

February 18, 2005

## NOTICE

Our file number: 05-103847-46

Health Canada is pleased to announce the release of the finalized guidance document ***Pharmaceutical Quality of Aqueous Solutions***. A draft version of this document was released for Stakeholder consultation in January 2004. This finalized version has been updated to include additional clarification as a result of comments that have been received (where appropriate) as well as to promote consistency with other Health Canada guidance documents. The comments received during the consultation process, together with discussions and recommendations, have been collated in a separate *Questions and Answers (Q&A) Document*, which is available *upon request*. Requests for this *Q&A Document* should be directed to the mailing address or e-mail address given below.

This guidance document supercedes the following Health Canada policy:

- *Waiver of Comparative Bioavailability Studies for Oral Solutions.*

Any questions regarding the content of the guidance should be directed to:

Bureau of Pharmaceutical Sciences  
Therapeutic Products Directorate, Health Canada  
Finance Building (A/L 0201D)  
Ottawa, Ontario  
K1A 1B9

Phone: (613) 941-3184  
Fax: (613) 957-3989  
E-Mail: [bps\\_enquiries@hc-sc.gc.ca](mailto:bps_enquiries@hc-sc.gc.ca)

This and other Guidance documents are available on the **Therapeutic Products Directorate / Biologics and Genetic Therapies Directorate / Marketed Health Products Directorate Website (s)** (<http://www.hc-sc.gc.ca/hpfb-dgpsa/tpd-dpt/>).



# **GUIDANCE FOR INDUSTRY**

## Pharmaceutical Quality of Aqueous Solutions

Published by authority of the  
Minister of Health

|                |            |
|----------------|------------|
| Date Adopted   | 2005/02/15 |
| Effective Date | 2005/02/15 |

**Health Products and Food Branch**

|  |  |
|--|--|
| <p>Our mission is to help the people of Canada maintain and improve their health.</p> <p style="text-align: right;"><i>Health Canada</i></p> | <p>HPFB's Mandate is to take an integrated approach to the management of the risks and benefits to health related to health products and food by:</p> <ul style="list-style-type: none"> <li>• Minimizing health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,</li> <li>• Promoting conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health.</li> </ul> <p style="text-align: right;"><i>Health Products and Food Branch</i></p> |
|--|--|

© Minister of Public Works and Government Services Canada 2005

Available in Canada through  
 Health Canada - Publications  
 Brooke Claxton Building, A.L. #0913A  
 Tunney's Pasture  
 Ottawa, Ontario  
 K1A 0K9

Tel: (613) 954-5995  
 Fax: (613) 941-5366

***Également disponible en français sous le titre :*** Qualité des produits pharmaceutiques des solutions aqueuses

Catalogue No. H42-2/98-2005E  
 ISBN 0-662-39615-4

## FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with the policies and governing statutes and regulations. They also serve to provide review and compliance guidance to staff, thereby ensuring that mandates are implemented in a fair, consistent and effective manner.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document *may be* acceptable provided they are supported by adequate scientific justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidances.

## TABLE OF CONTENTS

|     |  |                   |
|-----|--|-------------------|
| 1.  | OBJECTIVES .....   | <a href="#">1</a> |
| 2.  | SCOPE .....  | <a href="#">1</a> |
| 3.  | BACKGROUND .....   | <a href="#">1</a> |
| 4.  | GENERAL RECOMMENDATIONS FOR AQUEOUS SOLUTIONS .....  | <a href="#">2</a> |
| 5.  | WAIVERS OF THE REQUIREMENT TO DEMONSTRATE <i>IN VIVO</i><br>BIOEQUIVALENCE FOR AQUEOUS SOLUTIONS ..... | <a href="#">3</a> |
| 5.1 | Formulation .....  | <a href="#">3</a> |
|     | 5.1.1 Parenteral Aqueous Solutions .....   | <a href="#">4</a> |
|     | 5.1.2 Other Aqueous Solutions .....  | <a href="#">4</a> |
| 5.2 | Physicochemical Properties .....   | <a href="#">4</a> |
| 5.3 | Device Attributes .....  | <a href="#">5</a> |
| 5.4 | Other Considerations .....   | <a href="#">5</a> |
|     | APPENDIX 1 - Testing Parameters for Aqueous Solutions .....  | <a href="#">6</a> |

