MARIGOLD EXTRACT AND ISOLATES (LUTEIN AND ZEAXANTHIN)

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

Notes:

- Text in parentheses is additional optional information which can be included on the PLA and product label at the applicant's discretion.
- The solidus (/) indicates that the terms are synonyms or that the statements are synonymous. Either term or statement may be selected by the applicant.
- A product may include one or more of the ingredients listed in Table 1.

Date August 18, 2011

Proper name(s), Common name(s) and Source material(s)

Table 1 Proper and common names, and source materials for marigold extract and its isolates.

Proper name	Common name	Source material
Tagetes erecta L. (Asteraceae)[1]	marigold extract[2] xanthophylls[3]	flower[4]
(3R,3´R,6´R)-beta,epsilon-carotene-3,3´-diol[5]	lutein[6]	oleoresin from the flower of marigold (*Tagetes erecta* L. (Asteraceae))[10]
(3R,3'R)-beta,beta-carotene-3,3'-diol[5]	zeaxanthin[6]	
lutein esters[7]	lutein esters[8]	
zeaxanthin esters[9]	zeaxanthin esters[9]	

1. USDA 2010; FAO/WHO 2006
2. WHO 2005
3. ChemIDplus 2011; FAO/WHO 2006
4. FAO/WHO 2006; WHO 2005
5. ChemIDplus 2011a,b; USP 34
6. ChemIDplus 2011a,b; USP 34; WHO 2005
7. ChemIDplus 2011; USP 34
8. ChemIDplus 2011; WHO 2005
9. US FDA 2002
10. USP 34; FAO/WHO 2006; WHO 2005

Route(s) of administration

Oral

Dosage form(s)

- The acceptable pharmaceutical dosage forms include, but are not limited to chewables (e.g. gummies, tablets), caplets, capsules, strips, lozenges, powders or liquids where the dose is measured in drops, teaspoons or tablespoons.
- This monograph is not intended to include foods or food-like dosage forms such as bars, chewing gums or beverages.

Use(s) or Purpose(s)

Statement(s) to the effect of:

General

For lutein, lutein esters, zeaxanthin, and zeaxanthin esters:

Antioxidant for the maintenance of good health (Miranda et al. 2006; Blakely et al. 2003; Dwyer et al. 2001).

For marigold extract:

Provides antioxidants for the maintenance of good health (Miranda et al. 2006; Blakely et al. 2003; Dwyer et al. 2001).

Specific

For lutein, lutein esters, zeaxanthin, and zeaxanthin esters:

Antioxidant for the maintenance of eye health (Miranda et al. 2006; Blakely et al. 2003; Dwyer et al. 2001).

For marigold extract:

Provides antioxidants for the maintenance of eye health (Miranda et al. 2006; Blakely et al. 2003; Dwyer et al. 2001).

For all medicinal ingredients in Table 1:

- Helps to maintain eyesight in conditions (associated with sunlight damage), such as cataracts and age-related macular degeneration (Christen et al. 2008; Fletcher et al. 2008; Johnson et al. 2008; Moeller et al. 2008; Alves-Rodrigues and Shao 2004; Richer et al. 2004; Olmedilla et al. 2003; Brown et al. 1999).
- Helps to support eye health in conditions (associated with sunlight damage), such as cataracts and age-related macular degeneration (Christen et al. 2008; Fletcher et al. 2008; Johnson et al. 2008; Moeller et al. 2008; Alves-Rodrigues and Shao 2004; Richer et al. 2004; Olmedilla et al. 2003; Brown et al. 1999).
- Helps to reduce the risk of developing cataracts (Christen et al. 2008; Moeller et al. 2008; Brown et al. 1999; Chasan-Taber et al. 1999).
- Helps to improve macular pigment optical density (Johnson et al. 2008; Richer et al. 2004; Berendschot et al. 2000).

Dose(s)

Subpopulation(s): Adults

Quantities:

Note:

The maximum daily amount indicated below for lutein and zeaxanthin esters should not be exceeded when lutein esters and/or zeaxanthin esters are combined with marigold extract.

LUTEIN AND ZEAXANTHIN

Antioxidant:

Preparations providing up to 20 mg lutein per day (Christen et al. 2008; Fletcher et al. 2008; Johnson et al. 2008; Moeller et al. 2008).
optional: Preparations providing up to 2.5 mg of zeaxanthin per day (Christen et al. 2008; Fletcher et al. 2008; Johnson et al. 2008; Moeller et al. 2008).

