MULTIPLE INGREDIENT JOINT HEALTH PRODUCTS

This monograph is intended to serve as a guide to industry for the preparation of Product Licence Applications (PLAs) for natural health product (NHP) market authorization. The monograph 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 or statements are synonymous. Either term or statement may be selected by the applicant.

**Date**

June 13, 2014

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

**Table 1** Proper names, common names and source materials of joint health ingredients

<table>
<thead>
<tr>
<th>Proper name</th>
<th>Common name</th>
<th>Source material</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Boswellia serrata</em> Roxb. ex Colebr. (Burseraceae)</td>
<td>Boswellia</td>
<td>Stem bark oleogum resin</td>
</tr>
<tr>
<td></td>
<td>Indian frankincense</td>
<td>Trunk bark oleogum resin</td>
</tr>
<tr>
<td>Fruit bromelain</td>
<td>Fruit bromelain</td>
<td>Ananas comosus var. comosus (fruit or stem)</td>
</tr>
<tr>
<td></td>
<td>Juice bromelain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pineapple fruit bromelain</td>
<td></td>
</tr>
<tr>
<td>Stem bromelain</td>
<td>Stem bromelain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bromelain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pineapple stem bromelain</td>
<td></td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>Chondroitin sulfate</td>
<td>Chondroitin sulfate sodium obtained from one or more of the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bovine (Bovidae) – cartilage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Porcine (Suidae) – cartilage</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Avian (Phasianidae) – cartilage</td>
</tr>
<tr>
<td>(1E,6E)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione</td>
<td>Curcumin</td>
<td>Curcuma longa rhizome</td>
</tr>
<tr>
<td><em>Harpagophytum procumbens</em> (Burch.) DC. ex Meisn. (Pedaliaceae)</td>
<td>Devil's claw</td>
<td>Secondary root tuber</td>
</tr>
<tr>
<td>Fish oil</td>
<td>Fish oil</td>
<td>Engraulidae – whole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carangidae – whole</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clupeidae – whole</td>
</tr>
<tr>
<td>Proper name¹</td>
<td>Common name²</td>
<td>Source material³</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
<td>------------------</td>
</tr>
</tbody>
</table>
| **Glucosamine hydrochloride** | Glucosamine hydrochloride | • Osmeridae – whole⁵  
• Scrombridae – whole⁵  
• Ammodytidae – whole⁵  
• Salmonidae – whole⁵  
|  |  | • Shrimp (Penaeidae) – exoskeleton⁶  
• Krill (Euphausiidae) – exoskeleton⁶  
• Prawn (Penaeoidea and/or Sergestoidea) – exoskeleton⁶  
• Crab (Cancridae) – exoskeleton⁶  
• Lobster (Nephropidae) – exoskeleton⁶  
• *Aspergillus* sp. (Trichocomaceae) – fermented⁸  
• *Monascus* sp. (Elaphomycetaceae) – fermented⁸  
• *Rhizopus* sp. (Mucoraceae) – fermented⁸  |
| **Glucosamine sulfate** | Glucosamine sulfate | • Shrimp (Penaeidae) – exoskeleton⁶,⁷  
• Krill (Euphausiidae) – exoskeleton⁶,⁷  
• Prawn (Penaeoidea and/or Sergestoidea) – exoskeleton⁶,⁷  
• Crab (Cancridae) – exoskeleton⁶,⁷  
• Lobster (Nephropidae) – exoskeleton⁶,⁷  |
| **Hyaluronic acid** | Hyaluronic acid | • Hyaluronic acid/Sodium hyaluronate obtained from *Gallus gallus* comb ⁹  
• Sodium hyaluronate obtained from the extracellular capsule of *Streptococcus, Lancefield Groups A and C* ⁹  |
| **Hydrolyzed collagen** | Hydrolyzed collagen; Collagen hydrolysate | • Porcine skin  
• Porcine bones  
• Fish skin  
• Fish bones  
• Bovine skin/hide split  
• *Gallus gallus* cartilage  
|  |  | • Methylsulfonylmethane  
• Dimethyl sulfone  
• Sulfonylbismethane  |
|  |  | Methylsulfonylmethane (MSM)  
Methylsulfonylmethane (MSM)  |
| *Curcuma longa* L. (Zingiberaceae) | Turmeric | Rhizome  |
| *Salix alba* L. | White willow | Bark  |
| Vitamin A; Vitamin C; Vitamin D; Vitamin K; Boron; Calcium; Magnesium; Manganese; Beta-carotene |  | NHPD Multi-Vitamin/Mineral Supplements monograph  |
1 At least one of the following references was consulted per proper name: ChemIDPlus 2012; Martindale 2012; Merck 2012; Ph.Eur. 2012; USP 35; USDA 2011; USDA 2009; ICIDH 2008; Kralovec and Barrow 2008; Towheed and Anastassiades 2007; O’Neil et al. 2006; IUBMB 1992.

