticals Association), Mr. B. Licht (Puresource Inc.), Mr. G. Leong (Jamieson Laboratories Inc.), Mr. R. Lenz (Natural Factors Nutritional Products Inc.), Mr. W. Morkel (Dicentra Inc.), Dr. J.P. Powers (Body Plus Nutritional Product Ltd.) and Mr. Colin Watson (Swiss Herbal Remedies Ltd.).

The Report includes the recommendations ensuing from the Committee deliberations, with rationales and the range of views provided for each of the recommendations. The overall recommendation of the Committee is that the NHP Program should immediately implement its supported recommendations to expedite the application review process.

Recommendations

List of acronyms:

AHPA: American Herbal Products Association
ANSI: American National Standards Institute
EDQM: European Directorate for the Quality of Medicines & Health Care
EHIA: European Herbal Infusions Association
EMEA: European Medicines Agency
FDA: United States Food and Drug Administration
ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
TGA: Therapeutic Goods Administration (Australia)
USP: United States Pharmacopeial Convention
WHO: World Health Organization

#	Recommendation	Recommended by	Rationale for Recommendation
1	The NHPD should provide guidance to industry regarding the required rationale for skip lot testing.	All Absent: 2	Guidance is currently not provided in the Evidence for Quality of Finished Natural Health Products guidance document (June 2007). The United States Dietary Supplement Good Manufacturing Practices and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) could serve as a reference for incorporating language and guidance on skip lot testing to include in NHPD's revised Evidence for Quality of Finished Natural Health Products Guidance Document (draft, October 2009). Guidance to specific dosage forms and type of medicinal ingredient is important because microbial

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			testing could be reduced or eliminated for a vitamin tablet (low moisture content) made in a Good Manufacturing Practices compliant environment, if data for multiple batches is clean. More work to be done in consideration of composite batching.
2	The NHPD should emphasize acceptance of identification testing at the raw material stage as an acceptable alternative to finished product testing.	All	The further away from the field (growing), the more complicated testing becomes and the less reliable test methods. It may be easier for larger companies to test raw material but easier for smaller ones to do finished product testing.
3	The NHPD should facilitate the development of specific guidance, in consultation with industry and academic experts, on identity testing to better communicate appropriate techniques.	All	More comprehensive guidance will support industry, facilitate compliance and expedite the review process. The *Natural Health Products Regulations* are very much reliant on product testing for pre-market approval, Good Manufacturing Practices compliance, label claim and inspection. The development of guidance has been discussed by the research community and industry trade associations as an identified need since pharmacopieal methods do not exist for many ingredients. The existing report by the United States Food and Drug Administration (FDA) is out of date and does not provide the right context for natural health products regulations in Canada or the current Dietary Supplement Good Manufacturing Practices. Further work is currently being done by American Herbal Products Association (AHPA) to create a white paper on this topic. There are also discussions on-going within FDA regarding this updating and a meeting is planned for April 2010 at the International Conference on the Science of Botanicals, Oxford, Mississippi.

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4	Support (ex. Training, guidance) should be provided on method fitness for purpose. This applies to all testing, not just identity.	All	Due to the paucity of officially recognized methods, manufacturers and regulators alike are using literature methods that were not designed to operate in a quality assurance environment. Most commercial products are outside the scope and applicability of existing methods, including those demonstrated to be fit for purpose for raw materials and simple product matrices.
5	Probiotics: a) Clarify NHPD monograph; b) The NHPD should accept supplier's Certificate of Analysis for probiotic culture identity, rather than focusing on lot testing by manufacturers.	All	The current NHPD monograph is not clear. The NHPD has requested more specificity regarding revisions to the monograph. Individual companies do not have the ability/technology to in-house or contract identity tests (ex. strain specific tests like genetic-based methods). Probiotic supplier/manufacturer should be providing the identity information, often proprietary strains, as they have the means to conduct the genetic testing currently required. Manufacturers must qualify their suppliers (ex. conduct supplier audits), if they are to rely solely on the supplier Certificate of Analysis for identification testing.
6	Enzymes: The NHPD should a) create a monograph and b) accept a supplier Certificate of Analysis for source identity.	All	Individual companies do not have the ability/technology to in-house or contract identity tests (ex. genetic based methods). Supplier/manufacturer should be providing the identity information, often proprietary strains, as they have the means to conduct the genetic testing currently required. Manufacturers must qualify their suppliers (ex. conduct supplier audits), if they are to rely solely on the supplier Certificate of Analysis for identification testing