Eyesight:

Preparations equivalent to 6-20 mg lutein per day (Shao and Hathcock 2006; WHO 2005; Alves-Rodrigues and Shao 2004; Richer et al. 2004; Olmedilla et al. 2003; Brown et al. 1999).
optional: Preparations equivalent to 0.7-2.5 mg of zeaxanthin per day (Shao and Hathcock 2006; WHO 2005; Alves-Rodrigues and Shao 2004; Richer et al. 2004; Olmedilla et al. 2003; Brown et al. 1999).

LUTEIN AND ZEAXANTHIN ESTERS

Antioxidant:

Preparations providing up to 40 mg lutein esters per day (Christen et al. 2008; Fletcher et al. 2008; Johnson et al. 2008; Moeller et al. 2008).
optional: Preparations providing up to 5 mg of zeaxanthin esters per day (USP 34; Christen et al. 2008; Fletcher et al. 2008; Johnson et al. 2008; Moeller et al. 2008; FAO/WHO 2006).

Eyesight:

Preparations equivalent to 12-40 mg lutein esters per day (Bone and Landrum 2010; Shao and Hathcock 2006; WHO 2005; Alves-Rodrigues and Shao 2004; Richer et al. 2004; Olmedilla et al. 2003; Brown et al. 1999).
optional: Preparations equivalent to 1.5-5 mg of zeaxanthin esters per day (USP 34; Christen et al. 2008; Fletcher et al. 2008; Johnson et al. 2008; Moeller et al. 2008; FAO/WHO 2006).

MARIGOLD EXTRACT

The quantity of the marigold extract must be indicated on the PLA and label.

Lutein and zeaxanthin esters are potencies of marigold extract and must be indicated as such on the PLA and label. The amounts of the esters are described below and must be expressed as the quantity (mg) and/or percent (%) of the total quantity of the marigold extract. The marigold extract must contain less than 60% lutein esters.
Note: Disclosing the amount of zeaxanthin ester in a product is optional.

Antioxidant:

Preparations providing up to 40 mg lutein esters per day (Bone and Landrum 2010; Christen et al. 2008; Fletcher et al. 2008; Johnson et al. 2008; Moeller et al. 2008).
optional: Preparations providing up to 5 mg of zeaxanthin esters per day (USP 34; Christen et al. 2008; Fletcher et al. 2008; Johnson et al. 2008; Moeller et al. 2008; FAO/WHO 2006).

Eyesight:

Preparations equivalent to 12-40 mg lutein esters per day (Bone and Landrum 2010; Shao and Hathcock 2006; WHO 2005; Alves-Rodrigues and Shao 2004; Richer et al. 2004; Olmedilla et al. 2003; Brown et al. 1999).
optional: Preparations equivalent to 1.5-5 mg of zeaxanthin esters per day (USP 34; Christen et al. 2008; Fletcher et al. 2008; Johnson et al. 2008; Moeller et al. 2008; FAO/WHO 2006).

Directions for use:

For lutein and zeaxanthin esters, and marigold extract:

Take with a meal containing oil/fat (Chung et al. 2004; Roodenburg et al. 2000).

Duration(s) of use No statement required.

Risk information Statement(s) to the effect of:

Caution(s) and warning(s): No statement required.

Contraindication(s): No statement required.

Known adverse reaction(s):

For marigold extract:

Do not use if you are allergic to plants of the Asteraceae/Compositae/Daisy family.

Non-medicinal ingredients

Must be chosen from the current NHPD *Natural Health Products Ingredients Database* and must meet the limitations outlined in the database.

Storage conditions

Statement(s) to the effect of:

Store in tightly sealed, light- and oxygen-resistant container in a cool, dry place (USP 34).

Specifications

The finished product must comply with the minimum specifications outlined in the current NHPD *Compendium of Monographs*.

LUTEIN AND ZEAXANTHIN

- The medicinal ingredient must comply with the specifications outlined in either of the following references:
  FAO/WHO (2006): LUTEIN from *TAGETES ERECTA*
  USP 34: Lutein
  Lutein Preparation
- Lutein and zeaxanthin are preparations from the oleoresin of marigold (*Tagetes erecta* L.) petals obtained by hexane extraction and purified by saponification and crystallisation.

