ORIGINAL SUBMISSION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

GENERALLY RECOGNIZED AS SAFE *(GRAS)* NOTICE

Form Approved: OMB No. 0910-0342; Expiration Date: 03/31/2019
(See last page for OMB Statement)

FDA USE ONLY

GRN NUMBER	DATE OF RECEIPT
000686	01/05/2017
ESTIMATED DAILY INTAKE	INTENDED USE FOR INTERNET
NAME FOR INTERNET	
KEYWORDS	

Transmit completed form and attachments electronically via the Electronic Submission Gateway *(see Instructions)*; OR Transmit completed form and attachments in paper format or on physical media to: Office of Food Additive Safety *(HFS-200)*, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740-3835.

PART I – INTRODUCTORY INFORMATION ABOUT THE SUBMISSION

1. Type of Submission *(Check one)*

☒ New ☐ Amendment to GRN No. _____ ☐ Supplement to GRN No. _____

2. ☒ All electronic files included in this submission have been checked and found to be virus free. *(Check box to verify)*

3a. For New Submissions Only: Most recent presubmission meeting *(if any)* with FDA on the subject substance *(yyyy/mm/dd):* NA

3b. For Amendments or Supplements: Is your amendment or supplement submitted in response to a communication from FDA? *(Check one)* ☐ Yes ☐ No If yes, enter the date of communication *(yyyy/mm/dd):* _____

PART II – INFORMATION ABOUT THE NOTIFIER

1a. Notifier

Name of Contact Person	Position
KG Rao	President

Company *(if applicable)*: DolCas Biotech, LLC

Mailing Address *(number and street)*: 9 Lenel Road

City	State or Province	Zip Code/Postal Code	Country
Landing	New Jersey	07850	United States of America

Telephone Number	Fax Number	E-Mail Address
973-347-1958	973-347-0433	grao@dolcas-biotech.com

1b. Agent or Attorney *(if applicable)*

Name of Contact Person	Position
N/A	

Company *(if applicable)*:

Mailing Address *(number and street)*:

City	State or Province	Zip Code/Postal Code	Country

Telephone Number	Fax Number	E-Mail Address

PART III – GENERAL ADMINISTRATIVE INFORMATION

1. Name of Substance

BCM 95 (curcumin)

2. Submission Format: *(Check appropriate box(es))*

☐ Electronic Submission Gateway

☒ Paper

☒ Electronic files on physical media with paper signature page

If applicable give number and type of physical media

one copy on CD virus free

3. For paper submissions only:

Number of volumes 1

Total number of pages 128

4. Does this submission incorporate any information in FDA's files by reference? *(Check one)*

☐ Yes *(Proceed to Item 5)* ☒ No *(Proceed to Item 6)*

5. The submission incorporates by reference information from a previous submission to FDA as indicated below *(Check all that apply)*

☐ a) GRAS Notice No. GRN _____

☐ b) GRAS Affirmation Petition No. GRP _____

☐ c) Food Additive Petition No. FAP _____

☐ d) Food Master File No. FMF _____

☐ e) Other or Additional *(describe or enter information as above)* _____

6. Statutory basis for determination of GRAS status *(Check one)*

☒ Scientific Procedures *(21 CFR 170.30(b))* ☐ Experience based on common use in food *(21 CFR 170.30(c))*

7. Does the submission (including information that you are incorporating by reference) contain information that you view as trade secret or as confidential commercial or financial information?

☐ Yes *(Proceed to Item 8)*

☒ No *(Proceed to Part IV)*

8. Have you designated information in your submission that you view as trade secret or as confidential commercial or financial information *(Check all that apply)*

☐ Yes, see attached Designation of Confidential Information

☐ Yes, information is designated at the place where it occurs in the submission

☐ No

9. Have you attached a redacted copy of some or all of the submission? *(Check one)*

☐ Yes, a redacted copy of the complete submission

☐ Yes, a redacted copy of part(s) of the submission

☐ No

PART IV – INTENDED USE

1. Describe the intended use of the notified substance including the foods in which the substance will be used, the levels of use in such foods, the purpose for which the substance will be used, and any special population that will consume the substance *(e.g., when a substance would be an ingredient in infant formula, identify infants as a special population).*

DolCas intends to incorporate BCM-95® into selected food categories (yogurt, nutrition bars, smoothies and medical foods) as a nutrient supplement as defined by FDA in 21 CFR 170.30 at use levels described in Section IV (B)

2. Does the intended use of the notified substance include any use in meat, meat food product, poultry product, or egg product? *(Check one)*

☐ Yes ☒ No

PART V – IDENTITY

1. Information about the Identity of the Substance

	Name of Substance[1]	Registry Used *(CAS, EC)*	Registry No.[2]	Biological Source *(if applicable)*	Substance Category *(FOR FDA USE ONLY)*
1	BCM-95®(*Curcuma longa* L.)	458-37-7		turmeric rhizome	
2					
3					

[1] Include chemical name or common name. Put synonyms *(whether chemical name, other scientific name, or common name)* for each respective item (1 - 3) in Item 3 of Part V *(synonyms)*

[2] Registry used e.g., CAS *(Chemical Abstracts Service)* and EC *(Refers to Enzyme Commission of the International Union of Biochemistry (IUB), now carried out by the Nomenclature Committee of the International Union of Biochemistry and Molecular Biology (IUBMB))*

2. Description

Provide additional information to identify the notified substance*(s)*, which may include chemical formula*(s)*, empirical formula*(s)*, structural formula*(s)*, quantitative composition, characteristic properties *(such as molecular weight(s)),* and general composition of the substance. For substances from biological sources, you should include scientific information sufficient to identify the source *(e.g., genus, species, variety, strain, part of a plant source (such as roots or leaves), and organ or tissue of an animal source)*, and include any known toxicants that could be in the source.

BCM-95® is a reconstituted, purified and standardized turmeric extract,from the rhizome,which enhances the oral bioavailability of curcumin in blood. It contains a specialized unique blend of curcuminoids (curcumin, demethoxy curcumin and bisdemethoxy curcumin) and essential oil of turmeric.

BCM-95® consists of no less than 85% curcuminoids and 5-7% volatile oils.

3. Synonyms

Provide as available or relevant:

1	curcumin
2	turmeric
3	Biocurcumax™ and Biocurcumin™

PART VI – OTHER ELEMENTS IN YOUR GRAS NOTICE

(check list to help ensure your submission is complete – check all that apply)

- ☐ Any additional information about identity not covered in Part V of this form
- ☒ Method of Manufacture
- ☒ Specifications for food-grade material
- ☒ Information about dietary exposure
- ☒ Information about any self-limiting levels of use *(which may include a statement that the intended use of the notified substance is not-self-limiting)*
- ☒ Use in food before 1958 *(which may include a statement that there is no information about use of the notified substance in food prior to 1958)*
- ☒ Comprehensive discussion of the basis for the determination of GRAS status
- ☒ Bibliography

Other Information

Did you include any other information that you want FDA to consider in evaluating your GRAS notice?

☒ Yes ☐ No

Did you include this other information in the list of attachments?

☒ Yes ☐ No

PART VII – SIGNATURE

1. The undersigned is informing FDA that DolCas Biotech, LLC *(name of notifier)*

has concluded that the intended use*(s)* of BCM 95 (curcumin) *(name of notified substance)*

described on this form, as discussed in the attached notice, is (are) exempt from the premarket approval requirements of section 409 of the Federal Food, Drug, and Cosmetic Act because the intended use(s) is (are) generally recognized as safe.

2. ☒ DolCas Biotech, LLC *(name of notifier)* agrees to make the data and information that are the basis for the determination of GRAS status available to FDA if FDA asks to see them.

DolCas Biotech, LLC *(name of notifier)* agrees to allow FDA to review and copy these data and information during customary business hours at the following location if FDA asks to do so.

9 Lenel Road, Landing, NJ 07850 *(address of notifier or other location)*

DolCas Biotech, LLC *(name of notifier)* agrees to send these data and information to FDA if FDA asks to do so.

OR

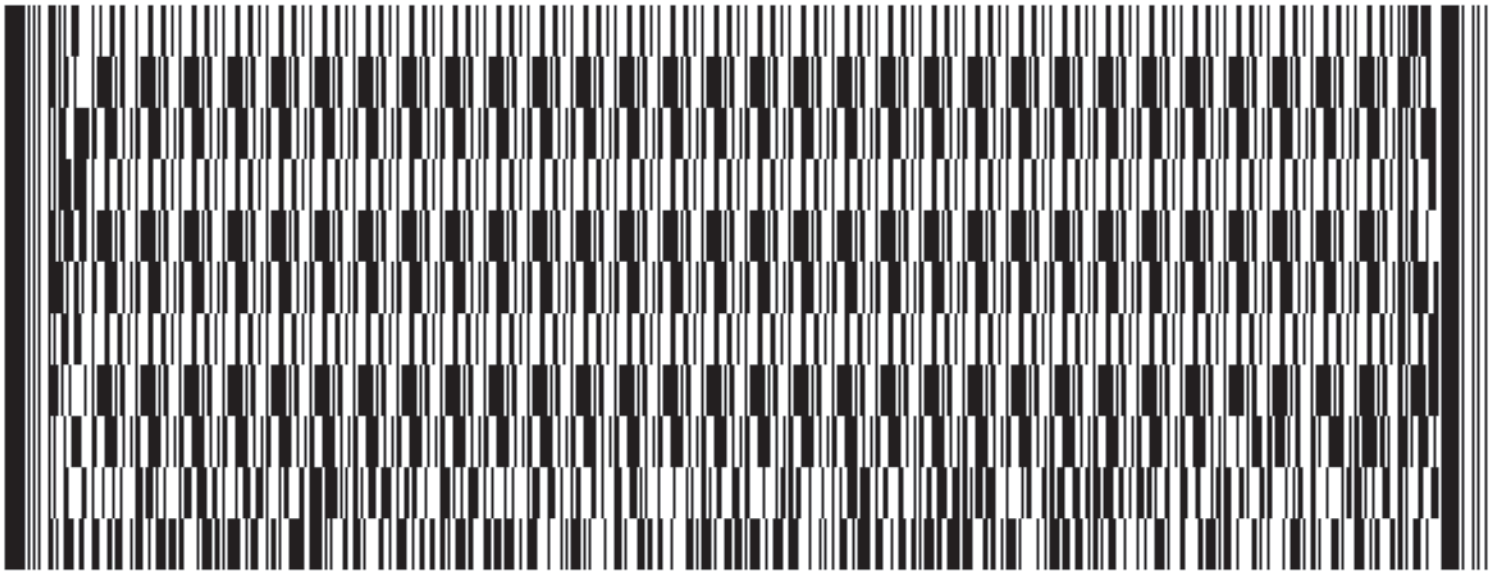
☐ The complete record that supports the determination of GRAS status is available to FDA in the submitted notice and in GRP No. ---------- *(GRAS Affirmation Petition No.)*

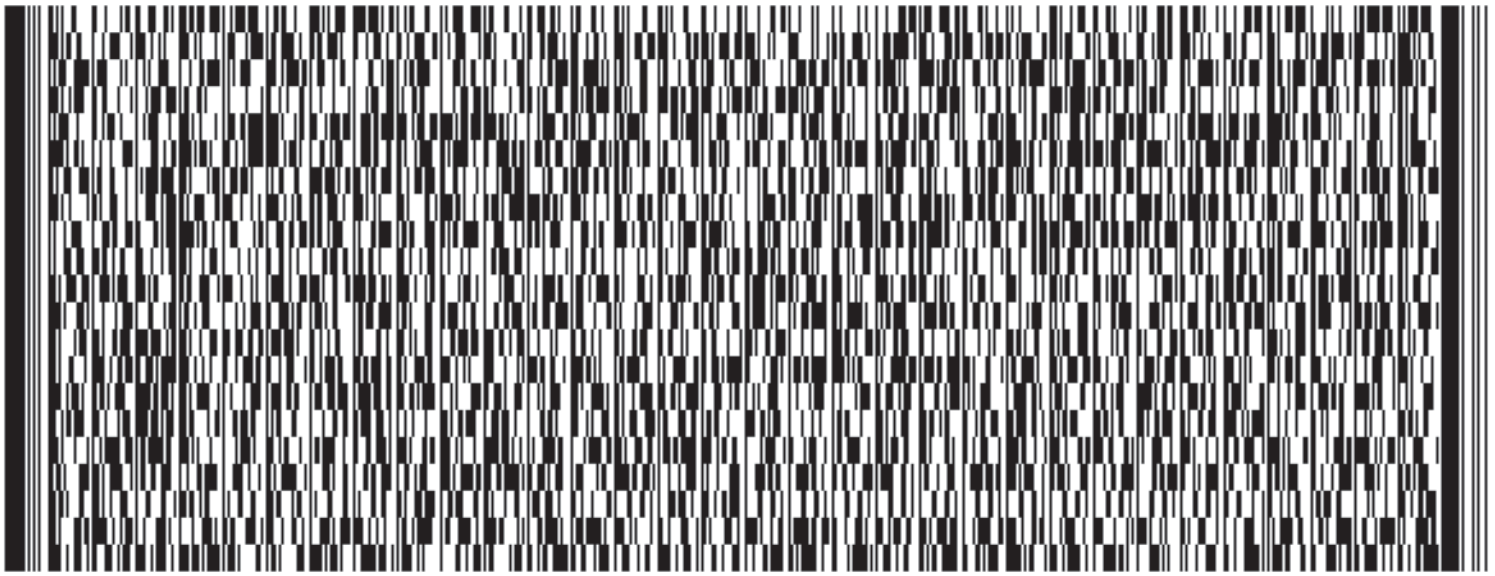
3. Signature of Responsible Official, Agent, or Attorney	**Printed Name and Title**	**Date (mm/dd/yyyy)**
K G Rao Digitally signed by K G Rao DN: cn=K G Rao, o=DolCas Biotech, ou=President, email=grao@dolcas-biotech.com, c=US Date: 2016.10.27 13:12:36 -04'00'	KG Rao, President	10/13/2016