2 At least one of the following references was consulted per common name: BP 2012; ChemIDPlus 2012; Martindale 2012; Merck 2012; Ph.Eur. 2012; USP 35; USDA 2009; Goel et al. 2008; ICIDH 2008; Kralovec and Barrow 2008; Towheed and Anastassiades 2007; O’Neil et al. 2006; Boon and Smith 2004; McGuffin et al. 2000; Moskowitz 2000; IUBMB 1992; Deodhar et al. 1980.


4 Cartilage must be derived from healthy and domestic animals used for food by humans (USP 35).

5 Corresponds to oil from the body of one or more of the following species in its natural triglyceride/triacylglycerol form and/or its concentrated esterified form:
  • Anchovy (any species of Engraulidae)
  • Jack or pompano (any species of Carangidae)
  • Herring, shad, sardine or menhaden (any species of Clupeidae)
  • Smelt (any species of Osmeridae)
  • Mackerel, tuna, or bonito (any species of Scombridae)
  • Sand lance (any species of Ammodytidae)
  • Salmonids (any species of Salmonidae)

6 The specific organisms used as source material(s) must be indicated in the Animal Tissue Form (ATF); simply indicating “crustaceans” is insufficient.

7 Acceptable salts include potassium chloride and sodium chloride (Kralovec and Barrow 2008). Example of labelling: glucosamine sulfate potassium chloride from shrimp.


9 The stabilizing salt (i.e. sodium) if present should be indicated.

Route(s) of administration

Oral

Dosage form(s)

- The acceptable pharmaceutical dosage forms include, but are not limited to capsules, chewables (e.g. gummies, tablets), liquids, powders, strips or tablets.
- 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

Notes

- It is mandatory for all products to cite at least one use or purpose statement from Table 2.
- A use or purpose statement is acceptable only if at least one medicinal ingredient associated with that statement is present at a dose at or above the minimum daily dose listed in Table 2.
Medicinal ingredients which do not meet the minimum daily dose for a use or purpose statement will be considered as acceptable complementary medicinal ingredients in product formulations.

The daily dose for glucosamine hydrochloride in combination with glucosamine sulfate is subject to the following limitations: the sum of the percents of their individual maximum daily doses must not exceed 120%; [(e.g. a product providing a daily dose of 2000 mg glucosamine hydrochloride (100% of the 2000 mg maximum daily dose) + 300 mg glucosamine sulfate (20% of the 1500 mg maximum daily dose) would be acceptable (100%+20%=120%)].