## 1. OBJECTIVES

As required by section C.02.018 of the *Food and Drug Regulations*, each lot or batch of a drug shall, prior to its availability for sale, be tested against the specifications for that drug. The purpose of this document is to provide guidance on the establishment of finished product release specifications for *aqueous solutions*, as well as recommendations for the various testing parameters that should be considered during the pharmaceutical development of these drug products.

This document is also intended to provide guidance on the quality of aqueous solutions for subsequent market entry products (e.g., generics) and certain changes to drug products contained in New Drug Submissions and Abbreviated New Drug Submissions. This includes recommendations for the testing parameters that should be used to establish bioequivalence based on pharmaceutical characteristics where a request for a waiver of the requirement to demonstrate *in vivo* bioequivalence has been included in the drug submission.

## 2. SCOPE

This document is intended to apply to drug submissions for aqueous solutions that are filed with the Therapeutic Products Directorate pursuant to Part C, Division 8 of the *Food and Drug Regulations*. It is not intended to apply to biological (Schedule D) nor to radiopharmaceutical (Schedule C) products.

## 3. BACKGROUND

Solutions are defined as *liquid preparations that contain one or more chemical substances dissolved, i.e., molecularly dispersed, in a suitable solvent or mixture of mutually miscible solvents*<sup>1</sup>. An *aqueous solution* is a solution with water as the predominant solvent. Dosage forms characterized as solutions are normally classified by their route of administration (e.g., oral, dermatological, ophthalmic, otic, nasal, inhalation, injection).

The International Conference on Harmonization (ICH) guidance document *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Products: Chemical Substances (Q6A)* provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new drug substances of synthetic chemical origin, and new drug products produced from them.

---

<sup>1</sup> United States Pharmacopeia, 27th Edition (2004)

ICH's *Q6A* guidance document outlines recommendations for *Universal Tests* (those that are considered generally applicable to all drug substances and / or drug products) and for *Specific Tests* (those that are considered specific to individual drug substances and / or drug products). With respect to the drug product, the *Q6A* guidance document includes recommendations for *Specific Tests* for the following dosage forms:

- solid oral dosage forms;
- liquid oral dosage forms;
- parenterals (small and large volume).

It is recognized in the *Q6A* guidance document that this is not meant to be an all-inclusive list. This document, *Pharmaceutical Quality of Aqueous Solutions*, provides additional guidance for other dosage forms that are not covered by the *Q6A* guidance document. Furthermore, as with other ICH guidance documents, the *Q6A* guidance document does not include recommendations for subsequent market entry products (e.g., generics).

This guidance document supercedes the following Health Canada policy:

- *Waiver of Comparative Bioavailability Studies for Oral Solutions.*

This guidance document should be read in conjunction with other applicable Health Canada documents that include recommendations for aqueous solutions, e.g.,:

- *Submissions for Generic Parenteral Drugs;*
- *Submissions for Generic Topical Drugs;*
- *Pharmaceutical Quality of Inhalation and Nasal Products.*

#### **4. GENERAL RECOMMENDATIONS FOR AQUEOUS SOLUTIONS**

Applicable Health Canada and ICH guidance documents and the pharmacopoeia should be consulted for general requirements when establishing the specifications for various dosage forms, including aqueous solutions (e.g., Health Canada's *Quality Guidance: NDSs and ANDSs for Pharmaceuticals*, ICH's *Q6A* guidance).

Appendix 1 provides a summary of the testing parameters that should be considered when establishing the finished product release specifications for the various types of aqueous solutions (e.g., oral, dermatological, ophthalmic, otic, nasal, inhalation, injection). Those parameters designated by an "S" would generally be included in the finished product release specifications of a particular dosage form. Stability studies should include testing of those attributes that are susceptible to change during storage.