LUTEIN AND ZEAXANTHIN ESTERS

Lutein and zeaxanthin esters are preparations of oleoresin of marigold (*Tagetes erecta* L.) petals obtained by hexane extraction and then purified and concentrated.

MARIGOLD EXTRACT

- Marigold extract is a hexane extraction of the oleoresin of marigold (*Tagetes erecta* L.) petals which provides less than 60% lutein.
- The medicinal ingredient may comply with the specifications outlined in the FAO/WHO (2006): LUTEIN from *TAGETES ERECTA*.

General specifications

- Some commercial lutein preparations are sold as "5% or 10% lutein". These preparations are actually purified lutein (esterified or free) typically added at 5-15% to an inert stabilizing medium (e.g. USP 34: Lutein Preparation). When using these preparations, the applicant must specify whether lutein is esterified or free and use the appropriate dose information. For these preparations, the stabilizing medium must be listed as a non-medicinal ingredient in the PLA and label and identified as "stabilizing agent" in the PLA.

- In all cases where lutein and zeaxanthin (free or esterified) are listed on the PLA form, potency testing at the finished product stage is required to verify the quantity as different preparations may provide different amounts of lutein and zeaxanthin.
  OR
  The manufacturer of the finished product should ensure that there are sufficient controls on the raw materials so that the quantity of lutein and zeaxanthin (esterified or free) is the actual amount of lutein and zeaxanthin and not the amount of the lutein and zeaxanthin with the stabilizing excipient.

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Appendix 1 Guidance For Lutein Products

Background information is provided to clarify the requirements for quality information and completion of a Product Licence Application (PLA) for different preparations of lutein using the following information for marigold extract, lutein and zeaxanthin, and lutein and zeaxanthin esters.

Free lutein versus esterified lutein and zeaxanthin

The natural form of lutein and zeaxanthin is the esterified form. They can be de-esterified by saponification and purified by crystallization. After saponification, lutein and zeaxanthin are in their "free" or un-esterified form. As a result of this process, the dose for lutein and zeaxanthin should be used.

Lutein and zeaxanthin esters must be de-esterified before they are absorbed into the body; only free lutein and zeaxanthin are found in the human serum. Extracts that provide esterified lutein and zeaxanthin should be given with a meal containing fat or oil to increase the bioavailability of the esterified lutein and zeaxanthin.

Esterified lutein and zeaxanthin preparations can be concentrated (Figure 1). When the esterified lutein and zeaxanthin are concentrated, the dose for lutein and zeaxanthin esters should be used.

Marigold hexane extracts can undergo saponification and crystallization to provide lutein and zeaxanthin in a non-esterified form (Figure 2). As a result of this process, the dose for lutein and zeaxanthin should be used.

Lutein and zeaxanthin from marigold

In their natural esterified form, lutein and zeaxanthin are present in marigold at a ratio of about 8.7 to 1. It is difficult to separate lutein and zeaxanthin from each other and it is always assumed that lutein preparations from marigold will also contain zeaxanthin. As such, providing a quantity on the PLA form for zeaxanthin esters from marigold extract is optional.

Marigold extract

A hexane extraction of the oleoresin of marigold (*Tagetes erecta* L.) petals results in a marigold extract with less than 60% lutein esters (Figures 1 and 2). For this preparation, the medicinal ingredient should be listed as marigold extract. In order to support the claims for the marigold extract, the potency of lutein esters must be provided and assayed for in the finished product. Assayed zeaxanthin esters may also be provided.

Stabilization of lutein esters and lutein

Most commercial lutein is sold as a lutein preparation. Typically, these preparations are purified lutein and zeaxanthin (esterified or free) added at 5-15% to an excipient (e.g. USP 34: Lutein Preparation) for stabilization. When this is the case, either doses for lutein and zeaxanthin and

lutein and zeaxanthin esters should be used and the excipient should be added to the non-medicinal ingredients section of the PLA form with the purpose "stabilizing agent".

Potency testing at the finished product stage

When lutein and zeaxanthin (free or esterified) are listed on the PLA form, potency testing at the finished product stage is required to verify the quantity as different preparations may provide different amounts of lutein and zeaxanthin.