### Table 2  Joint health uses or purposes and associated daily doses

<table>
<thead>
<tr>
<th>Medicinal ingredient</th>
<th>Use or purpose¹</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boswellia serrata</td>
<td>Helps to relieve joint pain and swelling associated with osteoarthritis of the knee.</td>
<td>1000 mg extracts standardized to 40% boswellic acid, in 3 divided doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1000 mg extracts standardized to 40% boswellic acid, in 3 divided doses</td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>Helps to relieve (joint) pain associated with osteoarthritis (of the knee).</td>
<td>800 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1200 mg</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Used in Herbal Medicine to help relieve joint inflammation</td>
<td>400 mg, 3 times per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>400 mg, 3 times per day</td>
</tr>
<tr>
<td>Devil’s claw</td>
<td>Used in Herbal Medicine to help relieve joint pain associated with osteoarthritis.</td>
<td>600 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7500 mg</td>
</tr>
<tr>
<td>Fish oil²</td>
<td>In conjunction with conventional therapy, helps to reduce the pain of rheumatoid arthritis.</td>
<td>2800 mg eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) with a EPA:DHA ratio of 0.5-2:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3000 mg EPA+DHA with a EPA:DHA ratio of 0.5-2:1</td>
</tr>
<tr>
<td>Glucosamine hydrochloride</td>
<td>Helps to maintain healthy cartilage/joint health.</td>
<td>1500 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2000 mg</td>
</tr>
<tr>
<td>Glucosamine sulfate</td>
<td>• Helps to relieve joint pain associated with osteoarthritis (of the knee).</td>
<td>1500 mg</td>
</tr>
<tr>
<td></td>
<td>• Helps to protect against the deterioration of cartilage.</td>
<td>1500 mg</td>
</tr>
<tr>
<td></td>
<td>• A factor in maintaining healthy cartilage and/or joint health.</td>
<td>1500 mg</td>
</tr>
<tr>
<td>Hyaluronic acid</td>
<td>Helps support joint health</td>
<td>48 mg, from Gallus gallus comb extract</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120 mg, from Gallus gallus comb extract</td>
</tr>
<tr>
<td>Medicinal ingredient</td>
<td>Use or purpose</td>
<td>Daily dose</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>---------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minimum³</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120 mg, from</td>
</tr>
<tr>
<td></td>
<td></td>
<td>microbial</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fermentation</td>
</tr>
<tr>
<td>Hydrolyzed collagen</td>
<td>Helps to reduce joint pain associated with osteoarthritis</td>
<td>1200 mg</td>
</tr>
<tr>
<td>Methysulfonylmethane (MSM)</td>
<td>Helps to relieve (joint) pain associated with osteoarthritis (of the knee).</td>
<td>1500 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1000 mg dried rhizome OR extracts standardized to 3-5% curcuminoids</td>
</tr>
<tr>
<td>Turmeric</td>
<td>Turmeric is (traditionally) used in Herbal Medicine as an anti-inflamatory to help relieve joint pain.</td>
<td>3000 mg dried bark, in divided doses</td>
</tr>
<tr>
<td></td>
<td>(White willow is traditionally) used in Herbal Medicine for the relief of minor joint pain (due to osteoarthritis)</td>
<td>45 mg total salicin, in divided doses</td>
</tr>
</tbody>
</table>


⁴ The EPA:DHA ratio for fish oil must be between 0.5 and 2:1 (Volker et al. 2000; Sköldstam et al. 1992) and potency must be expressed as the quantity (mg) and/or percent (%) of EPA and DHA (% w/w) relative to the total quantity of fish oil.
### Table 3 Uses or purposes related to joint and bone health and associated daily doses

<table>
<thead>
<tr>
<th>Medicinal ingredient</th>
<th>Use or purpose¹</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Minimum²</td>
</tr>
<tr>
<td>Boron</td>
<td>Helps maintain healthy calcium metabolism</td>
<td>0.7 mg</td>
</tr>
<tr>
<td>Bromelain</td>
<td>Used in herbal medicine to help relieve minor pain, swelling and inflammation (anti-inflammatory)</td>
<td>20 mg⁴ and 480 000 FCC papain units per day</td>
</tr>
</tbody>
</table>
| Calcium              | • Adequate calcium (and vitamin D) (throughout life) as part of a healthy diet, (along with physical activity) may help prevent bone loss/osteoporosis / may reduce the risk of developing osteoporosis (in peri- and postmenopausal women) (in later life).  
• Helps in the development and maintenance of bones | 65 mg | 1500 mg |
| Vitamin A; Vitamin C; Vitamin D; Vitamin K⁵; Magnesium; Manganese; Beta-carotene⁶ | Helps in the development and maintenance of bones | NHPD Multi-Vitamin/Mineral Supplements monograph |