Appendix 1 also provides a summary of the testing parameters that should be considered during the pharmaceutical development of the various types of aqueous solutions. Those parameters designated by a "D" would generally be performed during the developmental stages of a particular dosage form.

These recommendations would apply to new drug products, including subsequent market entry products (e.g., generics).

## **5. WAIVERS OF THE REQUIREMENT TO DEMONSTRATE *IN VIVO* BIOEQUIVALENCE FOR AQUEOUS SOLUTIONS**

Generally, results from comparative *in vivo* bioequivalence studies should be provided in support of the safety and efficacy of each proposed drug product and of each proposed strength included in an Abbreviated New Drug Submission (ANDS). Also, comparative *in vivo* bioequivalence studies are performed to support certain changes to drug products contained in New Drug Submissions, Abbreviated New Drug Submissions and their Supplements (e.g., "bridging" between the to-be-marketed product and the product used in clinical trials). In the absence of such studies, a justification supporting a request for a waiver of this requirement should be provided for each product and each strength.

Where the sponsor requests a waiver of the requirement to demonstrate *in vivo* bioequivalence for an aqueous solution, a comparison of the relevant pharmaceutical characteristics of the test product and the reference product should be provided. The reference product could be the Canadian Reference Product or the product used in the clinical trial, as appropriate.

Depending on the particular dosage form, a comparison of the relevant pharmaceutical characteristics would include comparison of the: (i) formulation, (ii) physicochemical properties, and (iii) device attributes.

### **5.1 Formulation**

According to Part C, Division 8 of the *Food and Drug Regulations*, in order for a subsequent-entry product to be the *pharmaceutical equivalent* of the Canadian Reference Product, it must contain identical amounts of the identical medicinal ingredients. The following sections outline additional considerations when comparing the formulations of the test and reference products to support the request for a waiver of the requirement to demonstrate *in vivo* bioequivalence.



### 5.1.1 Parenteral Aqueous Solutions

The information needed to support the request for a waiver of the requirement to demonstrate *in vivo* bioequivalence for parenteral aqueous solutions is described in the Health Canada policy *Submissions for Generic Parenteral Drugs*.

### 5.1.2 Other Aqueous Solutions

To support the request for a waiver of the requirement to demonstrate *in vivo* bioequivalence for other aqueous solutions (e.g., oral, dermatological, ophthalmic, otic), the non-medicinal ingredients in the formulation of the test product, when compared to the reference product, should be qualitatively *the same* and quantitatively *essentially the same*. For the purposes of this document, *essentially the same* would be interpreted as the amount (or concentration) of each excipient in the test product to be within  $\pm 10\%$  of the amount (or concentration) of each excipient in the reference product. A side-by-side comparison of the qualitative and quantitative formulations for the test and reference products should be provided.

Differences beyond these criteria should be scientifically justified and the potential impact on the safety and efficacy of the drug product should be discussed. Additional testing could be requested to support differences beyond these criteria (e.g., partition coefficient, buffering capacity). Exceptions could be justified for colouring or flavouring agents which are not known to influence the absorption characteristics of the drug.

However, those excipients that could potentially modify the absorption of the drug substance, should be qualitatively *the same* and quantitatively *essentially the same* (as defined above). These would include those excipients that could enhance absorption (e.g., polysorbate 80, polyethylene glycol, ethanol) and those that could inhibit absorption (e.g., sorbitol, manitol).

## 5.2 Physicochemical Properties

To support the request for a waiver of the requirement to demonstrate *in vivo* bioequivalence for aqueous solutions, the results of a study comparing the physicochemical properties of the test product against the reference product should be provided. Appendix 1 provides a summary of the testing parameters that should be considered for the comparative physicochemical property study for the test product against the reference product. Parameters designated by a "C" would generally be included in the comparative study of a particular dosage form.