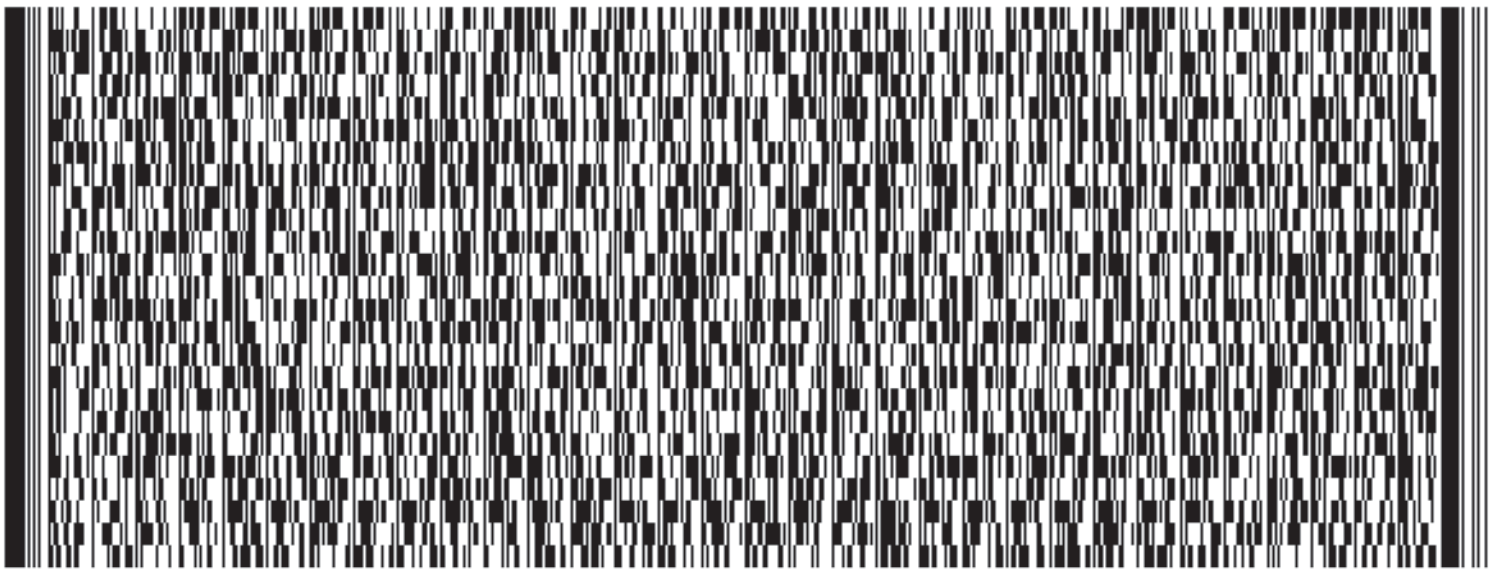
PART VIII – LIST OF ATTACHMENTS

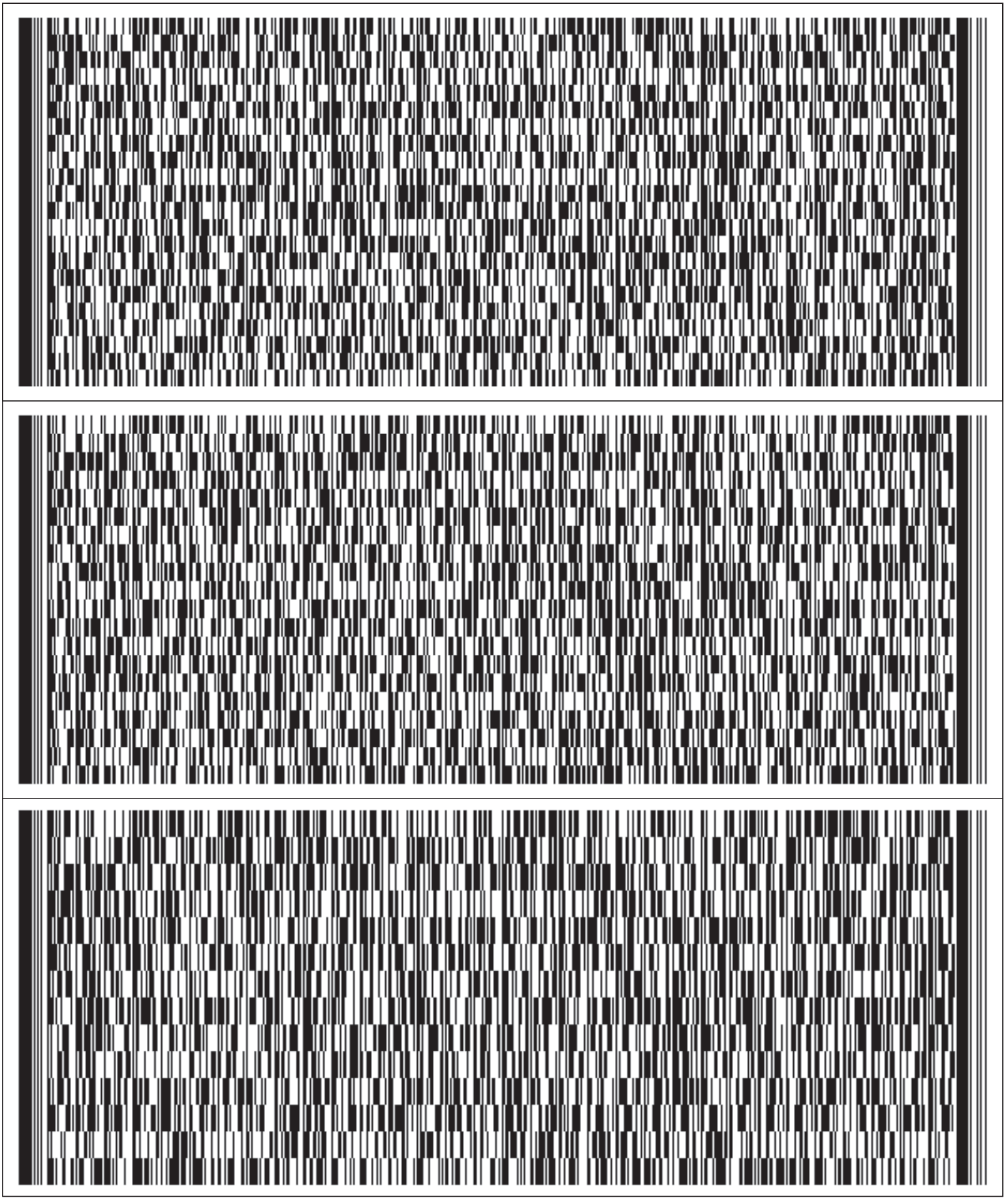
List your attached files or documents containing your submission, forms, amendments or supplements, and other pertinent information. Clearly identify the attachment with appropriate descriptive file names (or titles for paper documents), preferably as suggested in the guidance associated with this form. Number your attachments consecutively. When submitting paper documents, enter the inclusive page numbers of each portion of the document below.

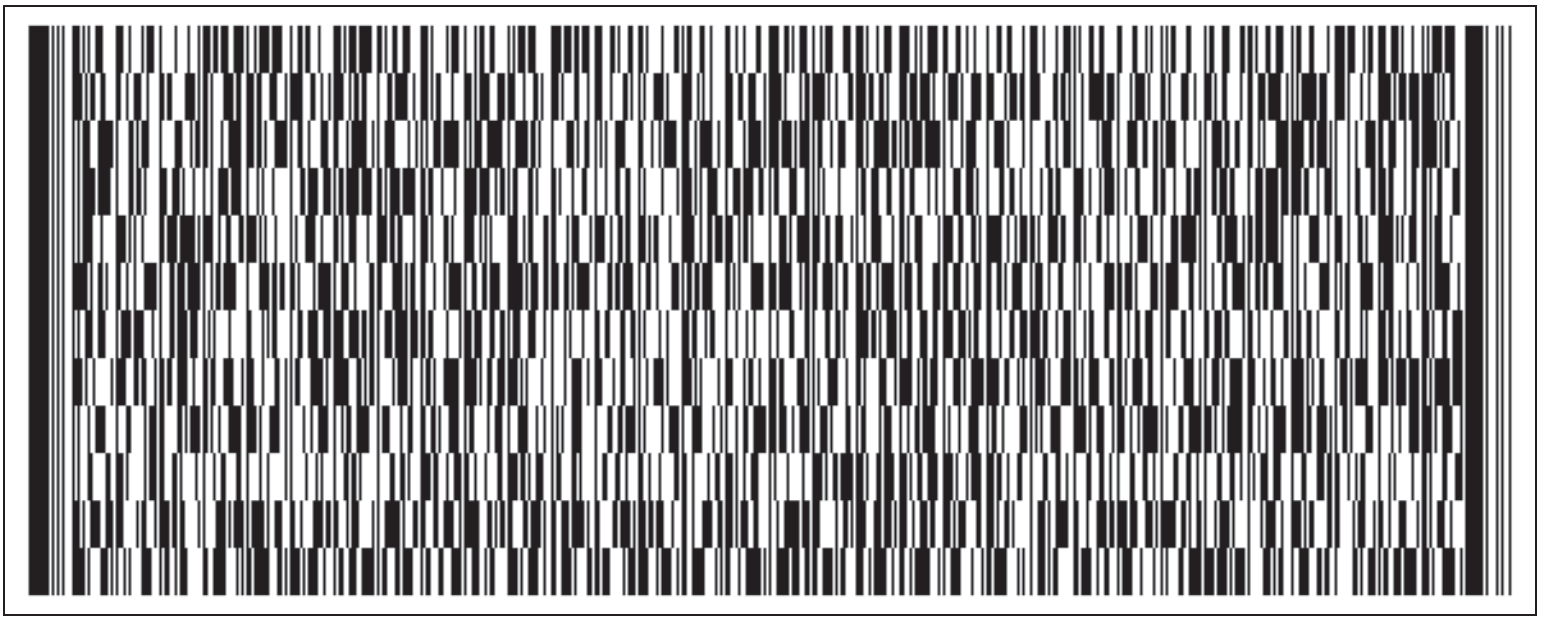
Attachment Number	Attachment Name	Folder Location (select from menu) (Page Number(s) for paper Copy Only)
	Summary of Safety Data And Food usage conditions For conclusion of General Recognition of Safety of BCM 95 (Curcumin)	5-74
	Appendix A - Flow chart of manufacturing Process for BCM 95	75
	Appendix B - Certificates of Analysis for Five Production Batches of BCM 95	77
	Appendix C - JECFA Specifications for Curcumin	83
	Appendix D - Accelerated and Long-Term Stability Report for BCM 95	87
	Appendix E - Elevated Temperature Stability Report	94
	Appendix F - Human Studies on Other Curcumin Preparations	99











GRN # 686

DolCas Biotech, LLC.

9 Lenel Road
Landing, N.J. 074850
973-347-1958
www.dolcas-biotech.com

Food and Drug Administration
Center for Food Safety & Applied Nutrition
Office of Food Additive Safety (HFS-255)
5100 Paint Branch Parkway
College Park, MD 20740-3835

Attention: Dr. Paulette Gaynor
Re: GRAS Notification - BCM-95® (Curcumin)

Dear Dr. Gaynor,

On behalf of DolCas Biotech, LLC, we are submitting for FDA review, Form 3667, one paper copy and the enclosed CD, free of viruses, containing a GRAS notification for BCM-95® (Curcumin).

An Expert Panel of independent qualified persons was assembled to assess the composite safety information of the subject substance with the intended use in select foods as outlined in the notification.