LUTEIN AND ZEAXANTHIN ESTERS FROM MARIGOLD

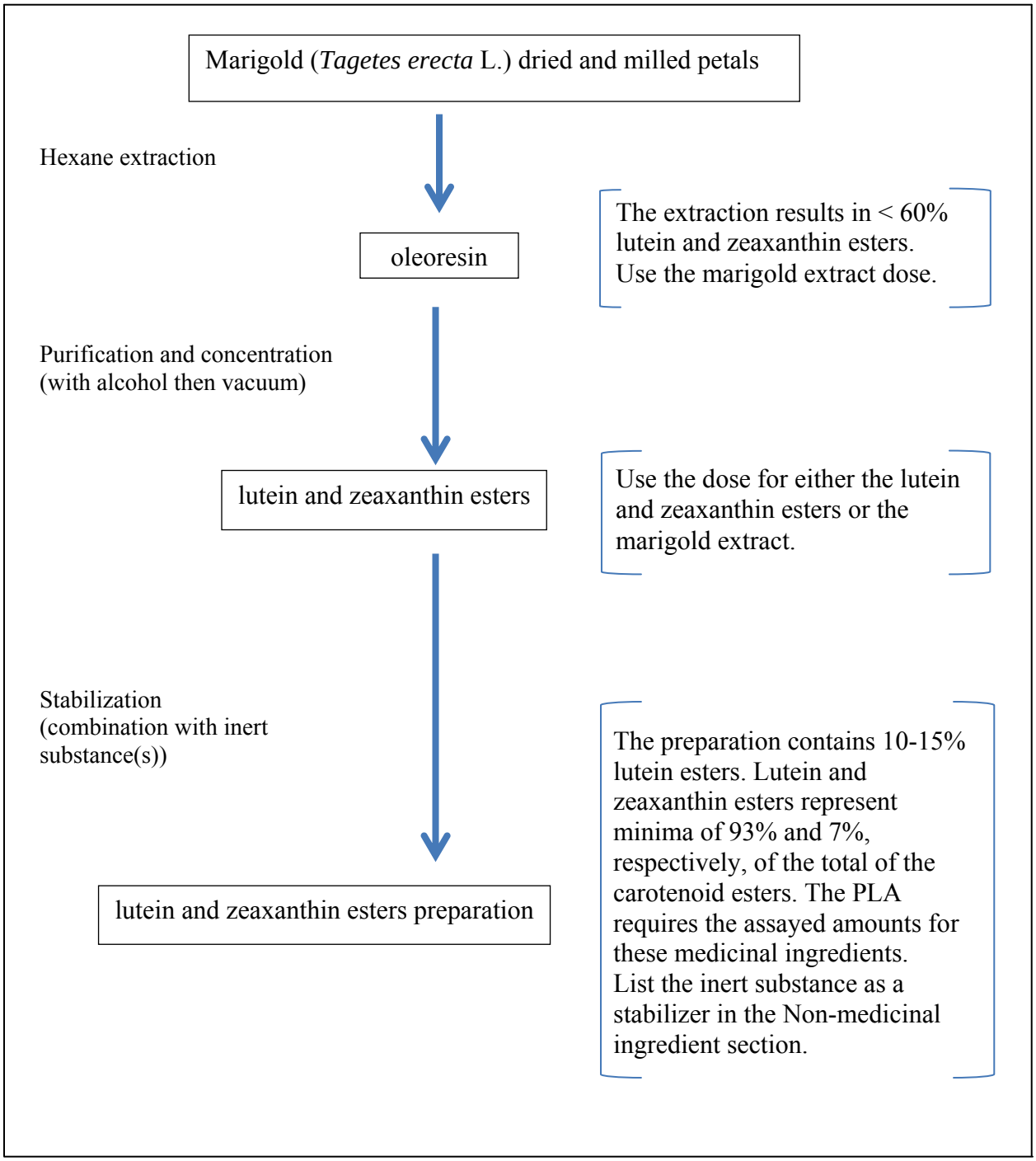

Figure 1 Process for obtaining lutein and zeaxanthin esters from marigold (*Tagetes erecta* L.) petals and guidance for product licence application (PLA). Lutein and zeaxanthin esters are extracted from the petals with a hexane solvent, purified and concentrated. Lutein and zeaxanthin esters are then stabilized with one or more inert substances. The information in brackets provides guidance for completing the PLA based on the resulting process protocol of the esters.