When comparing the physicochemical properties, the results for the test product and reference product should be *essentially the same*. For the purposes of this document, *essentially the same* would be interpreted as the results of the test product and the reference product are within  $\pm 10\%$ . Differences beyond this criterion should be scientifically justified and the potential impact on the safety and efficacy of the drug product should be discussed. A side-by-side comparison of the results for the test and reference products should be provided.

### 5.3 Device Attributes

Results of a qualitative and quantitative analysis of the physical and operating characteristics of the devices for the test product and the reference product (e.g., dimensions, materials used) should be provided. Differences should be scientifically justified and the potential impact on the safety and efficacy of the drug product (e.g., deposition and absorption characteristics, effect on patient compliance) should be discussed. This will be taken into consideration when determining whether the products are considered to be comparable dosage forms.

Other Health Canada guidance documents should be consulted for additional information (e.g., *Pharmaceutical Quality of Inhalation and Nasal Products*).

### 5.4 Other Considerations

Examples of points to consider when proposing a justification for the request for a waiver of the requirement to demonstrate *in vivo* bioequivalence where the test and reference products are not considered to be qualitatively *the same* and/or quantitatively *essentially the same* would include:

- are there known or suspected bioavailability problems?
- does the drug exert therapeutic activity in a narrow therapeutic range?
- does the drug require careful dosage titration and patient monitoring?
- is the drug considered to be highly toxic?

**APPENDIX 1 - Testing Parameters for Aqueous Solutions**

The following list of testing parameters should be considered during the pharmaceutical development and when establishing the finished product release specifications for these drug products. Stability studies should include testing of those attributes that are susceptible to change during storage.

This table also lists the testing parameters that are recommended to establish bioequivalence based on pharmaceutical characteristics where a request for a waiver of the requirement to demonstrate *in vivo* bioequivalence has been included in the drug submission.

This information should be read in conjunction with other applicable guidance documents (e.g., *Pharmaceutical Quality of Inhalation and Nasal Products*).

References to the United States Pharmacopeia (USP) general chapters for the various testing parameters have been included *as examples only*. Equivalent general chapters included in other pharmacopeia listed in Schedule B of the *Food and Drugs Act* would also be considered acceptable (e.g., British Pharmacopoeia (BP), European Pharmacopoeia (Ph.Eur.)).

**Table 1 - Testing Parameters for Aqueous Solutions**

| TESTING PARAMETER   | ROUTE OF ADMINISTRATION |       |        |      |                  |                  |          |
|---|-------------------------|-------|--------|------|------------------|------------------|----------|
|   | Oral                    | Derm. | Ophth. | Otic | Nasal            | Inhaln.          | Injectn. |
| <i>UNIVERSAL TESTS (generally applicable to all dosage forms)</i> |                         |       |        |      |                  |                  |          |
| Description   | S, C                    | S, C  | S, C   | S, C | S, C             | S, C             | S, C     |
| Identification  | S                       | S     | S      | S    | S                | S                | S        |
| Assay (drug substance)  | S                       | S     | S      | S    | S                | S                | S        |
| Impurities  | S                       | S     | S      | S    | S                | S                | S        |
| <i>SPECIFIC TESTS (specific to individual dosage forms)</i>       |                         |       |        |      |                  |                  |          |
| pH<br>(USP <791>)   | S, C                    | S, C  | S, C   | S, C | S, C             | S, C             | S, C     |
| Microbial Limits<br>(USP <61>) (if product is not sterile)        | S                       | S     | N/A    | S    | S<br>(multi-use) | S<br>(multi-use) | N/A      |