The attached documentation contains the specific information that addresses the safe human food uses for the subject notified substance as discussed in the GRAS final rule, 21 CFR Part 170.30(a)(b), Subpart E.

If additional information or clarification is needed as you and your colleagues proceed with the review, please feel free to contact us via telephone or email.

We look forward to your feedback.

Sincerely,

(b) (6)

Oct 25th 2016

KG Rao, President
DolCas Biotech, LLC
9 Lenel Road
Landing, N.J. 074850
973-347-1958 Ext. 201
grao@dolcas-biotech.com

Enclosure: GRAS Notification for DolCas Biotech, LLC - BCM-95® (Curcumin)
1 paper copy/1 virus – free electronic media

SUMMARY OF SAFETY DATA

AND FOOD USAGE CONDITIONS FOR CONCLUSION OF GENERAL RECOGNITION OF SAFETY

of

BCM-95® (Curcumin)

for

DolCas Biotech, LLC

DolCas Biotech, LLC
Landing, NJ
October 21, 2016

Table of Contents

TABLES

FIGURES

I. GRAS EXEMPTION CLAIM

A. Claim of Exemption From Requirement for Premarket Approval
(Pursuant to Proposed 21 CFR 170.36(c)(1)[1])

DolCas Biotech, LLC ("DolCas") has concluded that BCM-95® curcumin complex (also known as Biocurcumax™ and Biocurcumin™), meeting the specifications described in Table 9 of Section II (E), is Generally Recognized As Safe (GRAS) in accordance with Section 201(s) of the Federal Food, Drug, and Cosmetic Act. This determination was made by DolCas in concert with an appropriately convened panel of experts who are qualified by scientific training and experience to make such safety determinations. The GRAS evaluation is based on scientific procedures as described in the following sections, and the evaluation accurately reflects the conditions of the ingredient's intended use in foods.

(b) (6)

Signed:

K G Rao, President
DolCas Biotech, LLC
9 Lenel Rd.
Landing, NJ 07850

B. Name & Address of Notifier

DolCas Biotech, LLC
9 Lenel Rd.
Landing, NJ 07850

Person Responsible for the Notification:

K G Rao, President
DolCas Biotech, LLC
9 Lenel Rd.
Landing, NJ 07850

C. Common Name & Identity of Notified Food Substance

The common or usual name of BCM-95® is curcumin.

[1] See 62 FR 18938 (17 April 1997) which is accessible at http://www.gpo.gov/fdsys/pkg/FR-1997-04-17/pdf/97-9706.pdf.

D. Conditions of Intended Use in Food

DolCas intends to incorporate BCM-95® into selected food categories (yogurt, nutrition bars, smoothies and medical foods) as a nutrient supplement as defined by United States Food and Drug Administration (FDA) in 21 CFR 170.30 at use levels described in Section III (B).

E. Basis for GRAS Conclusion

Pursuant to 21 CFR 170.30 (a)(b), BCM-95® has been determined to be GRAS on the basis of scientific procedures as discussed in the detailed description provided below with corroborating information provided from the documented history of food use. A comprehensive scientific literature search conducted through September 25, 2016 was used in the preparation of this safety evaluation.

F. Availability of Information

The complete data and information that serve as the basis for this GRAS notice are available to the Food and Drug Administration for review upon request during normal business hours from DolCas Biotech, LLC.

G. Confidentiality

The data and information contained herein is not confidential nor comprised of trade secret(s) or contains commercial or financial information that is privileged or confidential and is therefore not exempt from disclosure under the Freedom of Information Act, 5 U.S.C.552.

H. INTRODUCTION

1. Objective

DolCas has undertaken a comprehensive GRAS evaluation of its product, BCM-95®. The primary purpose of this evaluation was to ascertain whether or not sufficient safety documentation is available to conclude that the selected human food uses of the curcumin preparation can be considered to be generally recognized as safe (GRAS).

2. Foreword

Background information needed to enable the subject GRAS evaluation was compiled to address the safety/toxicity of curcumin extracts, the intended food uses, and compositional details, specifications, and method of preparation. The information compiled also included any adverse reports as well as information that support conclusions of safety. Determining how much curcumin can be safely consumed (i.e. the

use levels) is critical in the determination of the safe exposure levels for curcumin when consumed as a food ingredient. The composite safety/toxicity studies, in concert with exposure information, ultimately provided the specific scientific foundation for the GRAS evaluation.

The safety/toxicity studies, consumption/exposure information, and other related documentation were augmented with an independent search of the scientific and regulatory literature conducted through September 25, 2016. Based upon the composite information, the GRAS notification was developed, using primarily publically available safety information. Those references that were deemed pertinent to the objective at hand are listed in Section VIII.

3. FDA GRAS Regulatory Framework

Ingredients for use in conventional foods must undergo premarket approval by FDA as food additives or, alternatively, the ingredients to be incorporated into such foods must be determined to be GRAS. The authority to make GRAS determinations is not restricted to FDA. In fact, GRAS determinations may be provided by experts who are qualified by scientific training and experience to evaluate the safety of food and food ingredients under the intended conditions of use.

In 1997, FDA altered the GRAS determination process by eliminating the formal GRAS petitioning process and replacing the petitioning process with a notification procedure. Effective October 17, 2016, FDA issued a final rule, *Subpart E—Generally Recognized as Safe (GRAS) Notice*, amending and clarifying the criteria for the use of a substance in food for humans and amending the regulations for a voluntary GRAS affirmation petition process with a voluntary notification process.

4. Regulatory Background for Curcumin

a. U.S. FDA

Curcumin is a constituent of Turmeric, the dried powdered rhizome of *Curcuma longa L*. In the United States, turmeric has been used as a coloring agent in food because of its bright yellow color. In India, it has been used for centuries as a food preservative and as a spice in curry dishes (Chainani-Wu, 2003).

FDA describes turmeric as the ground rhizome of *Curcuma longa L.* and regulates turmeric as a color additive; 21 CFR 73.600. Furthermore, turmeric oleoresin, described as the solvent extract of *Curcuma longa L.*, is regulated as a color additive (21 CFR 73.615). The use of turmeric as referenced in 21 CFR 182.10, and turmeric extract or turmeric oleoresin (21 CFR 182.20) is considered to be GRAS by FDA for use as a spice and a flavoring agent in foods.

A search of FDA's GRAS Notice Inventory website using the search terms "curcumin," "turmeric," and "*Curcuma longa*" identified one notification, GRN 460, related to turmeric-derived preparations. GRN 460, "Curcuminoids Purified from Turmeric (*Curcuma longa L.*)," was submitted by Sabinsa and filed by FDA on February 28, 2013. The subject of GRN 460 is a curcuminoids preparation consisting of >95% curcuminoids, with 75-81% curcumin, 2.2-6/5% bisdemethoxy curcumin and 15-22% desmethoxy curcumin, at use levels of up to 20 mg per serving as a flavor, flavor enhancer, or nutrient ingredient in a number of applications (Sabinsa, 2013). FDA noted that the use of curcuminoids in foods may require a color additive listing. FDA issued a "no questions" letter on August 23, 2013 for GRN 460.

b. Flavor & Extract Manufacturers Association (FEMA)

Turmeric, turmeric extract, and turmeric oleoresin are considered to be GRAS by the Flavor & Extract Manufacturers Association (FEMA) (Hall and Oser, 1965)

c. Self- Determination GRAS

In 2012, it was reported that Verdure Sciences (Noblesville, IN) obtained self-determined GRAS status for Longvida® Optimized Curcumin. As a result, Longvida® is reported to be a safe ingredient for a variety of food categories when used as a flavor enhancer and as an antioxidant at usage levels of 0.2% to 1.25%. The GRAS determination also covers Longvida® SD, which is a form of curcumin with enhanced water solubility for food and beverage applications. A review of the literature has revealed that Longvida®-optimized curcumin is comprised of tetrahydrocurcumin (TC), a more stable metabolite of curcumin.

d. Scientific Committee for Food (SCF)

Curcumin was evaluated by SCF in 1975. No Acceptable Dietary Intake (ADI) was set by SCF as they found that curcumin from natural foods could be classified as a color for which an ADI could not be established but which is nevertheless acceptable for use in food. The SCF (1975) identified several gaps in the data at the time of their evaluation and stated that selected additional studies---metabolic studies in several species and if possible in man; adequate long-term studies in another species---would be needed if considerable extension of use in food of this color was contemplated in the future.

e. Joint FAO/WHO Expert Committee on Food Additives (JECFA)

Curcumin was previously evaluated several times by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). In its latest evaluations, JECFA established food grade specifications for curcumin in 2004 (FAO, 2004) and finalized the specifications in 2006 (FAO, 2006).

f. European Food Safety Authority (EFSA)

The most recent safety review was conducted by the EFSA panel on *Food Additives and Nutrient Sources added to Food* (EFSA, 2010). This review was a reevaluation to consider additional literature that became available since a previous review by the EU Scientific Committee on Food (SCF, 1975) including the new data that led the to the JECFA establishment of an ADI (WHO, 2004). The Panel agreed with JECFA that curcumin is not carcinogenic based on carcinogenicity bioassays conducted by NTP (1993). The Panel also concluded that there were sufficient new data on lack of reproductive toxicity (study later published as Ganiger et al., 2007) and agreed with JECFA in establishing the ADI of 3 mg/kg bw/day based on the No Observed Adverse Effect Level (NOAEL) of 250-320 mg/kg bw/day from a reproductive toxicity study for decreased body weight gain in the F2 generation which was observed at the highest dose level, and an uncertainty factor of 10. The Panel concluded that, at the maximum levels of use, intake estimates from 1- to 10-year-old children at the mean and high percentile (95th percentile) groups were determined to be less than the ADI of 3 mg per kg bw per day for adolescents, adults and the elderly. The estimated mean exposure for toddlers and children was at the ADI, which the high level group exceeded the ADI. Additionally, EFSA found that the updated exposure estimates were lower than those determined in 2010 (EFSA, 2014).

g. Health Canada

In 2010, Health Canada published a monograph on, curcumin derived from *Curcuma longa* L. (rhizome) for use as a medicinal ingredient at levels not to exceed 400 mg taken 3 times per day (not more than 1,200 mg curcumin per day). No contraindications or known adverse reactions were noted (Health Canada, 2010a). Health Canada also listed uses as a "colour" additive and preservative antioxidant (Health Canada, 2014a).

That same year, Health Canada also published a monograph for turmeric (*Curcuma longa* L.) dried rhizome for use as an orally administered medicinal ingredient at levels indicated in Table 1. Health Canada further stipulated that "the only acceptable potencies are: 3-5% curcuminoids." No contraindications or known adverse reactions were noted (Health Canada, 2010b).

Table 1. Turmeric Use Levels Set Forth by Health Canada

CATEGORY	DRY RHIZOME USE LEVEL
Antioxidant	9 g/day
Traditional Chinese Medicine (TCM)	3-9 g/day (as a decoction)
Ayurveda	1-4 g/day (topical application)
Other uses	1-9 g/day

[a] Health Canada

In June 2014, Health Canada published a monograph to serve as a guide to industry for a Product License Application (PLA) to obtain market authorization for joint health products. This monograph identified both curcumin and turmeric (*Curcuma longa L.* rhizome) as allowable medicinal ingredients that can be used in joint health products (Health Canada, 2014b).

Furthermore, Health Canada included both curcumin and turmeric (*Curcuma longa L.* rhizome) in a list of ingredients for joint health products (Health Canada, 2014b).

h. Food Standards Australia New Zealand

Both curcumin and turmeric appear in a list of food additives prepared by Food Standards Australia New Zealand (FSANZ, 2014). Both are also referenced in the 2008 “Draft New Zealand Food (Supplemented Food) Standard” as an approved colorant in supplemented foods (vitamins and minerals).

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II. INGREDIENT IDENTITY, CHEMICAL CHARACTERIZATION, MANUFACTURING PROCESS & PURITY

A. Turmeric Botanical Classification

Curcuma longa L., a member of the ginger family Zingaberaceae (Peirce, 1999), is a perennial herb commonly referred to as turmeric. It grows in tropical areas, including Hawaii, Puerto Rico, and India. The aboveground portion of the plant consists of large, elliptic leaves and yellow flowers, which can grow to a height of over 3 feet. The rhizome is bright orange and is often boiled and dried for culinary purposes (Bremness, 2002; USDA, 2015).

The botanical classification (USDA, 2015) is as follows:

Kingdom	*Plantae*
Subkingdom	*Tracheobionta*
Superdivision	*Spermatophyta*
Division	*Magnoliophyta*
Class	*Liliopsida*
Subclass	*Zingiberidae*
Order	*Zingiberales*
Family	*Zingiberaceae*
Genus	*Curcuma L.*
Species	*Curcuma longa L.*

The dried root is commonly used as an ingredient in curry powders that are added to many Indian dishes and piccalilli. In Thai cuisine, the shoots and flowers are eaten as vegetables. In Indonesia, the leaves are used to flavor fish (Bremness, 2002). Turmeric is thought to be native to Southeast Asia where many related species of Curcuma occur in the wild, though turmeric itself is not known to occur in the wild.