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7	The NHPD should revise the Evidence for the Quality of Finished Natural Health Products Guidance Document to provide more guidance and clarity regarding: ▪ the conditions under which NHPD accepts limits set by pharmacopoeias in cases where the NHPD's limits may be stricter ▪ the conditions under which, with appropriate rationale, testing may not be required (exemption), e.g., ingredients soaked in alcohol the acceptable means of microbial reduction (e.g., irradiation for certain ingredients)	All	Where there is confidence regarding Good Manufacturing Practices compliance, within the risk-based approach, there should be less concern in granting an exemption. Where deficiencies are consistently being found, there should be less latitude. Clarification is required around current practice for acceptance of microbial limits based on acceptance of pharmacopoeial standards for compendial products. Provides clarity on acceptable techniques and helps to proactively address issues related to microbial testing. Reviewers and applicants may have different understanding about the limits. Applicants require better guidance regarding the conditions under which they can request/be granted an exemption, including clarity regarding what components are needed and when.
8	Select non-pathogenic microbial limits consistent with test data. For botanical products in solid dosage form consisting of dried, unprocessed herbs (and dried unprocessed herbal ingredients), adopt limits consistent with American national Standards Institute (ANSI) and AHPA recommendations and more liberal than the United States Pharmacopeial Convention (USP), European Pharmacopoeia, and World Health Organization (WHO) as follows:	All	The NHPD should establish limits for microbial tolerances that are reflective of normal and usual values obtained from materials produced under Good Manufacturing Practice and, if agricultural materials are involved, Good Agricultural and Collection Practices. The range of values for total aerobic count (TAC), yeasts and moulds, and coliforms or Enterobacteria at the 90th and 50th percentile levels on untreated botanical materials is reported in three publications: Microbiological Status of Untreated Herbal Materials, EHIA, Microbiological Quality of Herbal Medicinal Products, EDQM, and EHIA, Microbiological Status of Untreated Herbal Material, Microbial Screen of Medicinal Herbs Planta Medica, Czechoslovakia.

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	▪ Total aerobic plate count: 107 colony forming units/gram ▪ Total yeasts and moulds: 105 colony forming units/gram ▪ Total coliforms: 104 colony forming units/gram.		Comparing these findings with published limits from AHPA, ANSI, USP, and WHO shows that more than half of the samples would be rejected without microbial reduction treatment(s). The AHPA and ANSI limits would allow over half of the tested materials to pass and are closer to approximately the 90th percentile of the tested materials. Assuming the absence of a health risk the rejection of 50% of marketplace untreated botanical products consisting of dried unprocessed herbs is unwarranted. Microbial tolerances should not be set so low for products consisting solely of botanical ingredients that microbial reduction techniques would need to be routinely employed in order to meet them. This would result in unnecessary degradation of material quality and treatment of spoiled materials to give them the appearance of acceptable quality. Microbial reduction techniques may be justified when pathogens are present, but the focus should be on implementing Good Agricultural and Collection Practices instead of employing postharvest microbial reduction treatments to eliminate the presence of pathogens.
9	For specific product dosage forms, the NHPD should accept the British Pharmacoppeia, USP, and European Pharmacopoeia specifications in such cases as the products meet the complete pharmacopoeial requirements	All	Regarding limited testing, as Health Canada accepts other pharmacopoeias on a case-by-case basis, a company can submit standards. These are authoritative bodies currently accepted by NHPD; for consistency (For e.g. section 5.1.4 of the European Pharmacopoeia where specific microbial requirements are provided related to specific dosage forms).

