REVISION OF MONOGRAPH ON CAPSULES

Draft proposal for The International Pharmacopoeia

(September 2009)

DRAFT FOR COMMENT

Please send any comments on this document to Dr S. Kopp with a copy to Ms C. Mendy, Quality Assurance and Safety: Medicines, Essential Medicines and Pharmaceutical Policies, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41 22) 791 4730 or e-mail: kopps@who.int and mendyc@who.int by 16 October 2009.

During the past few years we have moved more towards an electronic system for sending out our draft monographs for comment, for convenience and in order to speed up the process. If you do not already receive our documents electronically, please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list.
# SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/09.339

**International Pharmacopoeia monograph on Capsules**

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<td>Progress noted by WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
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**Explanatory note:**

*Suggested text for deletion in “strike through”.*

*Suggested text to be added or changed is underlined.*
Proposed revision

Capsules

The requirements of this monograph do not necessarily apply to preparations that are intended for use other than by oral administration, such as vaginal or rectal capsules etc. Such preparations may require a special formulation, method of manufacture, or form of presentation, appropriate to their particular use. Starch capsules (often known as cachets) are not included in this monograph.

Definition

Capsules are solid dosage forms with hard or soft shells. They are of various shapes and sizes, and contain a single dose of one or more active ingredients. They are intended for oral administration, but preparations for alternative applications, such as vaginal or rectal, are also available in this presentation. These preparations may require a special formulation, method of manufacture, or form of presentation, appropriate to their particular use. For this reason they may not comply with certain sections of this monograph. Starch capsules (often known as cachets) are not described in this monograph.

Note from the Secretariat: see italic statement added above.

The different categories of capsules that exist include hard, soft, and modified release capsules. Their capsule surfaces may bear symbols or other markings. They should be sufficiently robust to withstand handling, including packaging, storage, and transportation, without cracking or breaking. They should be packaged and stored in a manner that protects them from microbial contamination.

Note from the Secretariat: this part is dealt with below under Manufacture and Storage.

Capsule shells are made of gelatin or other substances, the consistency of which may be modified by the addition of substances such as glycerol and sorbitol. Preservatives may also be necessary. Note from the Secretariat: excipients are dealt with below. The shell should disintegrate in the presence of digestive fluids so that the contents are released. The contents of capsules may be solid, liquid, or of a paste-like consistency. Capsule shells and contents may contain excipients such as diluents, solvents, surface-active substances, opaque fillers, antimicrobial agents, sweeteners, colouring matter authorized by the appropriate national or regional authority, flavouring substances, disintegrating agents, glidants, lubricants, and substances capable of modifying the behaviour of the active ingredient(s) in the gastrointestinal tract. The contents should not cause deterioration of the shell.
When excipients are used, it is necessary to ensure that they do not adversely affect the stability, dissolution rate, bioavailability, safety, or efficacy of the active ingredient(s); there must be no incompatibility between any of the components of the dosage form.

The different categories of capsule include:

– hard capsules
– soft capsules
– modified-release capsules

**Manufacture**

The manufacturing and filling processes for capsules should meet the requirements of good manufacturing practice (GMP).

Very broad guidelines concerning the main critical steps to be followed during production of capsules, indicating those that are the most important, are provided below. Additional guidelines specific for hard or soft capsules are provided in the respective subsections below.

**In the manufacture of capsules, measures are taken to:**

- ensure that the active ingredient(s) when present in solid state form have appropriate solid-state properties such as particle-size distribution and polymorphic form;
- ensure that mixing with excipients is carried out in a manner that ensures homogeneity;
- minimize the degradation of the active ingredient(s);
- minimize the risk of microbial contamination;
- minimize the risk of cross contamination.

The particle size of the active ingredient(s) is may be of primary significance in determining the rate and extent of dissolution and the bioavailability of the drug product, and the uniformity of a drug product, especially for substances of low solubility in aqueous media. The uniformity of the final drug product is affected by the particle size of the active ingredient(s) as well as the excipients.

Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production.