¹ At least two of the following references were consulted per use or purpose: Hunt CD 2012; FDA 2008; Tang et al. 2007; IOM 2006; NAMS 2006; Shils et al. 2006; Devirian and Volpe 2003; Brown and Josse 2002; Walker et al. 2002; Groff and Gropper 2000; NIH 2000; Blumenthal 1998; Hunter et al. 1997; IOM 1997; Nielsen et al. 1987.

² At least one of the following references was consulted per minimum daily dose: Hunt CD 2012; IOM 2006; Walker et al. 2002; Blumenthal 1998.

³ At least one of the following references was consulted per maximum daily dose: Hunt CD 2012; IOM 2006; Kerkhoffs et al. 2004; Singer et al. 2001.

⁴ Dose unit information must include the quantities of both the enzyme preparation and its enzymatic activity, in FCC PU. Note that:
• One papain unit (PU) is defined as that quantity of enzyme that liberates the equivalent of 1 μg of tyrosine per hour under the conditions of the assay (FCC 8).
• One gelatin digestion unit (GDU) is approximately equivalent to 15 000 FCC papain units (1 GDU ≈ 15 000 FCC PU).
The recommended use for Vitamin K is “Helps in the maintenance of bones” only.

The recommended use for Beta-carotene is “Source of vitamin A/Provitamin A to help in the development and maintenance of bones”.

### Dose(s)

### Subpopulation(s)

Adults (≥ 18 y)

### Quantity(ies)

Refer to Tables 2 and 3.

### Direction(s) for use

#### Table 4 Directions for use

<table>
<thead>
<tr>
<th>Medicinal ingredient</th>
<th>Direction(s) for use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boron</td>
<td>If product is not a source of Vitamin D and Calcium: Take with vitamin D and calcium (Devirian and Volpe 2003; Zittermann 2003).</td>
</tr>
<tr>
<td>Bromelain</td>
<td>Optional: Take with food/meal (NHPD 2012).</td>
</tr>
<tr>
<td>Calcium</td>
<td>Take a few hours before or after taking other medications or natural health products (Sweetman 2007, ASHP 2005).</td>
</tr>
<tr>
<td>Methysulfonylmethane (MSM), for products providing ≥ 1500 mg per day</td>
<td>• Take with food (Kim et al. 2006). • Avoid taking at bedtime (Kim et al. 2006).</td>
</tr>
</tbody>
</table>

### Duration of use

### Notes

- ▶ A minimum duration of use statement is required for all products citing use or purpose statements associated with boswellia, chondroitin sulfate, devil’s claw, glucosamine (hydrochloride and sulfate), hydrolyzed collagen or methysulfonylmethane (MSM).
- ▶ If more than one duration of use statement is indicated for a particular product formulation, only the shortest applicable duration of use statement is required on the PLA and product label. For example, a product citing use or purpose statements for chondroitin sulfate and glucosamine hydrochloride need only include the following duration of use statement on the product label: “Use for a minimum of 1 month to see beneficial effects.”
- ▶ A maximum duration of use statement is required for all products containing bromelain or white willow.