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10	The NHPD should clarify the guidance to emphasize Good Agricultural and Collection Practices and Good Manufacturing Practices as opposed to routine microbial reduction techniques.	All	Normal non-pathogenic microbial loads are not associated with a health risk. The best control of herbal microbiological quality is through implementation of Good Agricultural and Collection Practices and Good Manufacturing Practices.
11	The NHPD should ensure that requests for testing exemptions, with rationale, be reviewed by assessment officers with microbiology expertise.	All	Decrease in frustration between Health Canada Assessment Officer and sponsor (applicant); expedites the process.
12	In moving forward, the NHPD should continually gather information on microbial testing techniques, method fitness and information concerning when testing should be required.	All	Ultimately product specific microbial limits, based on data and development of rational rather than prescriptive routine tests is preferred.
13	The WHO Guidelines for Quality of Herbs (2007) recommends tolerance limits (absence) for Shigella and Clostridium in herbal products. As no justification was provided that these are likely or certain contaminants for herbals, it is not recommended these tests be added routinely to all finished products.	All	Shigella and Clostridium produce toxins. Would microbial reduction techniques remove toxin? If the test is just for the microbial, a reduction step could be used to meet the limit imposed without reducing the actual risk. Forcing microbial reduction techniques routinely is problematic. Critical control points for pathogen entry are water and potentially the manufacturing process itself; thus adherence to Good Manufacturing Practices is sufficient. The Committee's Working Group #2 on Product Testing is not aware/has not come across data or literature that suggests testing for these organisms should be routinely added to herbal products.

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14	Use term “elemental impurities.”	All	Consistent with science; note that common term, heavy metals, is not accurate; USP made change.
15	The NHPD should establish tolerances based on sound science used by other jurisdictions. For each natural health product total daily intake revise the current elemental limit to the following: ▪ Arsenic (inorganic): 10 µg/day; Note: To be consistent with the current NHPD convention of presenting limits this becomes the following daily limit based on a 70 kg person; ▪ Arsenic (inorganic): 0.14 µg/kg body weight.	All	Harmonization; must be based on scientific rationale, i.e. no safety risk. Reviews of tolerances established by other jurisdictions have been conducted recently and tolerances have been established by AHPA, and proposed by USP, and can be considered for adoption. Routine testing of all products by all companies every time may not provide significant product safety improvements without placing an undue burden on some small manufacturers. Current NHPD limits for arsenic and mercury are set based on errors in the current ANSI 173 and need to be corrected. USP held a meeting with the Institute of Medicine and convened an advisory panel to deal with the issue of elemental impurities in drugs and dietary supplements. Currently they have proposed limits for both as well as a proposal for methods of analysis, and publication of comments and responses to earlier USP proposals. This information, except the limits for USP drugs, is available from http://www.usp.org/hottopics/metals.html. AHPA’s revised Heavy Metals Analysis and Limits (2009) provides limits, rationale, test method comparisons, etc. Manufacturers must not allow levels of elemental impurities to rise to this and other elemental impurity limits if materials are readily available that routinely deliver significantly lower levels.