B. Common or Usual Name of BCM-95® (Also known as Biocurcumax™ and Biocurcumin™)

The DolCas product with the commercial name of BCM-95®, also known as Biocurcumax™ and Biocurcumin™ and the subject of this safety evaluation, has the

common or usual name of Curcumin Complex from *Curcuma longa* L., as produced and sold by DolCas.

C. Chemical and Identity Characterization of BCM-95®

BCM-95® is a reconstituted, purified and standardized turmeric extract from *Curcuma longa* L., designed to enhance the oral bioavailability of curcumin in blood. It contains a specialized unique blend of curcuminoids (curcumin, desmethoxycurcumin and bisdesmethoxycurcumin) and essential oils of turmeric (turmerone, atlantone, and Zingiberene). BCM-95® consists of no less than 85% curcuminoids and 5-7% essential oils. Below describes the chemical composition of turmeric, from which BCM 95® is derived, along with the chemical composition of the turmeric constituent that also comprise the subject substance.

1. Identity and Chemical Characterization of the Turmeric Rhizome (Curcuma spp.) from which BCM 95® is Derived

Turmeric (*Curcuma longa L.*), species has been the subject of extensive research and chemical characterization, identifying, to date, identifying at a minimum, 235 compounds. These compounds are comprised primarily of phenolic compounds and terpenoids including 22 diarylheptanoids and diarylpentanoids, eight phenylpropene and other phenolic compounds, 68 monoterpenes,109 sesquiterpenes, five diterpenes, three triterpenoids, four sterols, two alkaloids, and 14 other compounds with the curcuminoids and essential oils as the major bioactive ingredients (Li, S., 2011).

DolCas has determined the typical composition of the turmeric rhizome (from which BCM 95® is derived) and essential oils (also referred to as volatile oils in the scientific literature) as represented in Table 2, 3 and 4. The information below is representative of the physical and chemical information for the major components of BCM 95®.

a. Turmeric Rhizome (Curcuma spp.)

DolCas has determined the typical composition of the turmeric rhizome as represented in Table 2 and 3.

Table 2. Typical Composition of Turmeric Rhizome

Component	Percentage (%)
Curcuminoids	4.5
Essential oil of turmeric	5
Turmerones	1.5
Fixed oils	4
Resin	3
Fiber	5.1
Protein	10.1
Starch	52

Table 3. Chemical Composition of Turmeric

COMPONENT	CONCENTRATION
Protein	6.3%
Fat	5.1%
Minerals	3.5%
Carbohydrates	69.4%
Moisture	13.1%

[a] Adapted from Chattopadhyay et al., (2004).

b. Turmeric Essential Oils

The typical chemical composition of turmeric essential oils is provided, as described in the literature, in Table 4. It has been noted in the scientific literature that the main bioactive components of the *Curcuma longa* L. essential oil are the sesquiterpines ar-turmerone (16.7- 25.7%), α-turmerone (14.7- 18.3%), and β-turmerone (14.70-18.4%)(Ferreira et al., 2013).

Table 4. Chemical Composition of Turmeric Essential Oil

COMPONENT	CONCENTRATION
α-phellandrene	1%
Sabinene	0.6%
Cineol	1%
Borneol	0.5%
Zingiberene	25%
Sesquiterpenes	53%
ar-turmerone	16.7- 25.7%
α-turmerone	14.7- 18.3%
β-turmerone	14.70-18.4%

[a] Adapted from Chattopadhyay et al., (2004) and Ferreira et al., (2013), Naz, S., (2010).

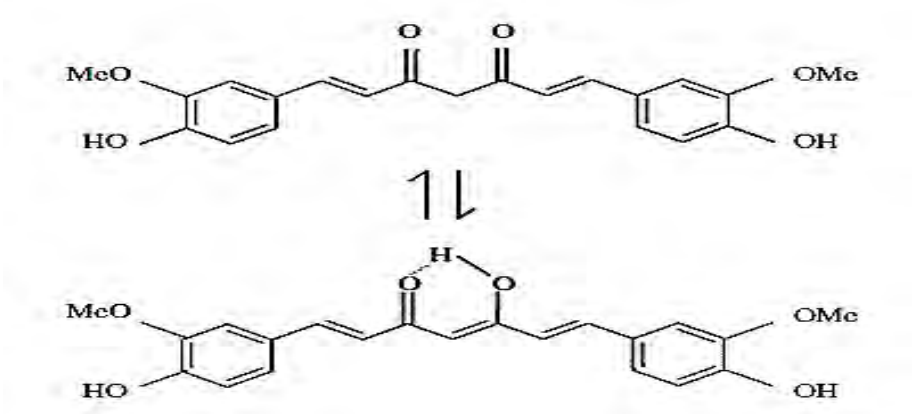
2. Identity and Chemical Characterization of Curcuminoids and Essential Oil in BCM 95®

Curcuminoids, a major naturally occurring phenol constituent of turmeric and having a pronounced yellow color, are extracted from the ground rhizomes of *Curcuma longa L*. Curcuminoids are composed of curcumin (diferloylmethane, diferulylmethane), desmethoxycurcumin (demethoxycurcumin, monodemethoxycurcumin), and bisdesmethoxycurcumin (bisdemethoxycurcumin; didemethoxycurcumin). These components of the curcuminoid family are generally present at 71-77%, 10-20% and 5%, respectively (Sharma et al., 2005).

a. Curcumin (Diferloylmethane, Diferulylmethane)

Curcumin, the major constituent of the curcuminoid class, was first isolated in 1815, characterized in 1910 as a low molecular weight phenol comprising 2-8% of most turmeric preparations (Sharma et al., 2005). The chemical structure was later determined in 1973. Curcumin [1,7-bis-(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] can be further classified as a bis-a,b-unsaturated b-diketone and exists in equilibrium with its enol tautomer. In acidic and neutral solutions, the bis-keto form predominates. Figure 1. is representative of the bis-keto form of curcumin (top) and the enolate form (bottom). Curcumin is insoluble in water, but dissolves in ethanol, acetone and dimethylsulfoxide (DMSO) with a molecular weight of 368.37 Daltons and a melting point of 176-177˚C (Chattopadhyay et al., 2004; Sharma et al., 2005). The chemical identity of curcumin is described in Table 5.

Figure 1. Chemical Structure of Curcumin



[a] Curcumin in the bis-keto form (top), which predominates at acidic and neutral pH and the enolate form (bottom), which is found at pH ~8 (Sharma et al., 2005).

Table 5. Chemical Identity of Curcumin

CURCUMIN (Diferloylmethane Diferulylmethane; Natural Yellow 3)	
Chemical Abstracts Services (CAS) No:	458-37-7
Appearance & odor:	Orange-yellow powder; mild odor or odorless
Melting point:	183°C
Vapor Density:	13 (Air = 1)
Solubility in water:	Insoluble
Other solubility:	Soluble in glacial acetic acid, ethyl acetate, methanol and tetrahydrofuran; slightly soluble in acetone, benzene and carbon disulfide; insoluble in ether and petroleum ether
Formula:	$C_{21}H_{20}O_6$
Molecular weight:	368.41 Daltons

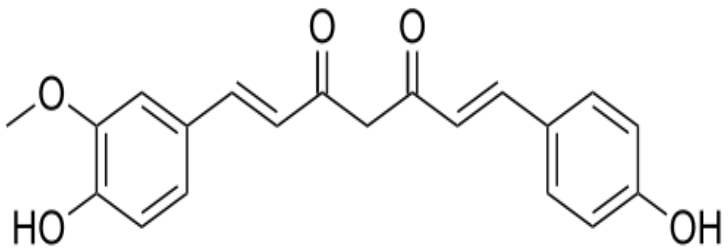
b. Desmethoxycurcumin (demethoxycurcumin, monodemethoxycurcumin)

The chemical identity of desmethoxycurcumin, a curcuminoid extracted from the ground rhizomes of *Curcuma longa* L. is represented below in Table 6 and Figure 2.

Table 6. Chemical Identity of Desmethoxycurcumin

Desmethoxycurcumin (Demethoxycurcumin; Monodemethoxycurcumin)	
Chemical Abstracts Services (CAS) No:	22608-11-3
Appearance & odor:	Orange powder; mild odor
Melting range:	172-174ºC
Solubility in water:	Insoluble
Other solubility:	Soluble in ethyl acetate, methanol and tetrahydrofuran
Formula:	$C_{20}OH_{18}O_5$
Molecular weight:	338.35 Daltons

Figure 2. Chemical Structure of Desmethoxycurcumin



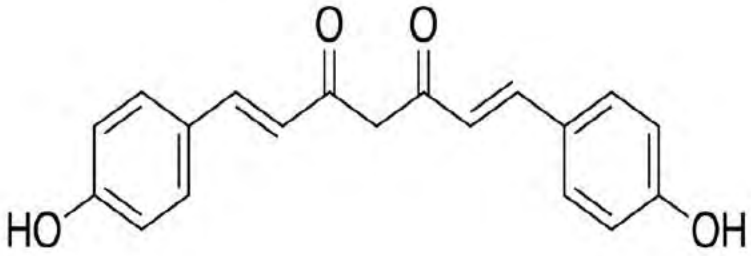
c. Bis-desmethoxycurcumin

The chemical identity of bis-desmethoxycurcumin is represented Table 7 and Figure 3.

Table 7. Chemical Identity of Bisdesmethoxycurcumin

Bisdesmethoxycurcumin (Bisdemethoxycurcumin; Didemethoxycurcumin)	
Chemical Abstracts Services (CAS) No:	24939-16-0
Appearance & odor:	Orange powder; mild odor
Melting range:	227- 229ºC
Solubility in water:	Insoluble
Other solubility:	Soluble in ethyl acetate, methanol and tetrahydrofuran
Formula:	$C_{19}H_{16}O_4$
Molecular weight:	308.33 Daltons

Figure 3. Chemical Structure of Bisdesmethoxycurcumin



d. BCM 95® - Turmeric Essential Oil - Ar-Turmerones

The chemical identity of the key turmeric essential oil in BCM 95®, Ar-Turmerone, is represented Table 8 and Figure 4.

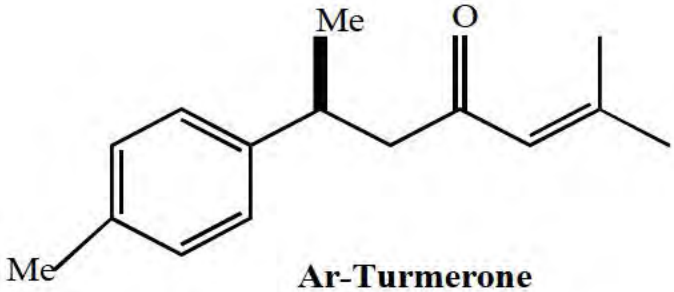
Table 8. Chemical Identity of Ar-Turmerone

Ar-Turmerone	
Chemical Abstracts Services (CAS) No:	180315-67-7
Appearance & odor:	Orange-yellow, occasionally slightly fluorescent liquid with an odor reminiscent of tubers
Specific gravity at 15°C:	0.938 – 0.967
Optical rotation	-13° to -25°
Refractive Index:	1.512 to 1.517 at 20°C
Acid number:	0.6 to 3.1
Ester number:	6.5 to 16
Ester number after acetylation:	28 to 53
Solubility:	Soluble in 4 to 5 volume of 80% alcohol; soluble in 0.5 to 1 volume of 90% alcohol
Synonyms:	Turmerone, Tumerone, Ar-Tumerone

H
O
CH_3O
OCH_3
HO
OH

Figure 4. Chemical Structure of Ar-Turmerone

Curcumin



Ar-Turmerone

D. Manufacturing Process

The rhizomes of turmeric are dried and powdered to form powdered turmeric. The powdered turmeric is extracted with ethyl acetate. After extraction, a solution and a residue are obtained; the residue is separated from the solution, and ethyl acetate or ethanol is again added to the residue for extraction. The resultant residue is similarly extracted with ethyl acetate several times. The solution from each of the ethyl acetate extraction steps is combined and filtered. The solvent from the filtered solution is stripped to form an extract. Then the extract is cooled to obtain crystals of curcuminoid and a liquid. The crystals of curcuminoid are isolated from the liquid by filtration. The crystals are then powdered to form a powdered curcuminoid mixture.