### Minimum duration of use
Table 5  Minimum duration of use

<table>
<thead>
<tr>
<th>Medicinal ingredient</th>
<th>Minimum duration of use1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrolyzed collagen</td>
<td>Use for a minimum of 5 months to see beneficial effects.</td>
</tr>
<tr>
<td>Chondroitin sulfate</td>
<td>Use for a minimum of 3 months to see beneficial effects.</td>
</tr>
<tr>
<td>Devil’s claw</td>
<td>Use for a minimum of 2-3 months to see beneficial effects.</td>
</tr>
<tr>
<td>Boswellia</td>
<td>Use for a minimum of 2 months to see beneficial effects.</td>
</tr>
<tr>
<td>glucosamine hydrochloride</td>
<td></td>
</tr>
<tr>
<td>glucosamine sulfate</td>
<td>Use for a minimum of 1 month to see beneficial effects.</td>
</tr>
<tr>
<td>methysulfonylmethane (MSM)</td>
<td></td>
</tr>
</tbody>
</table>

1 At least one of the following references was consulted per duration of use: Bruyère et al. 2012; Benito-Ruiz et al. 2009; Clark et al. 2008; Bjordal et al. 2007; Mehta et al. 2007; Sontakke et al. 2007; Kim et al. 2006; Usha and Naidu 2004; ESCOP 2003; Kimmatkar et al. 2003; Houpt et al. 1999; Qiu et al. 1998.

Maximum duration of use

Products containing bromelain and/or white willow

For prolonged use, consult a health care practitioner (NHPD 2012; EMEA 2009; Beer and Wegener 2008; Biegert et al. 2004; Chrubasik 2000).

Risk Information  Statement(s) to the effect of

Caution(s) and warning(s)

All products

- If you are pregnant or breastfeeding, consult a health care practitioner prior to use.
- If symptoms worsen, consult a health care practitioner.

Table 6  Caution(s) and warning(s)

<table>
<thead>
<tr>
<th>Medicinal ingredient</th>
<th>Caution(s) and warning(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boron</td>
<td>If you have been diagnosed with estrogen-dependant cancer, consult a health care practitioner prior to use (Nielsen et al. 1992).</td>
</tr>
<tr>
<td></td>
<td>If you have a kidney disorder, consult a health care practitioner prior to use (Usuda et al. 1996).</td>
</tr>
<tr>
<td>Bromelain</td>
<td>If you have a gastrointestinal lesion/ ulcer, are taking an anticoagulant/ blood thinner, anti-inflammatory or antibiotic, or are having surgery, consult a health care practitioner prior to use (Martindale 2011; Brinker 2010; Blumenthal et al. 2000).</td>
</tr>
<tr>
<td>Curcumin</td>
<td>If you are taking antiplatelet medication or blood thinners, consult a health care practitioner prior to use (Mills and Bone 2005; Brinker 2001).</td>
</tr>
<tr>
<td></td>
<td>If you have gallstones or a bile duct obstruction, consult a health care practitioner prior to use (Mills and Bone 2005; Brinker 2001).</td>
</tr>
<tr>
<td>Ingredient</td>
<td>Precaution</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Fish oil AND White willow combined</td>
<td>If you have a gastrointestinal lesion/ulcer, are taking blood thinners or are having surgery, consult a health care practitioner prior to use (Block et al. 2012, 2013; Larson et al. 2008).</td>
</tr>
<tr>
<td>Hydrolyzed collagen, for doses above 2.8 g per day</td>
<td>If you have liver or kidney disease or if you have been instructed to follow a low protein diet, consult a health care practitioner prior to use (Shils et al. 2006; Goldman and Ausiello 2004).</td>
</tr>
<tr>
<td>Manganese</td>
<td>Doses &gt; 5 mg If you have gallstones or a bile duct obstruction, consult a health care practitioner prior to use (IOM 2001; Krieger et al. 1995)</td>
</tr>
<tr>
<td>Turmeric</td>
<td>If you have stomach ulcers or excess stomach acid, consult a health care practitioner prior to use (Brinker 2001; McGuffin et al. 1997).</td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Doses &gt; 6 µg If you are taking blood thinners, consult a health care practitioner prior to use (ASHP 2005; Franco et al 2004; IOM 2001; Hansten et al 1997)</td>
</tr>
<tr>
<td>White willow</td>
<td>If you are taking anticoagulants or products containing acetylsalicylic acid (ASA) or other salicylates, consult a health care practitioner prior to use (EMEA 2009).</td>
</tr>
</tbody>
</table>