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16	The NHPD should allow applicants to develop rationale to justify higher limits where the daily dose exceeds 10 grams.	For: 3 Against: 9 Abstain: 1	Elemental impurity quantitative limits are determined at the highest labelled dose of a supplement, and should be applicable only to natural health products that are consumed in a total daily amount of 10 grams or less. Products whose daily dose exceeds 10 grams (ex. Protein powder) contribute to higher percentage of total daily intake. Current limits assume natural health products are a fraction of one's daily intake of elemental impurities. Higher limits are justified to the extent that a natural health product replaces other sources of elemental impurity intake.
17	Limits should be based on 2 significant figures.	All	Scientifically accurate.
18	In guidance document, clarify and highlight that raw material testing is accepted. It should be clearly explained that limits are based on finished products.	All	It was recommended that a chart format or example be used, such as that provided in the USP Elemental Contaminants in Dietary Supplements (PF36 (1) 2010), to demonstrate the relationship between raw material and finished products.
19	Provide a working definition of the term "known method" as the expression is used in Section 2.5.2 of the Evidence for Quality of Finished Natural Health Products guidance document both the current and draft versions. A suggested definition is as follows: *A method that can be shown to yield*	All	Section 2.5.2 of the Evidence for Quality of Finished Natural Health Products guidance document states: "In the case of medicinal ingredients where there is no known method for analysis of the medicinal ingredient... quantification by "input" is considered to be acceptable." However, no definition of the term "known" is provided. The recommended definition is consistent with the Australian Therapeutic Goods Administration (TGA) position in Guidance for Listed Complimentary Medicines

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	consistent and accurate results when applied to the finished product. NHPD should introduce the terms "demonstrated to be suitable for intended use" and "fit for purpose" in to the guidance documents.		(2009) that an input method is acceptable where "the formulation of the medicine may be of such complexity that a validated assay method for the ingredient in the finished product is unavailable or is difficult to achieve." This is consistent with the FDA's position for dietary supplements that testing to a product specification may be exempted if "you determine and document that...there is no scientifically valid method for testing or examining such exempted product specification at the finished batch stage" [Section 111.210 of US Food and Drug Administration Good Manufacturing Practices for Dietary Supplements] These terms are consistent with US Dietary Supplement Good Manufacturing Practices.
20	Where a "known" method, as described in recommendation 1, does not exist NHPD should accept quantification by input (for isolates, synthetics, and standardized extracts), and the applicant must: a) Demonstrate that they exercised due diligence in investigating the existence of a potential test method b) If a potential method exists, provide evidence that attempts to establish accuracy and precision of the method failed.	All	The onus should be on the applicant to demonstrate that a suitable method fit for its intended purpose is not available. It is not the NHPD's role to conduct research and development on behalf of the industry. This is consistent with the TGA's position that the onus is on industry to rely on existing knowledge and expertise to investigate the validity of potential assay methods.

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21	The NHPD should permit quantification by input for medicinal ingredients that are included: a) in the formulation but are not present at therapeutic levels but contribute to the claim, and b) at therapeutic dosage to support indications not directly related to the claim. Ingredients quantified by input on these grounds must have a sufficient safety ceiling (e.g., present in amounts 80% or less than the dosage supported by positive results in safety studies).	All	Refer to Recommendation from Report #1 on Standards of Evidence for Non-traditional Natural Health Products (SOE). The NHPD's Safety and Efficacy reviewers currently assess "complementary" and /or "support" ingredients differently from primary ingredients by permitting them to be present in sub-therapeutic amounts, providing another ingredient or combination of the other ingredients delivers the full therapeutic effect. Since these ingredients are not necessary to achieving the therapeutic effect, and since they pose little safety risk, there is minimum benefit to be derived from a quantitative assay.
22	For ingredients that qualify for quantification by input, for overages NHPD should permit an upper tolerance equal to that of the overage + 5%. Applicants must provide a rationale for the overage and overages must be included in the Master Production Formulae and finished product specifications.	For: 12 Abstain: 1	The NHPD currently accepts limits of 95-105% of label claim for ingredients quantified by input (Guidance Document on Evidence for the Quality of Finished NHPs, June 2007) but any overage would likely exceed the 105% limit. The FDA does not require justification for overages in dietary supplements [Federal Register Final Rule June 25, 2007], but overages should not be applied arbitrarily and therefore should be justified and documented in the master formula.