The liquid after removal of crystals consists of essential oils of turmeric and a resin. The liquid is then steam distilled to isolate the essential oils of turmeric to a 10-15% Ar-turmerone. The 10-15% Ar-turmerone fraction is further steam distilled to an essential oil fraction that consists of a minimum of 45% Ar-turmerone

The curcuminoid powder prepared from the crystals is blended with required quantity of purified essential oils of turmeric and dried. A flow chart for the manufacturing process is provided in Appendix A.

E. Product Specifications

The product specifications for BCM-95® and the results of the analyses of five production batches are listed below in Table 9 (see certificates of analysis attached as Appendix B). These specifications meet or exceed the requirements of JECFA specifications for curcumin (FAO, 2006). Dolcas also has provided data that the product is essentially oxalate free (< 5 ppm based on sensitivity of method). A copy of the JECFA specifications is attached in **Error! Reference source not found.**.

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Table 9. Finished Product Specifications and Analysis for BCM-95® (5 Batches)

Product name: BCM-95®
Latin Name: *Curcuma longa L.L.*
Country of Origin: India
Harvest Type: Cultivated -
Plant Part Used: Rhizome

Description	Specification	(b) (4)	[redacted]	[redacted]	[redacted]	[redacted]	Method
Physical Characteristics							
Identification	Pass	Complies	Complies	Complies	Complies	Complies	TLC
Color	Orange red	Complies	Complies	Complies	Complies	Complies	Visual
Appearance	Powder	Complies	Complies	Complies	Complies	Complies	Visual
Flavor	Characteristic	Complies	Complies	Complies	Complies	Complies	Organoleptic
Odor	Characteristic	Complies	Complies	Complies	Complies	Complies	Organoleptic
Analytical Assay							
Herb extract Ratio[a]	25:1	Complies	Complies	Complies	Complies	Complies	In House Specification
Solubility (in Acetone)	Soluble	Complies	Complies	Complies	Complies	Complies	IP
Solubility (in water)	Insoluble	Complies	Complies	Complies	Complies	Complies	IP
Moisture	NMT 2%	0.30%	0.35%	0.35%	0.4%	0.30%	USP 24 <921>
Extraction solvent	100% Ethyl Acetate	Complies	Complies	Complies	Complies	Complies	In House Specification
Particle Size range	20-30 mesh	Complies	Complies	Complies	Complies	Complies	USP 24 <786>
Allergens	None detected	Complies	Complies	Complies	Complies	Complies	Elisa
Tap Density (g/mL)	> 0.60	0.72	0.70	0.71	0.73	0.71	USP 24 <616>
Bulk Density (g/mL)	> 0.39	0.54	0.55	0.56	0.55	0.54	USP 24 <616>
Pesticide Residue	Complies with USP	Complies	Complies	Complies	Complies	Complies	USP 24 <561>
Excipients	None	Complies	Complies	Complies	Complies	Complies	In House Specification
Carriers	None	Complies	Complies	Complies	Complies	Complies	In House Specification
Residual Solvents[b]							

Description	Specification	1303 B-56	1303 B-57	1303 B-58	1303 B-59	1303 B-60	Method
Ethyl Acetate	NMT 5000 ppm	3,473	3,275	3,863	2,533	1,679	USP <467>
Ethyl Alcohol	NMT 50 ppm	Complies	Complies	Complies	Complies	Complies	USP <467>
Methanol	NMT 50 ppm	Complies	Complies	Complies	Complies	Complies	USP <467>
Isopropanol	NMT 50 ppm	Complies	Complies	Complies	Complies	Complies	USP <467>
Dichloromethane	NMT 30 ppm	Complies	Complies	Complies	Complies	Complies	USP <467>
Hexane	NMT 25 ppm	Complies	Complies	Complies	Complies	Complies	USP <467>
Acetone	NMT 30 ppm	Complies	Complies	Complies	Complies	Complies	USP <467>
Heavy Metals							
Total Heavy Metals	< 10 ppm	Complies	Complies	Complies	Complies	Complies	ICP – MS
Arsenic	< 1 ppm	Complies	Complies	Complies	Complies	Complies	ICP – MS
Lead	< 0.5ppm	Complies	Complies	Complies	Complies	Complies	ICP – MS
Mercury	< 1 ppm	Complies	Complies	Complies	Complies	Complies	ICP – MS
Microbial Assay							
Total Plate Count	<1,000 cfu/g	20	30	30	20	30	AOAC, BAM
Yeast & Mold	<100 cfu/g	Complies	Complies	Complies	Complies	Complies	AOAC, BAM
Salmonella	Absent /25 g	Complies	Complies	Complies	Complies	Complies	AOAC, BAM
E. coli	Absent /10 g	Complies	Complies	Complies	Complies	Complies	AOAC, BAM
Staphylococcus Aureus	Absent /10 g	Complies	Complies	Complies	Complies	Complies	AOAC ,BAM
Pseudomonas Aeruginosa	Absent /10 g	Complies	Complies	Complies	Complies	Complies	AOAC, BAM
Aflatoxin	Absent	Complies	Complies	Complies	Complies	Complies	AOAC, BAM
Coliforms	Absent /10 g	Complies	Complies	Complies	Complies	Complies	AOAC, BAM
Assay for Actives							
Volatile Compounds of Turmeric	Present	Complies	Complies	Complies	Complies	Complies	UV – Vis
Total Curcuminoids Complex Consisting of - Curcumin - Curcuminoids - Volatile Oils	NLT 95%	95.7%	95.9%	95.7%	95.9%	95.8%	HPLC

Description	Specification	1303 B-56	1303 B-57	1303 B-58	1303 B-59	1303 B-60	Method
(from Turmeric Rhizome)							
Total Curcuminoids	NLT 86%	87.3%	87.8%	86.8%	87.7%	87.6%	HPLC
Curcumin	NLT 65%	68.5%	68.1%	68.3%	68.8%	68.5%	HPLC

[a] Typical Yield of Curcumin is 4%; e.g. 25 kg of rhizomes produces 1 kg of BCM-95®
[b] Residue specifications are required by JECFA for acetone, hexane, methanol, ethanol, isopropanol and ethyl acetate (FAO, 2006). All other solvents listed are customer-driven specifications.

F. Stability of BCM-95®

As demonstrated in an accelerated stability study, BCM-95® is stable and exhibits a room temperature shelf life of 3 years and 5 months with respect to its curcuminoid content. Based on the stability study at different temperatures, BCM-95® is stable at elevated temperatures (up to 60^{o}C) for more than 24 hours. Both accelerated and long-term stability reports on BCM-95® are provided in Appendix D. Appendix E contains the *Elevated Temperature Stability Report* on BCM-95® at temperatures 40^{0}C, 50^{0}C, and 60^{0}C.

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III. INTENDED FOOD USES & ANTICIPATED DIETARY EXPOSURES

A. Introduction

The average intake of turmeric in the diet in India is about 2-2.5 g by a 60 kg individual, and this corresponds to an intake of about 60-100 mg of curcumin per person per day (Chainani-Wu, 2003). Another author estimates that the average intake of turmeric by Asians ranges from 0.5 to 1.5 g/person/day (Chattopadhyay et al., 2004). According to the Food and Agriculture Organization of the United Nations, over 2,400 metric tons of turmeric is imported each year into the US for use in cooking and coloring and for other purposes (Sharma et al., 2005).

B. Intended Dietary Uses

Table 10 lists proposed food categories and intended uses levels for BCM-95®. FDA's methodology was used to estimate mean and high total consumption of curcumin from proposed uses using USDA survey data on daily consumption of various food types (FDA, 2006). FDA's methodology is recognized as a method that overestimates consumption. The maximum dietary exposure of BCM-95® from these foods is 182.51 mg curcumin per day. DolCas does not intend to use BCM-95® to intentionally impart color to food; any coloring resulting from its use in food as an added nutrient will be unintentional.

In addition, DolCas also intends to incorporate BCM-95® at a level of 500 mg/serving for use in medical foods. The medical food use is recommended to consist of up to 2 servings per day. The medical food use is not intended to be long term therapy. The medical food will only be used as necessary as directed by a physician; however the table below assumes a two serving per day average use level.

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Table 10. Proposed Food Categories and Intended Use Levels for BCM-95®

Food Category	USDA Category	Use Level of BCM 95® (mg/serving)	Serving Size (g)	USDA Mean Grams of Food Consumed (All Individuals)	Mean Grams curcumin Consumed (All Individuals)	Mean Grams x 2 grams curcumin Consumed (All Individuals)	Reference Number
Yogurt	Yogurt	40	225	8	1.42	2.84	**Ref. 2**, Table 9.4, p. 29
Nutrition bars	Special category	60	45	45	60	120	**Ref. 3**
Smoothie	Fluid milk (not consumed with cereal)	40	244	182	29.84	59.67	**Ref. 1**, Appendix B (All Individuals) p. 240
Total					91.26	182.51	

Reference 1: Foods Commonly Eaten in the United States Quantities Consumed Per Eating Occasion and in a Day, 1994-96 Helen Smiciklas-Wright, Diane C. Mitchell, Sharon J. Mickle, Annetta J. Cook, Joseph D. Goldman. Available at: http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/Portion.pdf (Accessed January 14, 2015).
Reference 2: DATA TABLES: Results from the USDA's 1994-96 Continuing Survey of Food Intakes by Individuals and 1994-96 Diet and Health Knowledge Survey Table Set 10 Food Surveys Research Group, Beltsville Human Nutrition Research Center, Agricultural Research Service, U.S. Department of Agriculture, 10300 Baltimore Ave., Bldg. 005, Rm 102, BARC-West, Beltsville, Maryland 20705-2350. Available at: http://www.barc.usda.gov/bhnrc/foodsurvey/home.htm (Accessed January 14, 2015).
Reference 3: Based off of Kellogg's Special K Nourish Bar Nutritional Information, Available at: http://www.specialk.com/en_us/products/nutrition-bars/dark-chocolate-nut-delight.html (Accessed January 14, 2015).

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IV. SELF-LIMITING LEVELS OF USE

This section is not applicable to this notification.

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V. COMMON USE OF BCM95® PRIOR TO 1958

Turmeric has at least 6,000 years of documented human consumption in Asia (Brouk, 1975). Curcuma appeared in the “Yao Xing Lun” of Chinese medicine in the Tang dynasty (A.D. 618-907) and was included in the Compendium of Materia Medica in the Ming dynasty (A.D. 1590) (Yue et al., 2010). Chinese medicine reports the use of the rhizome to treat clots, bruises, and epilepsy. In Thailand, turmeric is used to treat cobra venom (Bremness, 2002).

Turmeric is most extensively cultivated in India, followed by Bangladesh, China, Thailand, Cambodia, Malaysia, Indonesia, and the Philippines. It is also cultivated on a small scale in most tropical regions in Africa, America, and Pacific Ocean Islands. However, India is the largest producer, consumer, and exporter of turmeric (Ravindran, 2007).

It should be noted that while there are references to a long time historical use of turmeric and curcumin (as curcuma), these references are considered to be secondary references and are not used for the basis of a GRAS conclusion but as corroborative information.

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VI. NARRATIVE- GRAS CONCULSION

A. GRAS Criteria

FDA defines "safe" or "safety" as it applies to food ingredients as:

> "…reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance."[2]

Amplification is provided in that the determination of safety is to include probable consumption of the substance in question, the cumulative effect of the substance, and appropriate safety factors. It is FDA's operational definition of safety that serves as the framework against which this evaluation is provided.

Furthermore, in discussing GRAS criteria, FDA notes that:

> "…General recognition of safety requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food."
>
> "General recognition of safety through experience based on common use in food prior to January 1,1958, shall be based solely on food use of the substance prior to January 1, 1958, and shall ordinarily be based upon generally available data and information."[3]

Practically speaking, the standard for establishing GRAS status is "reasonable certainty of no harm under the intended conditions of use." FDA discusses in more detail what is meant by the requirement of general knowledge and acceptance of pertinent information within the scientific community, i.e., the so-called "common knowledge element," in terms of the two following elements:[4]

- Data and information relied upon to establish safety must be generally available, and this is most commonly established by utilizing published, peer-reviewed scientific journals; and
- There must be a basis to conclude that there is consensus (but not unanimity) among qualified scientists about the safety of the substance for its intended use, and this is established by relying upon secondary scientific literature such as published review articles, textbooks, or compendia, or by obtaining opinions of

[2] See 21 CFR 170.3(i).
[3] See 21 CFR 170.30(a).
[4] See 62 FR 18938 (17 April 1997) http://www.gpo.gov/fdsys/pkg/FR-1997-04-17/pdf/97-9706.pdf.

expert panels or opinions from authoritative bodies, such as the National Academy of Sciences.

The apparent imprecision of the terms “appreciable,” “at the time,” and “reasonable certainty” demonstrates that the FDA recognizes the impossibility of providing absolute safety in this or any other area (Lu, 1988; Renwick, 1990; Rulis and Levitt, 2009).