FREE LUTEIN AND ZEAXANTHIN FROM MARIGOLD

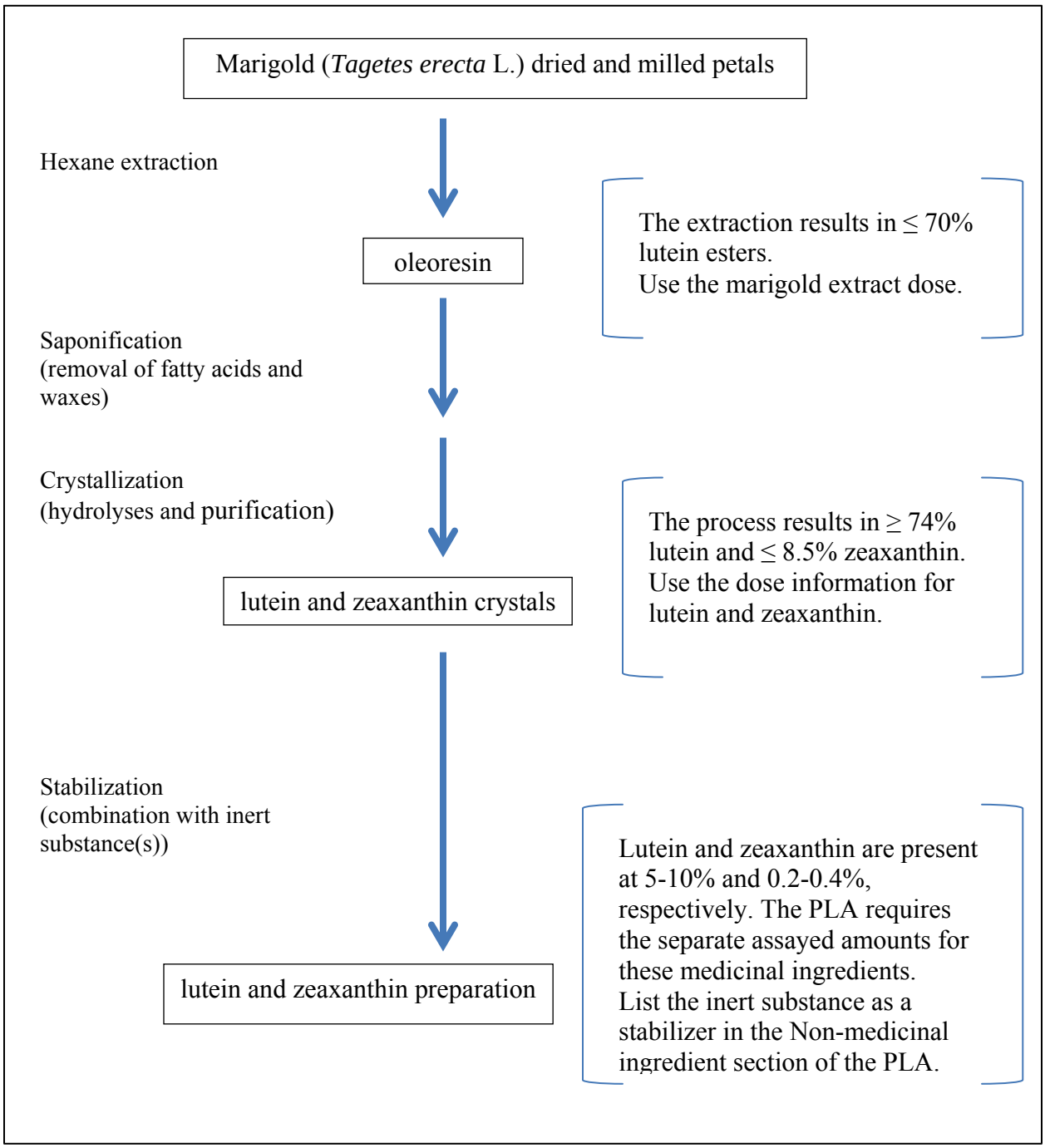

Figure 2 Process for obtaining lutein and zeaxanthin from marigold (*Tagetes erecta* L.) petals and guidance for product licence application (PLA). Lutein and zeaxanthin esters are extracted from the petals with a hexane solvent. Lutein and zeaxanthin esters are de-esterified by saponification. They are then crystallized and stabilized to provide free lutein and zeaxanthin. The information in brackets provides guidance for completing a PLA based on the resulting process protocol of the free form lutein and zeaxanthin.