Packaging is required to be adequate to protect capsules from light, moisture and damage during transportation.

*[Note from the Secretariat: general information on Manufacture moved here.]*
Visual inspection

Unpack and inspect at least 20 capsules. They should be smooth and undamaged. Evidence of physical instability is demonstrated by gross changes in physical appearance, including hardening or softening, cracking, swelling, mottling, or discoloration of the shell.

Uniformity of mass

Capsules comply with the test for 5.2 Uniformity of mass for single-dose preparations, unless otherwise specified in the individual monograph.

Uniformity of content

A requirement for compliance with the test for 5.1 Uniformity of content for single-dose preparations is specified in certain individual capsule monographs where the active ingredient is 5% or less of the total formulation. In such cases, the test for 5.2 Uniformity of mass for single-dose preparations is not required.

Dissolution/disintegration test

Where a choice of test is given ("Either test A or test B may be applied"), follow the instructions in the monograph. Where a requirement for the "Dissolution test" compliance with a dissolution test is specified in the individual monograph, compliance with 5.3 Disintegration test for tablets and capsules is not required.

Labelling

Every pharmaceutical preparation must comply with the labelling requirements established under GMP.

The label should include:

(1) the name of the pharmaceutical product;

(2) the name(s) of the active ingredient(s); International Nonproprietary Names (INNs) should be used wherever possible;

(3) the amount of the active ingredient(s) in each capsule and the number of capsules in the container;

(4) the batch (lot) number assigned by the manufacturer;

(5) the expiry date and, when required, the date of manufacture;

(6) any special storage conditions or handling precautions that may be necessary;
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(7) directions for use, warnings, and precautions that may be necessary; and
(8) the name and address of the manufacturer or the person responsible for placing the product on the market.

Storage

Capsules should be kept in well-closed containers. They should be protected from light, excessive moisture, or dryness, and should not be subjected to temperatures above 30°C. Additional special packaging, storage, and transportation recommendations are specified provided, where necessary, in the individual monograph.

Requirements for specific types of capsules

**Hard capsules**

Definition

Hard capsules have shells consisting of two prefabricated cylindrical sections that fit together. One end of each section is rounded and closed, and the other is open. The contents of hard capsules are usually in solid form (powder or granules).

Manufacture

The manufacturing and filling processes for hard capsules should meet the requirements of Good Manufacturing Practice (GMP), especially with regard to cross-contamination. The following information is intended to provide very broad guidelines concerning the main critical steps to be followed during production of hard capsules, indicating those that are the most important.

In the manufacture of hard capsules, measures are taken to:

- ensure that the active ingredient(s) have appropriate solid state properties such as particle-size distribution and polymorphic form;
- ensure that mixing with excipients is carried out in a manner that ensures homogeneity;
- minimize the degradation of the active ingredient(s);
- minimize the risk of microbial contamination;
- minimize the risk of cross-contamination.

The particle size of the active ingredient(s) is may be of primary significance in determining the rate and extent of dissolution, the bioavailability, and the uniformity of a drug product, especially for substances of low solubility in aqueous media. In order to obtain a suitable formulation, it is usually necessary to mix the active ingredient(s) with a
number of excipients. It is essential that such mixing is carried out in a manner that ensures homogeneity.

[Note from the Secretariat: general information on Manufacture have been moved under the main part of the monograph which is applicable to all types of capsules]

Sometimes, the physical characteristics of the mixture of the active ingredient(s) and excipients allow it to be directly filled into the shell, but it may occasionally be necessary to granulate before filling. Normally the granulate needs to be mixed with lubricants and/or disintegrating agents. The use of excessive amounts of lubricants should be avoided since these may deleteriously affect the capsules.

A uniform mass of the capsule mixture is volumetrically fed into the narrower lower section of the shell body which is then closed by slipping the larger section or cap over it. The security of the closure may be ensured by suitable means.

Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production. In-process controls during hard capsule production should include the particle size of the active ingredient(s), the homogeneity and moisture content of the mixture and/or granulate (as well as of the shells), the size of granules, the flow of the final mixture, and the uniformity of mass, capsule size, integrity of the seals, and disintegration or dissolution rate (e.g. for modified-release capsules) of the finished dosage form.