B. Discussion of Safety of BCM-95®

Many published studies are available on various preparations of curcumin, including on BCM-95® itself and similar preparations that contain turmerone.

1. JECFA Safety Review

There is a long review history of curcumin by JECFA. At their seventy-eighth meeting, JECFA reviewed all other relevant studies and established a tentative ADI of 0-1 mg/kg bw on the basis of chronic mouse study conducted by the National Toxicology Program (NTP, 1993) on turmeric oleoresin (curcumin content 79-85%). The key effect on liver weight in mice was used to establish the tentative ADI based on a NOEL of 220 mg/kg bw, and a 200–fold safety factor was used to give the 0-1 mg/kg bw ADI. JECFA acknowledged the lack of carcinogenic activity seen in the NTP studies and expressed a willingness to recalculate the ADI after review of an adequately conducted animal study for reproductive effects. Subsequently JECFA reviewed a reproductive study conducted in rats (Ganiger et al., 2007). The only effects in this study were minor body weight differences in the F2 generation derived from mating of the F1 generation at the high dose of 850 - 1100 mg/kg bw/day. The NOAEL was established as the mid-dose in this study of 250-320 mg/kg bw/day, and the ADI was reestablished without a tentative designation as 0-3 mg/kg bw/day based on the use of a 100-fold safety factor (WHO, 2004).

It should be noted that there are conflicting studies indicating that curcumin has antifertility effects. Most notably in a study by Ghosh et al. (2011), anti-gonadotrophic effects were observed including complete inhibition of ovulation in albino rats at both oral doses studied (25 and 50 mg/kg bw/day). These results are surprising since in the more rigorous two generation reproductive study conducted in rats by Ganinger et al. (2007) there was no interference with reproduction at doses several fold higher.

a. Expert Panel Opinion

In reviewing the afore mentioned study by Ghosh et al., the Panel notes that there was an absence of many experimental details and results in the publication by Ghosh et al., including the documentation of the strain and source of rats used and the results were described in the narrative without any tabular or graphical presentation of the data. In view of the documented consumption of curcumin in India of 1 gram/person/day or more

(equivalent to 16 mg/kg bw/day) and the fact that India has one of the highest birth rates in the world, the results of the Ghosh study do not seem credible. The Panel has agreed that the results of the more rigorous study by Ganinger et al. that were reviewed by JECFA are more comprehensive and indicate the lack of any antifertility effects at current levels of exposure.

b. DolCas Opinion

DolCas also reviewed the JEFCA opinion and Ghosh et al. (2011) and Ganinger et al. (2007) studies. DolCas concludes that the Ghosh study is lacking in scientific rigor and the resulting data from the Ganinger study coupled with the opinion of both JEFCA and the independent Expert Panel supports the conclusion for a lack of antifertility effects at the current levels of dietary exposure.

2. Safety of the Combination of Turmerone with Curcumin

The safety of the proposed combination of turmerone with curcumin is supported by several studies on BCM-95® which showed an absence of adverse effects. These studies are summarized in a published article (Aggarwal et al., 2016) and include acute oral toxicity studies in rats and mice and subchronic oral toxicity study in rats where the NOAEL was 1000 mg/kg bw/day, the highest dose tested. In addition, a lack of mutagenicity was seen *in vitro* in bacteria and a lack of clastogenicity was seen *in vitro* in mammalian bone marrow cells. Further, there was a lack of effect *in vivo* in a mouse micronucleus test.

DolCas finds the compilation of scientific literature on curcumin supports the conclusion of Generally Recognized As Safe (GRAS).

C. Common Knowledge Elements Supporting GRAS Conclusion

The safety review of BCM-95® is primarily supported by a substantial number of publically available studies in laboratory animals and human subjects that have been published in the scientific literature or are otherwise publicly available.

Turmeric, turmeric extract and turmeric oleoresin have long been considered as GRAS by FDA for use as a spice and a flavoring agent in foods. In addition, FDA considers turmeric and turmeric oleoresin to be safe as a color additive for use in food. JECFA has reviewed curcumin several times and has established an ADI of 0-3 mg/kg bw. EFSA confirmed the safety of curcumin and endorsed the ADI established by JECFA (EFSA, 2010). In addition is has been reported that Verdure Science, and Sabinsa have made self-affirmed GRAS determinations for similar curcumin extracts. Many other reviews have been conducted by several independent scientists, and they consider curcumin to be of low

toxicity and well-tolerated by oral administration in humans at doses of 1 gram per person per day or greater (Chattopadhyay, 2004; Sharma, 2005; Epstein et al., 2010).

DolCas, having reviewed the body of scientific knowledge thus concludes that the common knowledge requirement needed for a valid GRAS conclusion has been fulfilled.

D. Panel Findings

The independent Expert Panel reviewed the complied scientific data, evaluating the information in order to determine if a GRAS conclusion based on scientific procedures could be made for BCM 95®. The Expert Panel was comprised of scientists qualified by both training and experience.

1. Safety Discussion on BCM-95® By An Independent Panel Of Qualified Experts

"The Expert Panel notes that scientific literature on curcumin has been well reviewed by several independent scientists and support exists for levels higher than 3 mg/kg bw/day as safe for use in humans. Key points made by these reviews include:

- Epstein et al., (2010) suggested that oral doses up to 12 g/d are well tolerated in human subjects based on the study by Lao et al., (2006).

- Chattopadhyay et al., (2004) pointed out that the average intake of turmeric by Asians varies from 0.5 to 1.5 g/person/day without report of adverse effects. This reviewer cites human trials to also indicate that curcumin has no apparent toxicity when administered at doses of 1–8 g/day (Chainani-Wu, 2003) and 10 g/day (Aggarwal et al., 2003).

- Sharma et al., (2005) cites a phase I human trial with 25 subjects using up to 8000 mg of curcumin per day for 3 months noting the absence of toxicity from curcumin (Cheng et al., 2001), and five other human trials using 1125 – 2500 mg of curcumin per day have also found it to be safe (Deodhar et al., 1980; Satoskar et al., 1986; James, 1994; Lal et al., 1999; Lal et al., 2000).

The Expert Panel also agrees with the JECFA conclusion that there is no conclusive evidence of carcinogenicity based on the state-of-the-art bioassays in rats and mice that were conducted by the National Toxicology Program (NTP, 1993), while also noting the lack of genotoxicity found in other assays.

The Expert Panel has reviewed the studies on turmerone and various preparations of curcumin with turmerone and has not found any additional safety concerns. "

2. Expert Panel Review of Manufacturing Process for Safety

"The Expert Panel has reviewed the manufacturing procedure and product specifications for BCM-95®, noting that the manufacturing process does not introduce any harmful ingredients or chemicals of concern. The specifications are rigorous and establish a good basis for a food grade product. The Panel also finds that documentation from DolCas indicates that the manufacturing is conducted in compliance with FDA Good Manufacturing Practices (GMP) regulations. Long-term studies have shown that the product is stable.

3. Panel Opinion

"The Expert Panel is of the opinion that there is a strong presumption of safety for BCM-95®. The JECFA ADI of 3 mg per kg/bw per day for curcumin is based on a significant number of toxicology and clinical studies on curcumin. FDA responded to GRN 460 for curcumin with a "no questions" letter and had no objection to proposed uses that did result in exposure that is greater than the JECFA ADI. DolCas has published toxicology studies on their product (Aggarwal et al. 2016) which corroborate the toxicology and clinical studies on curcumin that supported the JECFA ADI. The scientific literature does not provide any evidence to expect and increased risk of allergy due to oral exposure to BCM-95®.

Based on the chemical characterization of BCM-95® and a review of the published literature on BCM-95® and other preparations of curcumin, the Expert Panel concludes that consumption of BCM-95® at 3 mg/kg bw/day or 180 mg/person/day is generally recognized as safe when consumed by the general population from the proposed uses in conventional foods. In addition, the Expert Panel has reviewed the use of up to 1,000 mg/day in medical foods. The Panel notes that use in medical foods will be intermittent and only when necessary to manage symptoms of certain patients as directed by a physician. This medical supervision when viewed in concert with the fact that curcumin consumption in India has been estimated at greater than 1,000 mg/person/day plus, as well as the recognition of several well conducted clinical studies at 1,000 mg/person/day without adverse effects, in the collective provide support for the safety of BCM-95® at this dose."

4. Common Knowledge Elements Supporting GRAS Conclusion

The convened Expert Panel reviewed the assembled scientific literature and also offered their conclusion regarding the fulfillment of "common knowledge" requirement.

"The Expert Panel agrees that there is sufficient information in the literature that there would be a consensus of experts that would conclude that BCM-95® is safe for the proposed food uses.

The Expert Panel believes that a consensus of scientists reviewing the above published studies (Reference Section VI (C)) would conclude that BCM-95® is generally recognized as safe for its intended use at 180 mg/person/day for the general population and for the use in medical foods at levels of 1000 mg/person/day for intermittent use under medical supervision. The Expert Panel agrees that there is sufficient information in the literature that there would be a consensus of experts that would conclude that BCM-95® is safe for the proposed used. Consequently, the common knowledge requirement needed for a valid GRAS conclusion has been fulfilled."

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5. Expert Panel Conclusions[5]

"The Dolcas curcumin product, referred to as BCM-95® that is produced in accordance with FDA Good Manufacturing Practices requirements and which complies with the food grade specifications depicted in Table 9 of this safety evaluation is Generally Recognized As Safe when used as an ingredient in smoothies, yogurt and nutritional bars at levels summarized in Table 10, resulting in a maximum dietary level in the general adult population of 3 mg/kg bw/day or 180 mg/person/day. In addition, the use of up to 1,000 mg/person/day in medical foods on an intermittent basis as directed by a physician is also Generally Recognized As Safe."

"We have independently and collectively evaluated the above-referenced information and offer this GRAS declaration based on scientific procedures in accordance with FDA's standard for food ingredient safety, i.e., reasonable certainty of no harm under the intended conditions of use. "

June 29, 2016

(b) (6)

Richard C. Kraska, Ph.D., DABT

(b) (6)

Robert S. McQuate, Ph.D.

(b) (6)

Kara Lewis, Ph.D.

[5] The detailed educational and professional credentials for some of the individuals serving on the Expert Panel can be found on the GRAS Associates website at www.gras-associates.com. Drs. Kraska and McQuate worked on GRAS and food additive safety issues within FDA's GRAS Review Branch earlier in their careers and subsequently continued working within this area in the private sector. Dr. Lewis has extensive experience in preparing GRAS dossiers. All three panelists have extensive technical backgrounds in the evaluation of food ingredient safety. Each individual has previously served on multiple GRAS Expert Panels. Dr. Kraska served as Chair of the Panel.

E. Dolcas Biotech's Conclusion of Generally Recognized As Safe for Notified Substance, BCM 95®

DolCas has concluded that the notified substance, BCM 95® (also known as Biocurcumax™ and Biocurcumin™ and commonly referred to as curcumin) is GRAS and that the safety standards, per 21 CFR Part 170.30 Subpart E, of reasonable certainty of no harm, based on scientific procedures and common knowledge as described herein, are met. This conclusion is based on the in-depth review of the collective generally available scientific data regarding the safety of BCM 95® curcumin, common knowledge and general consensus among qualified experts corroborated by the written GRAS conclusion of an independent Expert Panel of qualified persons whom reviewed all publicly available referenced safety data.

We certify that this GRAS notification is complete and is a balanced representation of all data available.

October 21, 2016

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K G Rao, President

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VII. SUPPORTING DATA FOR THE SAFETY ASSESSMENT ON BCM-95® & CURCUMIN TO SUPPORT A GRAS CONSULSION

A. Safety Data on Curcumin

The publically available scientific literature on curcumin is expansive. Both the biological activity and toxicity of multiple preparations of curcumin with different composition have been evaluated. Examples of formulations of curcumin that have been investigated are included in Table 11.