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23	The NHPD should consider redefining and/or clarifying the terms “potency” and “quantity versus “strength” and “composition” to ensure the term employed is an accurate reflection of the measurement being made.	For: 11 Abstain: 2	There are inconsistencies between Canada’s use of these terms and other jurisdictions. The US Dietary Supplement Good Manufacturing Practices state that the manufacturer must establish product specifications for the identity, purity, strength, and composition of the finished batch of the dietary supplement; while Canadian *Natural Health Products Regulations* refer to potency and quantity. The challenge is that when NHPD Assessment Officer’s use potency instead of strength, then for cases where the measure is truly potency, i.e. the amount responsible for the biological response, ends up being relegated to the quantity section. Potency is a biological measurement and strength is a chemical measurement. You can have two materials with the same amount of an identified constituent but they can have very different biological responses or potencies due to differences in other constituents. Therefore strength can refer to the amount of a particular constituent while reserving potency as a measure of biological activity for incompletely defined materials. Are Canada’s current definitions /concepts of “potency” and “quantity” supported in other jurisdictions? Would making a change to the terms and /or definitions vis-à-vis potency/strength put Canadian industry at a competitive disadvantage? The term biological activity for incompletely defined materials is commonly used as the true potency test, but this concept may be more appropriate in the context of clinical trial applications, not release testing of finished products. What would be the impact of making a change to harmonize with accepted

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			definitions of “potency” and “strength”? Industry has now had to adapt to Canada’s definition, will moving to the more generally acceptable definitions now cause more confusion and administrative exhaustion?
24	The NHPD should consider redefining the term “purity” as separate from “contamination”, as opposed to contamination being a subset of purity.	For: 11 Abstain: 2	There are inconsistencies between Canada’s use of these terms and other jurisdictions. The NHPD guidance document includes chemical and microbial contaminants for determination of purity. Section 2.4.3 Purity says: “Under section 44 (2) (a) of the Regulations, the finished product specifications shall contain detailed information regarding the purity of the natural health product, including statements indicating its purity tolerances. The finished product specifications should include tests and methods and tolerance limits for the microbial and chemical contaminants as outlined in the following Microbial Contaminants and Chemical Contaminants sections. “. Further, section 44(2) deals with specifications of purity, identity, and potency but do not include contaminants. Contaminants are captured under purity. Whereas in the cGMP (Good Manufacturing Practices) for Dietary Supplement, contamination and adulterants are separated from purity. There are many definitions for purity, one routinely used in analytical science for specifying materials is “a quantitative assessment of homogeneity or uniformity” and not “the condition or quality of being pure; freedom from anything that debases, contaminates, pollutes, etc.: the purity of ….” Purity of materials and contamination of materials are different concepts,

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			traditionally used differently by industry. Purity is how much specified material is there compared to 100% of the specified material; as such a 100% pure material can still be contaminated. For example, it makes little sense to specify material that has 100 ppb of a pesticide as 100% pure minus 100 ppb, or 99.99999% pure. It is contaminated pure material. It makes sense to specify purity and contaminants as separate concepts as 1) they are and 2) they are employed this way by industry. US Dietary Supplement Good Manufacturing Practices states that for each dietary supplement you manufacture you must establish product specifications for identity, purity, strength, and composition and limits on those types of contamination that may adulterate, or that may lead to adulteration of, the finished batch of the dietary supplement.
25	The NHPD should continue to accept the following approaches for establishing product stability; Basic stability information on raw materials and from similar natural health product formulas in the same container closure system may be used to justify an initial expiry date, in the absence of stability data. Accelerated studies to justify an initial expiration could be used when combined with stability data on raw	For: 11 Abstain: 2	New products may not have shelf-life data available at time of product launch given the inherent market driven/market innovation nature of the industry in small to large size companies. Justification based on scientific knowledge of raw material stability, appropriate overages, data from similar formulas and accelerated stability trials could be used to justify an initial expiration (Guidance Section on Stability Testing of Dietary Supplements form USP Good Manufacturing Practices 2750). Defined storage conditions are in the draft NHPD stability fact sheet (2009). Where accelerated studies are used to project a tentative shelf life date that is beyond a date