| TESTING PARAMETER   | ROUTE OF ADMINISTRATION |       |        |      |                  |                  |          |
|---|-------------------------|-------|--------|------|------------------|------------------|----------|
|   | Oral                    | Derm. | Ophth. | Otic | Nasal            | Inhaln.          | Injectn. |
| Uniformity of Dosage Units (USP <905>) (if packaged in a single-unit container)                         | S                       | S     | S      | S    | S                | S                | S        |
| Delivered Dose Uniformity (USP <601>) (if packaged with a device for delivery)                          | N/A                     | D, C  | N/A    | N/A  | S, C (multi-use) | S, C (multi-use) | N/A      |
| Antimicrobial Preservative Content (if present)   | S                       | S     | S      | S    | S                | S                | S        |
| Antimicrobial Preservative Effectiveness (if present) (USP <51>)  | D                       | D     | D      | D    | D                | D                | D        |
| Antioxidant Preservative Content (if present)   | S                       | S     | S      | S    | S                | S                | S        |
| Non-aqueous Solvent Content (if present)  | D                       | D     | D      | D    | D                | D                | D        |
| Critical Excipient Content (e.g., absorption modifier) (if present)                                     | D                       | D     | D      | D    | D                | D                | D        |
| Viscosity (USP <911>)   | C                       | C     | C      | C    | C                | C                | N/A      |
| Specific Gravity or Density (USP <841>)   | C                       | C     | C      | C    | C                | C                | C        |
| Osmolality (mol/kg) / Osmolarity (mol/L) (if tonicity is declared on the product labelling) (USP <785>) | N/A                     | N/A   | S, C   | C    | C                | C                | S, C     |
| Surface Tension   | C                       | C     | C      | C    | C                | C                | C        |
| Buffering Capacity (if product contains a buffer)   | D, C                    | D, C  | D, C   | D, C | D, C             | D, C             | D, C     |
| Particulate Matter (USP <788> / <789>)  | N/A                     | N/A   | S      | N/A  | N/A              | N/A              | S        |
| Sterility (if sterility is declared on the product labelling) (USP <71>)                                | S                       | S     | S      | S    | S                | S                | S        |
| Bacterial Endotoxins / Pyrogens (USP <85> / USP <151>)  | N/A                     | N/A   | N/A    | N/A  | N/A              | N/A              | S        |

| TESTING PARAMETER  | ROUTE OF ADMINISTRATION |       |        |      |       |         |          |
|--|-------------------------|-------|--------|------|-------|---------|----------|
|  | Oral                    | Derm. | Ophth. | Otic | Nasal | Inhaln. | Injectn. |
| <i>CONTAINER CLOSURE SYSTEM TESTS</i>  |                         |       |        |      |       |         |          |
| Physical Dimensions  | S                       | S     | S      | S    | S, C  | S, C    | S        |
| Containers - Physicochem Tests/Plastics (USP <661>)  | D                       | D     | D      | D    | D     | D       | D        |
| Biological Reactivity (USP <87>/<88>)  | N/A                     | N/A   | D      | N/A  | N/A   | N/A     | D        |
| Extractables/Leachables  | D                       | D     | D      | D    | D     | D       | D        |
| Deliverable Volume, Minimum Fill, or Volume for Injection (if applicable) (USP <698>, USP <755>, or USP <1>) | S                       | S     | S      | S    | D     | D       | S        |
| Droplet Size or Volume (if administered as drops)  | D, C                    | D, C  | D, C   | D, C | N/A   | N/A     | N/A      |
| Droplet Size Distribution (if administered as a spray)   | D, C                    | D, C  | D, C   | D, C | D, C  | D, C    | N/A      |
| Device Attributes (if applicable)  | D                       | D     | D      | D    | D, C  | D, C    | D        |
| Container Closure Integrity (if sterility declared on the product labelling )                                | N/A                     | N/A   | D      | N/A  | D     | D       | D        |
| Weight Loss (if packaged in semi-permeable containers)   | D                       | D     | D      | D    | D     | D       | D        |
| Migration of Container Label Adhesives (if packaged in semi-permeable containers)                            | D                       | D     | D      | D    | D     | D       | D        |

S = generally included in the finished product release specifications

D = generally performed during pharmaceutical development

C = generally included in a comparative study of the physicochemical properties

N/A = not applicable or not required