Table 11. Examples of Curcumin Preparations in Published Scientific Literature

Curcumin Preparation	Composition	Selected Citation(s)
BCM-95® (Arjuna Natural Extracts)	88% total curcuminoids (curcumin, demethoxycurcumin bisdesmethoxycurcumin) and volatile oils from rhizomes of *Curcuma longa L.*L.	Sanmukhani et al., (2014)
Commercially available natural curcumin (obtained from extraction from turmeric)	Mixture of three curcuminoids: curcumin (1a, ca.70-75%), demethoxycurcumin (1b, ca. 15-20%), and bisdemethoxycurcumin (1c, ca. 5-10%)	Cuomo et al., (2011)
Curcumin Phospholipid Products (Meriva®)	Standardized mixture of natural curcuminoids and lecithin in a 1:2 ratio, with 2 parts microcrystalline cellulose (20% natural curcuminoid mixture, 40% phosphatidylcholine, and 40% microcrystalline cellulose). Similar ratio of curcuminoids as natural curcumin 16.89% curcuminoids, of which 93.82% was curcumin with a ratio of curcumin to Epikuron 130 of 1:4. Epikuron 130 P is a “deoiled, powdered soybean lecithin enriched with 30% phosphatidylcholine”. Natural curcuminoid mixture (20%), phosphatidylcholine (40% and microcrystalline cellulose (40%). Curcuminoid mixture contained 75% curcumin, 15% demethoxycurcumin, and 10% bisdemethoxycurcumin.	Cuomo et al., (2011) Marczylo et al., (2007) Belcaro et al., (2010)
Curcuvet®	Curcumin 13.02%; demethoxycurcumin 4.03%; bisdemethoxycurcumin 2.95%, total curcuminoids 20.0% + phospholipids 80%)	Cucuzza et al., (2008) Farinacci et al., (2009 a, b)
Monomolecular curcumin	Curcumin only, generally obtained by synthesis.	Cuomo et al., (2011)

Curcumin Preparation	Composition	Selected Citation(s)
Curcumin-C3® Complex	Curcumin (synthesized + small amounts of 20% of desmethoxycurcumin and bisdemethoxycurcumin).	Irving et al., (2013)
Lipicur®	400 mg lipoic acid plus 400 mg curcumin phytosome (Meriva®) plus 4 mg piperine.	Huamn: Storka et al., (2015), Di Pierro et al., (2013)
Cucumagalactomannosides	Made from fenugreek (Trigonella goenumgraecum) – derived soluble dietary fiber made of galactose and mannose units, delivers high levels of curcumin, 1 to 1.5 µM for 6 to 8 hours after administration compared with 0.04 to 0.08 µM for less than 1 hour.	Liju et al., (2015)
Theracurmin® (Liquid type, CR-011L)	10% curcumin, 2% other curcuminoids such as demethoxycurcumin and bisdemethoxycurcumin, 46% glycerin, 4% gum ghatti, and 38% water.	Huma: Kanai et al. (2011, 2012, 2013) Sasaki et al., (2011)
Longvida® Optimized Curcumin	Solid lipid curcumin particle, 400 ng contains approximately 60 mg curcumin, excipients, and small amounts of other curcuminoids present in turmeric extract.	Human: Cox et al., (2014) Animal: Dadhaniya et al., (2011)
Curcumin Micronized Powder	curcumin micronisate produced concentrated powder form" technology* blending 25% curcumin powder with 58.3% triacetin and 16.7% panodan (E472e.Solution is sprayed onto silicon dioxide	Schiborr et al., (2014)
Curcumin Liquid Micelles	Composed of 7% curcumin powder (equivalent to 6% curcumin) and 93% Tween-80 (Kolb, Hedingen, Switzerland)	Schiborr et al., (2014)
Curcumin loaded polymeric nanoparticles of Eudragit S100	Preparation of hydrogel nanoparticles: combination of hydroxyl propyl methyl cellulose and polyvinyl pyrrolidone.	Dandekar et al., (2010)
Curcumin nanoparticles	Wet-milling technique with narrow particle size distribution in the range of 2-40 nm	Yin et al., (2013)

* Brunner, G., Applications of supercritical fluids. Ann. Rev. Chem. Biomol. Eng. 2010, 1, 321–342

B. Biological Activity of Curcumin

1. Gastrointestinal System

Turmeric increases mucin secretion in rabbits and may act as a gastroprotectant against irritants (Lee et al., 2003). However, the ability of curcumin to protect against stomach ulcers is in question. In guinea pigs, 50 and 20 mg curcumin/kg bw has been shown to

protect the stomach from phenylbutazone and 5-hydroxytryptamine-induced ulcers, respectively (Dasgupta et al., 1969, Sinha et al., 1974). However, 0.5% curcumin failed to protect against histamine-induced ulcers (Bhatia et al., 1964). In a study that was reviewed by JECFA in WHO Food Additive Series 17 (WHO, 1982), 50 mg/kg bw and 100 mg/kg bw curcumin produces ulcers in rats after daily administration for 6 days (Gupta et al., 1980). A more recent study demonstrates the anti-ulcer activity of curcumin in rats at doses in the range of 20-80 mg/kg bw given for 6 days. The protection against ulcers was likely through decreased acid secretion and effects on other ulcerative effectors (Tuorkey and Karolin, 2009).

In the intestine, curcumin enhances the activity of enzymes such as lipase, sucrase and maltase (Platel and Srinivasan, 1996). Antiflatulent activity of curcumin was observed in rats (Bhavani Shankar and Sreenivasa Murthy, 1979) and antispasmotic activity of sodium curcuminate has been observed in isolated guinea pig ileum (Rao et al., 1982).

In the liver, increased bile production was observed in dogs by both curcumin and essential oil of C. longa (Jentzsch et al., 1959; Ozaki and Liang, 1988). In rat hepatocytes, curcumin and its analogs have shown protective activity against carbon tetrachloride (CCl4), D-galactosamine, peroxide and ionophore-induced toxicity (Hikino, 1985; Song et al., 2001; Kang et al., 2002). In the pancreas, curcumin also increases the enzyme activity of pancreatic lipase, amylase, trypsin and chymotrypsin (Platel and Srinivasan, 2000).

2. Cardiovascular System

Evidence from available studies shows that curcumin attenuates the severity of damage caused by myocardial infarction (Nirmala and Puvanakrishnan, 1996). Curcumin also improves Ca^{2+}-transport in the cardiac muscle, which could possibly aid pharmacological intervention to correct defective Ca^{2+} homeostasis (Sumbilla et al., 2002). It has also been shown that curcumin has significant hypocholesteremic effects in hypercholesteremic rats (Patil and Srinivasan, 1971).

3. Nervous System

The antioxidant activity of curcumin and a manganese complex of curcumin results in the protective action against vascular dementia (Vajragupta et al., 2003; Thiyagarajan and Sharma, 2004).

4. Lipid Metabolism

In rat plasma, curcumin reduces low density lipoprotein (LDL), very low density lipoprotein (VLDL), and total cholesterol in liver with an increase in alpha-tocopherol. This suggests an *in vivo* interaction between curcumin and alpha-tocopherol to increase the bioavailability of vitamin E and decrease cholesterol levels (Kamal-Eldin et al., 2000). The

fatty acid content of serum after ethanol-induced liver damage is significantly decreased by curcumin treatment (Akrishnan and Menon, 2001)

5. Anti-Inflammatory Activity

In rats and mice, curcumin is effective against carrageenan-induced edema (Ghatak and Basu, 1972; Rao et al., 1982; Srivastava and Srimal, 1985; Brouet and Ohshima, 1995; Srimal and Dhawan, 1985). In addition, the volatile oil of *C. longa* shows potent anti-inflammatory effects (Yegnanarayan et al., 1976). In humans, curcumin administration has resulted in relief from rheumatic symptoms (Deodhar et al., 1980). It has been found that the anti-inflammatory effect of curcumin is mediated through inhibition of NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells) activation and the down regulation of cyclooxygenase-2 and nitric oxide synthase through suppression of NFkB activation (Surh et al., 2001). Curcumin also has been shown to aid wound healing in diabetic mice (Sidhu et al., 1999).

6. Antioxidant Effects

Curcumin acts as a scavenger of free radicals (Ruby et al.; 1995, Subramanian et al., 1994) and can protect hemoglobin from oxidation (Unnikrishnan and Rao, 1995). *In vitro,* curcumin mediates inflammation by significantly inhibiting the generation of reactive oxygen species (ROS) like superoxide anions, H_2O_2 and nitrite radical formation by activated macrophages. Curcumin also lowers ROS *in vivo* (Joe and Lokesh, 1994) and since ROS have been implicated in the development of various pathological conditions (Bandyopadhyay et al., 1999, Halliwell, 1998, Halliwell and Gutteridge, 1990), curcumin can control diseases through antioxidant activity.

In contrast, curcumin has also shown pro-oxidant activity. One study reported that curcumin failed to prevent H_2O_2-induced single-strand DNA breaks, and also caused DNA damage (Kelly et al., 2001). Curcumin has also been shown to cause oxidative damage of rat hepatocytes and the human erythrocytes (Galati et al., 2002).

7. Anticarcinogenic Effects

Curcumin acts as a potent anticarcinogenic compound via various mechanisms. One mechanism is the induction of apoptosis and inhibition of cell-cycle progression (Chen and Huang, 1998). Curcumin also suppressed tumor growth through the inhibition of iNOS (nitric oxide synthase) and COX-2 (cyclooxygenase-2) production (Brouet and Ohshima, 1995). However, curcumin affects distinct cell lines differently. Leukemia, breast, colon, hepatocellular and ovarian carcinoma cells all undergo apoptosis in the presence of curcumin. However, lung, prostate, kidney, cervix, melanoma cells and CNS malignancies all show resistance to the cytotoxic effect of curcumin (Khar et al., 2001).

8. Anticoagulant Activity

Curcumin demonstrates anticoagulant activity by inhibiting collagen and adrenaline-induced platelet aggregation *in vitro* and in the rat thoracic aorta *in vivo* (Srivastava et al., 1985).

9. Antifertility Activity

Turmeric extracts have a history of use as a folk medicine in India as an antifertility and aborcifacient agent (Ghosh et al., 2011). Curcumin inhibits the motility of sperm in humans (Rithaporn et al., 2003) and inhibits the growth of flank organs in the hamster (Liao et al., 2001). In rats, the oral administration of turmeric rhizome extracts resulted in a 100% antifertility effect at doses of 100 or 200 mg/kg bw (Garg, 1974). These same authors did not find anti-ovulatory effects in rabbits at doses of up to 200 mg/kg bw of this extract. As a result of their review of these studies, JECFA requested a multigeneration reproduction/teratology study (WHO, 1982). The committee subsequently reviewed an unpublished multigeneration reproductive study in rats (later published as Ganiger et al. (2007). The results of this study were sufficient for The Committee to allocate an ADI of 0-3 mg/kg bw for curcumin, based on the NOEL of 250-320 mg/kg bw per day in the multigeneration study, and the application of a safety factor of 100 (WHO, 2004).

In a more recent study, the histopathological examination of ovaries in albino rats after curcumin administration revealed that curcumin has an antiovulatory effect (Ghosh et al., 2011). Two groups of six animals each received oral curcumin doses of either 25 mg/kg bw or 50 mg/kg bw for 10 days. Animals were sacrificed and histopathological examination of the ovaries and uteri were done. Vaginal smears were also observed in treatment and control animals to determine the occurrence of ovulation during the oestrus cycle. In the control group there were normal ovaries, uterus and oestrus cycle. In the curcumin treated groups there was no evidence of ovulation and no features of ovulation in the histopathological examination of the ovaries. The authors concluded that curcumin appears to suppress the oestrus phase in rats.

In another study, the oral administration of curcumin did not affect fertility in mice (Naz, 2011). However, curcumin did reduce human and murine sperm motility and function in vitro, and also reduced the in vivo fertility in female mice when administered intravaginally (i.v.) and intraperitoneally (i.p.). The in vitro incubation of human and murine sperm with curcumin caused a concentration-dependent decrease in sperm forward motility. Another study was performed to determine the effect of curcumin on the in vivo fertility in female mice. Ten to 500 µg of curcumin dissolved in DMSO was administered orally each night before mating, and by the i.p. and i.v. routes. The oral administration of curcumin did not affect fertility. The administration of curcumin via i.p. and i.v. caused a significant reduction in fertility. The mice that were treated with curcumin were successfully mated

again without any curcumin treatment, demonstrating that the contraceptive effect of curcumin may be reversible.

The antifertility effect of an aqueous extract of *Curcuma longa L.* was investigated in the male mouse (Mishra and Singh, 2009). Male Parkes mice were orally administered 600 mg *Curcuma longa L.* extract/kg bw/day for 56 and 84 days. Recovery studies were also performed. Histological examination shows that the mice treated with the test article had non-uniform degenerative changes in the seminiferous tubules including marked reduction in diameter, loosening of germinal epithelium and mixing of spermatids of different stages of spermatogenesis. The epididymis and seminal vesicle also showed histological changes compared to control animals. In addition, the treatment had adverse effects on motility, viability, morphology and number of spermatozoa. In treated animals, there were also reductions in serum testosterone, fertility and litter size after mating. After 56 days of treatment withdrawal, the above parameters were recovered to control levels.

The contraceptive effect of *Curcuma longa L.* extract in males was also demonstrated in the albino rat (Ashok and Meenakshi, 2004). Rats were fed daily oral doses of *C. longa* aqueous extract and 70% alcoholic extract for 60 days. In both of the treated groups, reductions in sperm motility and density were observed. The authors concluded that *C. longa* may have affected androgen synthesis by inhibiting the Leydig cell function or the hypothalamus pituitary axis, which results in arrested spermatogenesis.