Packaging is required to be adequate to protect hard capsules from light, moisture and damage during transportation.

Disintegration test

Hard capsules comply with 5.3 Disintegration test for tablets and capsules.

Use water as the immersion fluid unless hydrochloric acid (0.1 mol/l) VS is specified in the individual monograph. Operate the apparatus for 30 minutes and examine the state of the capsules.

If capsules float, use a disc as described under 5.4 Disintegration test for suppositories.

Soft capsules

Definition

Soft capsules have thicker shells than hard capsules, and antimicrobial preservatives are usually added. The shells are of one piece and various shapes. The contents of soft
capsules are usually solutions or suspensions of the active ingredient(s) in non-aqueous liquids. Partial migration of the contents into the shell may occur (and vice versa) depending on the nature of the materials used and the product in question.

**Manufacture**

The manufacturing processes for soft capsules should meet the requirements of Good Manufacturing Practice. The following information is intended to provide very broad guidelines concerning the main steps to be followed during production, indicating those that are the most important.

The particle size of the active ingredient(s) is may be of primary significance in determining the rate and extent of dissolution, the bioavailability, and the uniformity of a drug product, especially for substances of low solubility in aqueous media. In order to obtain a suitable formulation, it is usually necessary to mix the active ingredient(s) with a number of excipients. It is essential that such mixing is carried out in a manner that ensures homogeneity.

Soft gelatin capsules are usually formed, filled, and sealed in one operation. However, shells for extemporaneous use are sometimes prefabricated. Liquids may be incorporated directly. Solids are usually dissolved or dispersed in a suitable excipient(s) to give a solution or dispersion of thick consistency.

Throughout manufacturing, certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production. In-process controls during soft capsule production should include the particle size of the active ingredient(s), the homogeneity of the mixture, the viscosity of the contents, and the uniformity of mass, capsule size, integrity of the seals, and disintegration or dissolution rate (e.g. for modified-release capsules) of the finished dosage form.

Packaging is required to be adequate to protect hard capsules from light, moisture and damage during transportation.

*[Note from the Secretariat: general information on Manufacture have been moved under the main part of the monograph which is applicable to all types of capsules]*

**Disintegration test**

Soft capsules comply with 5.3 Disintegration test for tablets and capsules, using water as the immersion fluid unless hydrochloric acid (0.1 mol/l) VS is specified in the individual monograph. Operate the apparatus for 30 minutes and examine the state of the capsules.
Modified-release capsules

Definition

Modified-release capsules are hard or soft capsules in which the contents or the shell or both contain additives excipients or are prepared by special procedures such as micro-encapsulation which, separately or together, are designed to modify the rate, place or time of release of the active ingredient(s) in the gastrointestinal tract.

Sustained-release capsules (Extended- or Prolonged-release capsules)

Definition

Sustained-release capsules are designed to slow the rate of release of the active ingredient(s) in the gastrointestinal tract.

All requirements for these specialized dosage forms are given in the individual monographs.

Delayed-release capsules (gastro-resistant/enteric capsules)

Definition

Delayed-release capsules are hard or soft capsules prepared in such a manner that either the shell or the contents resist the action of gastric fluid but release the active ingredient(s) in the presence of intestinal fluid.

Manufacture

The statements given under either hard or soft capsules apply, as appropriate to delayed-release capsules.

Disintegration test

Delayed-release capsules comply with 5.3 Disintegration test for tablets and capsules, using hydrochloric acid (0.1 mol/l) VS as the immersion fluid. Operate the apparatus for 2 hours, unless otherwise specified in the individual monograph (but in any case for not less than 1 hour), and examine the state of the capsules. No capsule should show signs of disintegration or rupture permitting the contents to escape. Replace the acid by phosphate buffer solution, pH 6.8, TS with added pancreatin R where specified in the individual monograph. Operate the apparatus for 60 minutes and examine the state of the capsules.

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