**Contraindication(s)**

*Products containing white willow*

- If you are pregnant or breastfeeding, do not use this product (Brinker 2010; EMEA 2009; Wichtl 2004; ESCOP 2003; Barnes et al. 2002; Blumenthal et al. 2000).
- If you are allergic to acetylsalicylic acid (ASA) or other salicylates, do not use this product (Brinker 2010; EMEA 2009; Wichtl 2004, ESCOP 2003; Barnes et al. 2002; Blumenthal et al. 2000).

**Known adverse reaction(s)**

*Products containing boswellia and/or bromelain*

Hypersensitivity (e.g. allergy) has been known to occur; in which case, discontinue use (Martindale 2011; Brinker 2010; WHO 2009; Murray and Pizzorno 2006; Blumenthal et al. 2000; Baur and Fruhmann 1979).

*Products containing boswellia, bromelain, hydrolyzed collagen, methysulfonylemethane and/or white willow*

Some people may experience mild gastrointestinal disturbances such as diarrhoea, abdominal pain, heartburn, nausea and vomiting; in which case, discontinue use (Martindale 2011; Brinker...
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2010; EMEA 2009; Sontakke et al. 2007; Brien et al. 2006; Kim et al. 2006; Wichtl 2004;
ESCOP 2003; Kimmatkar et al. 2003; Barnes et al. 2002; Blumenthal et al. 2000; McGuffin
2000; Moskowitz 2000).

Products providing > 350 mg magnesium per day

Some people may experience diarrhea (IOM 2006, IOM 1997).

Storage conditions

All products

Store in airtight container, protected from light (Ph.Eur. 2012; USP 35).

Products containing fish oil, except those encapsulated

Refrigerate after opening (Wille and Gonus 1989).

Products containing hydrolyzed collagen

Protect from heat and moisture (Ph.Eur. 2012).

Non-medicinal ingredients

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

Specifications

- The finished product specifications must be established in accordance with the requirements described in the NHPD Quality of Natural Health Products Guide.
- The medicinal ingredient must comply with the requirements outlined in the Natural Health Products Ingredients Database (NHPID).
- In order to minimize the risk of Transmissible Spongiform Encephalopathies (TSEs) from products sourced from bovine tissues, product licence applicants must have a veterinary certificate on file and must ensure that the following criteria have been met (Ph.Eur. 2012):
  i. Source animal is fit for human consumption;
  ii. Source material can be traced back to the herd or animal;
  iii. Avoidance of cross-contamination with high-infectivity tissues is ensured during sourcing;
  iv. Manufacturing procedures that are known to reduce infectivity are implemented (e.g. procedures that are in accordance with those outlined in Chapter 5.02.08 of the
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European Pharmacopoeia 2012 ‘Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products’).

- Peroxide, anisidine, and totox values of fish oil and omega-3 fatty acids derived from fish oil must be in accordance with the methods set out by the Association of Analytical Community (AOAC) and/or Pharmacopoeial analytical methods. These specifications are necessary to ensure the oxidative stability of the fish oil and the omega-3 fatty acids derived from fish oil (HC 2013). Refer to Table 7 below.

- The dioxins, polychlorinated dibenzo-para-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs); the dioxin-like polychlorinated biphenyls (dioxin-like PCBs; and the polychlorinated biphenyls (PCBs) are contaminants in oils from marine sources. Testing for these contaminants are required and must be performed using either the analytical method of the European Commission Regulation EU 252/2012 (EU 2012) or the U.S. Environmental Protection Agency’s method 1613B for PCDDs and PCDFs and method 1668A for PCBs (USP 35; US EPA 2010, 2008,1994). Applicants are advised to consult the Council of the European Union document on these contaminants for further information (EU 2011). Refer to Table 8 below.