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	materials, supplier information (outsourced product) and similar natural health product formulas.		supported by actual shelf-life studies, stability studies should be conducted at appropriate testing intervals until it is verified or adequate shelf life is determined. Accelerated conditions defined according to labelled product conditions (e.g., Room temperature storage can use 40°C as the accelerated temperature).
26	The NHPD should accept the USP Dietary Supplement Compendium (Impact of Stability Studies and Expiration Dating on Dietary Supplements guidelines, page 1327, 2009) as an approved approach to extrapolating shelf-life from accelerated stability studies.	All Absent: 3	While there are “rule of thumb” guidelines, many guidelines are based on single-entity pharmaceutical products (ICH). This provides industry with one possible route to determining shelf-life of new products using accelerated stability studies.
27	Qualitative approaches, with rationale, should be accepted to support stability/shelf-life in situations where medicinal ingredients are quantified by input, as opposed to assay.	All Absent: 2	By applying “matrixing” principles and trend projections, companies can rationalize expiry periods if the formula fits within a certain matrix by placing a specific formula on a stability program. Expiry dates can be determined from the extrapolation from a single “worst case” formula. Stability methods to analyze products for which ingredients are quantified by input must be rationalized. Suitable methods may include the use of chromatographic fingerprint methods or a total potency or activity approach for combination type biological products, as long as the method fitness is clearly defined (ICH Q1D Bracketing and Matrixing Designs (2002), and EMEA Guideline on Specifications: Test Procedures and Acceptance Criteria

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			for Herbal Substances, Herbal Preparations and Herbal Medicinal Products/Traditional Herbal Medicinal Products (2006) and Reflection Paper on Markers Used for Quantitative and Qualitative Analysis of Herbal Medicinal Products and Traditional Herbal Medicinal Products (2008)).
28	In the cases where companies can provide a rationale based on similar products & packaging systems the NHPD should accept verification of assigned expiry dates based on a minimum of 2 data points that include t=0 and endpoint.	All Absent: 2	Requirement for a specific number of batches and testing frequency is too onerous for industry. The stability period of a product is considered verified with the confirmation that it meets the assigned specifications at the beginning and at the end of its assigned expiry period.
29	The NHPD should accept Zone 1 conditions as the primary controlled temperature and humidity storage condition for products sold in Canada at room temperature.	All Absent: 2	Room temperature in Canada is defined according to Zone 1 conditions i.e., (21 0C/45% RH) by Dietz et al. and ICH guidelines Drug Stability Testing, Classification of Countries According to Climatic Zone (1993). Canada has been classified as a zone 1 country. Other conditions identified in the draft NHPD stability fact sheet (2009).
30	The NHPD should accept but not require ICH guidelines be followed for evaluating stability data.	All Absent: 2	The June 2004 Guidance Paper from ICH, Evaluation of Stability Data (Q1E), provides method concepts used to evaluate stability data but not all information contained within the guidance are appropriate to natural health products, for example the schedule of pull dates for re-testing. To adopt the guidance in its entirety would place an unnecessary burden on Industry.

Reference List

The following is a list of the reference documents consulted by the NHP-PAC and its Working Group #2 on Product Testing Requirements Connected to Good Manufacturing Practices Requirements for Natural Health Products:

American Herbal Products Association (2003) Standardization White Paper, Text

American Herbal Products Association (2001) Marker Compound Guidance Document

American Herbal Products Association (2003) Retail Labelling

American Herbal Products Association (2001) Manufacturing & Sale of Bulk Botanical Extracts, Guidance Document

American National Standards Institute (2009) JC Heavy Metal Issue Document

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United States, Food & Drug Administration (2003) Guidance Paper from ICH, Stability Testing of New Drug Substances and Products (Q1AR2)

United States, Food & Drug Administration (2009) The Impact of Stability Studies and Expiration Dating on Dietary Supplements

United States, Food & Drug Administration (2002), Health Professionals Letter Enterobacter Sakazakii Infections Associated with Powdered Infant Formula

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World Health Organization (2004) Enterobacter Sakazakii & Microorganisms in Powdered Infant Formula