- **Bromelain**
  i. Details of the manufacturing of the enzyme at the raw material stage should include fermentation medium, and the isolation process of the medicinal ingredient.
  ii. The specifications must include testing for enzymatic activity of the medicinal ingredient at appropriate stages of formulation and manufacturing using the assay outlined in the current Food Chemicals Codex (FCC): PLANT PROTEOLYTIC ACTIVITY.
  iii. Where published methods are not suitable for use, manufacturers will use due diligence to ensure that the enzymes remain active to the end of the shelf life indicated on the product label.

- **Hyaluronic acid**
  i. Information pertaining to the molecular weight of the hyaluronic acid must be available upon request for characterization (e.g. Certificate of Analysis, Technical Data Sheet, Product Information, etc). The molecular weight of hyaluronic acid obtained from *Gallus gallus* comb must be 800 kDa. The molecular weight of sodium hyaluronate from *Streptococcus equi* must be between 30-900 kDa
  ii. Information regarding Method of preparation must be provided upon request
  iii. For all products obtained through microbial fermentation, the species of *Streptococcus* used must be provided upon request and should be substantiated by the evidence. Information regarding manufacturing processes that reduce or eliminate pyrogenic or inflammatory components of the cell wall must be submitted upon request.
  iv. The content of sulfated glycosaminoglycans, nucleic acids, protein, and microbial contamination derived from this ingredient must be in accordance with the methods set out by the European Pharmacopoeia:
    - Sulfated glycosaminoglycans: maximum 1%, if the ingredient is extracted from *Gallus gallus* comb
    - Nucleic acids: the absorbance of solution at 260 nm is maximum 0.5
    - Protein: maximum 0.3%
    - Microbial contamination: Total Aerobic Microbial Count of $10^2$ CFU/g

- **Hydrolyzed Collagen**
i. For the purpose of this monograph, hydrolyzed collagen has no jelling power and is soluble in cold water (Schrieber and Gareis 2007; Moskowitz 2000).

ii. The average molecular weight of hydrolyzed collagen is approximately 2-6 kDa (Moskowitz 2000; Oesser et al. 1999).

**Table 7** Maximum values of oxidative stability parameters for fish oil (HC 2013)

<table>
<thead>
<tr>
<th>Oxidative stability parameter</th>
<th>Maximum value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peroxide value (PV)</td>
<td>5 mEq/kg</td>
</tr>
<tr>
<td>p-Anisidine value (AV)</td>
<td>20 mEq/kg</td>
</tr>
<tr>
<td>Totox value</td>
<td>26 mEq/kg (calculated as (2 x PV) + AV)</td>
</tr>
</tbody>
</table>

**Table 8** Acceptable limits of dioxins and dioxin-like polychlorinated biphenyls in oils from marine sources

<table>
<thead>
<tr>
<th>Dioxin and dioxin-like polychlorinated biphenyl contaminants</th>
<th>Maximum level&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum of PCDDs + PCDFs</td>
<td>2.0 pg TEQ TEF/g oil</td>
</tr>
<tr>
<td>Sum of dioxins and dioxin-like PCBs&lt;sup&gt;2&lt;/sup&gt;</td>
<td>10.0 pg TEQ TEF/g oil</td>
</tr>
</tbody>
</table>

<sup>1</sup> Expressed in World Health Organization (WHO) toxic equivalents using WHO-toxic equivalent factors (TEFs). Analytical results relating to 17 individual dioxin congeners of toxicological concern are expressed in a single quantifiable unit: 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxic equivalent concentration or TEQ (EU 2006).

<sup>2</sup>The dioxin-like PCBs that can be determined by Method 1668B are the 12 PCBs designated as toxic by WHO: congeners 77, 81, 126, 169, 105, 114, 118, 123, 156, 157, 167, and 189 (EPA 2008; EU 2006).

**References cited**


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