C. Metabolism of Curcumin

Standard curcumin exhibits minimal bioavailability due to poor absorption from the gut. The major portion of ingested curcumin is excreted in an unmetabolized form in the feces (Sharma et al., 2005). A small portion that is absorbed is converted into water-soluble metabolites and is excreted. Therefore, the ability of standard curcumin to impart a biological effect on target tissues is very limited (Antony et al., 2008).

An early study in rodents demonstrated that an oral dose of 1 g/kg bw of standard curcumin resulted in the excretion of 75% of the dose in feces and a negligible amount in the urine (Wahlstrom and Blennow, 1978). An intravenous study in rodents resulted in large quantities of curcumin and tetrahydrocurcumin and hexahydrocurcumin metabolites in the bile. After dosing, more than 50% was excreted in the bile within 5 hours (Ravindranath and Chandrasekhara, 1981; Holder et al., 1978). A preclinical oral study in rats showed that metabolic reduction of curcumin happens within minutes of administration. Small amounts of curcumin were detected in the plasma of the rats with higher levels of curcumin glucuronide and curcumin sulfate in the plasma (Ireson et al., 2002). A study using 2% curcumin in the diet (equating to 1.2 g curcumin/kg bw) for 14 days showed that low nanomolar levels are detectable in the plasma, with concentrations in the liver and mucosal tissue of the colon ranging from 0.1 to 1.8 nmol/g tissue.

In humans, low systemic bioavailability was demonstrated in pilot and Phase I clinical trials performed with standard curcumin. An explanation for the poor systemic availability when administered orally may be efficient first-pass metabolism by the liver, leaving a limited amount to be passed on to the rest of the system. However, some degree of intestinal metabolism and absorption does occur as suggested by the detection of metabolites in the plasma of patients consuming high daily doses of curcumin (Sharma et al., 2005). In a pilot study where patients consumed 3.6 g of curcumin for 7 days prior to hepatic surgery, only trace levels of metabolites were detected in the peripheral blood samples and liver (Garcea et al., 2004). The authors of this pilot study concluded that the dose of oral curcumin required to produce hepatic levels high enough to exert pharmacological activity cannot be readily attained and such an approach of administering curcumin orally is probably not feasible.

BCM-95® is a curcumin preparation with enhanced bioavailability from a unique blend of curcuminoids and the essential oil of turmeric. The bioavailability of BCM-95® is 7-8 times higher than for standard curcumin. Moreover, curcumin is retained in the blood for significant levels---even at 8 hours post administration. This was demonstrated in a cross-over study to evaluate the human oral bioavailability of BCM-95® (Antony et al., 2008). Metabolism in the blood was analyzed 1, 2, 3, 4.5, 6 and 8 h after dosing with 4 x 500 mg capsules of BCM-95® and compared with a similar dose of standard curcumin. It was also compared to a curcumin-lecithin piperine preparation which has been used in other studies and shown to provide enhanced bioavailability. Results showed that the absorption of curcumin was faster from the BCM-95®, peaking in the first hour and reaching a maximum at 4.5 h. After 8 h, some residual curcumin remained in the blood. The absorption of standard curcumin was slower, peaking at 2 hours and disappearing after 4.5 hours. The relative bioavailability of BCM-95® was about 6.93-fold compared to standard curcumin.

D. Toxicology Studies on (BCM-95®)

1. Acute Study

Swiss albino mice and Wistar albino rats (10 male and 10 females) were used for an acute toxicity study (Aggarwal et al., 2016). BCM-95® was administered orally at the dose level of 5,000 mg/kg bw and a group of five males and five females were administered vehicle control. The animals were observed for a period of 14 days. No mortality or treatment related toxic signs and symptoms were observed. The body weight gain between the treated group and the control was not significantly different. At the end of the study, necropsy did not reveal any pathologically significant abnormality. The $LD_{50,}$, maximum tolerated dose, and minimal lethal dose of BCM-95® for rats and mice is >5,000 mg/kg bw.

2. Subchronic Studies

A 90-day repeated dose oral toxicity study was performed in Wistar rats in accordance with the guidelines OECD 408 (Aggarwal et al., 2016). Four groups of 20 animals (10 male and ten female) received *via* oral gavage either 0 (vehicle control), 100, 500 and 1000 mg/kg bw BCM-95® for 90 days. Two additional satellite groups of 10 rats (5 male and 5 female) ---also designated as "satellite control" and "satellite high dose", were administered vehicle and 1000 mg/kg bw BCM-95®, respectively, for 90 days. After terminal sacrifice of the test and control group animals, the satellite animals were kept under observation for an additional 28 days to determine any delayed toxic effect. There were no treatment related toxic signs in any of the BCM-95® treatment groups or high dose satellite treatment group compared to the control group. The body weight gains of all of the treatment groups and satellite dose animals were comparable to their control counterparts. Feed consumption of the dose groups was also comparable to the control animals. No variations were observed in the hematological parameters of any of the treatment animals compared to controls. In addition, no differences in any of the biochemical parameters between treatment and control animals were reported. No differences were observed between treatment and control groups on the analysis of the urine samples collected at the end of the experiment. For the animals sacrificed at day 90 and in the satellite animals observed for an additional 28 days, organ weights of the treatment groups were comparable to the control group. There were no histopathological differences between any of the treatment groups and their counterpart controls. The NOAEL of BCM-95® is 1000 mg/kg bw in Wistar rats, the highest dose tested.

In an additional rat study, BCM-95® was administered to four groups of five female rats in the diet at the levels of 0, 100, 250, and 750 mg/kg bw/day for 45 days (Aggarwal et al., 2016). At the end of the study period, hematological, biochemical and histological analyses were performed. No death or abnormality occurred in the control or treated animals, and no adverse physical changes were observed. Clinical, hematological and biochemical parameters in BCM-95®-treated animals were comparable to untreated controls. There was no significant change in clotting time although an increase in total leukocyte count was observed in treated animals. Serum total protein, albumin, globulin, SGOT, SGPT and blood glucose were not affected although serum alkaline phosphatase increased in rats receiving high doses of BCM-95®. While serum total cholesterol was decreased, hepatic cholesterol and triglycerides were not affected in BCM-95®-treated animals. These exposures of BCM-95® also did not produce any histological lesions in liver.

3. Genotoxicity & Mutagenicity Studies on BCM-95®

In an Ames test (bacterial reverse mutation assay), BCM-95® was tested against the *Salmonella typhimurium* strains TA-98, TA-100, TA-102, TA-1535 and TA-1537 with and

without metabolic activation at the concentrations of 1000, 2000, 3000, 4000 and 5000 µg/plate (Aggarwal et al., 2016). The colony count in the test groups was not significantly different from the negative control group. Adequate responses in the positive control plates confirmed the sensitivity of the *Salmonella* strains. The test was negative for mutagenicity in all the strains with and without metabolic activation.

A mammalian bone marrow chromosome aberration test was performed using BCM-95® in albino Wistar rats (Aggarwal et al., 2016). A group of 20 rats (10 males and 10 females) was administered BCM-95® orally at a single dose of 2000 mg/kg bw, and a negative control group was administered vehicle only. A positive control group was administered cyclophosphamide at a dose of 50 mg/kg bw intraperitoneally. Bone marrow was processed at sacrifice, 18 and 24 hours after dosing. No evidence of structural or chromosomal aberrations was observed at 2000 mg/kg bw BCM-95®. The total number of aberrations in the treatment group was not significantly different than the control group. It was concluded that BCM-95 ® had no clastogenic activity under the conditions of the study up 2000 mg/kg bw.

A mammalian erythrocyte micronucleus test in mice was performed using BCM-95® (Aggarwal et al., 2016). A total of 60 animals (30 males and 30 females) was distributed into three main groups and orally administered either 2000 mg BCM-95®/kg bw, negative vehicle control, or a positive control of cyclophosphamide. Bone marrow was processed at the times of sacrifice which were 24 and 48 hours after dose administration. No mortality or toxic signs were observed in any of the animals, nor were significant observed changes found in the number of immature and mature erythrocytes or in the total number of erythrocytes of treated male and female animals at the 2000 mg/kg bw treatment level at 24 and 48 hours compared to the controls. In addition, there were no observable effects in the micronuclei at 24 or 48 hours in the treatments groups compared to the negative control. It was concluded that BCM-95® did not show any clastogenic potential in the micronucleus test.

4. Other Studies in Animals on BCM-95®

The effect of 300 mg BCM-95®/kg bw was assessed by studying the markers of liver function in a group of male Sprague-Dawley rats with carbon tetrachloride (CCl_4)-induced liver injury and alcohol-induced liver injury (Dolcas, unpublished study). CCl_4-induced hepatitis was produced in rats by administering a low dose of CCl_4 for three months. Alcohol-induced hepatitis was produced by administering alcohol to rats for three months. One group of rats receiving CCl_4 or alcohol for three months also received daily BCM-95® in the feed. Liver injury was assessed by changes in parameters such as an increase in serum enzymes, e.g., glutamic-oxaloacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT) and lactate dehydrogenase (LDH), a decrease in albumin-globulin ratio, an increase in serum lipids such as cholesterol and triglyceride and an increase in

serum bilirubin. BCM-95® appeared to have a protective effect against CCl_4-induced liver injury as evidenced by a decrease in the level of serum enzymes, increase in albumin/globulin (A/G) ratio, decrease in serum cholesterol and triglyceride (TG), bilirubin and urea. BCM-95® also appears to reduce steatosis as evidenced by a decrease in the level of cholesterol and TG in the liver. It also appeared to have an antifibrotic effect as evidenced by a decrease in the extent of accumulation of collagen in liver. Treatment with BCM-95® appeared to offer a protective effect against alcoholic hepatitis based on the observed reversal of changes in abnormal liver function tests such a serum transminases, serum lipids and bilirubin. The extent of steatosis and fibrosis caused by alcohol appeared to be less in rats receiving BCM-95®, indicating a protective effect against alcoholic hepatitis. However, evaluation of biochemical parameters indicated that it offers only a partial protective effect.

Leray et al. (2011) studied the effect of a blend of BCM-95® and citrus polyphenol-supplemented diet on the inflammatory state in obese cats. Two groups of cats (n=8, 3 males, 5 females) were fed a diet supplemented with either citrus extracts (protein 34·3 %, fat 15·4 %, starch 30·6 %, hesperidin (Natural Orange Extract; Exquim SA, Barcelona, Spain) 0·05% and naringin (citroflavonoids soluble; Exquim SA) 0·1% diet) or with highly bioavailable curcumin extract from *C. longa* (protein 34·2%, fat 16·5%, starch 28%, Bio-Curcumin (BCM-95®, Frutarom, Londerzeel, Belgium) 0·09% diet), for two 8-week periods in a crossover design. Many markers of inflammation were unaffected by either treatment, except for a decreased concentration of plasma acute-phase protein (APP). The authors concluded that hesperidin and naringin or BCM-95® have beneficial effects on the obesity-related inflammatory state. No adverse effects were reported in any of the experimental animals throughout the study period.

Sanmukhani, et al. (2011) conducted a study in rats and mice where they investigated the antidepressant-like activity of BCM-95® and its combination with fluoxetine and imipramine. Efficacy was evaluated by using the forced swimming test (FST) in glass jar and the tail suspension test (TST) after acute (three doses) dosing in mice; and the forced swimming test with activity wheel after chronic (14 days) dosing in rats. Locomotor activity was also tested after acute dosing in mice. Both the acute model of FST and TST, and the chronic model of FST with water wheel showed significant antidepressant-like activity of curcumin in 100 mg/kg dose of BCM-95®compared with the vehicle control. The effect of BCM-95® (100 mg/kg) was similar to that of fluoxetine and imipramine, but its addition to fluoxetine and imipramine did not improve their antidepressant activity. BCM-95® increased both the swimming and climbing behavior in FST. It was concluded that the antidepressant-like activity could be due to an increase in serotonin, norepinephrine and dopamine levels in the brain. No signs of neurotoxicity were observed in this study.

E. Clinical Studies on BCM-95®

Several clinical studies have been conducted on BCM-95® that were designed to show efficacy in maintaining health.

1. Joint Health

The safety and efficacy of BCM-95® and Boswellia serrat (Bospure®) extracts were evaluated and compared with a selective COX-2 inhibitor in 28 healthy subjects (Kizhakkedath et al., 2013). The BCM-95® formulation was administered twice a day at a dose of 500 mg, and was more successful than the COX-2 inhibitor administration of 100 mg twice a day for joint health symptoms. The treatment was well-tolerated and no adverse effects were observed in vital signs, hemogram, liver and renal function tests.

Chandran and Goel (2012) studied the safety and efficacy of BCM-95® in patients with rheumatoid arthritis (RA). Forty-five (38 female, 7 male, mean age 47.88 years) patients diagnosed with RA were divided into three groups receiving either 500 mg BCM-95® or diclofenac sodium (50 mg) alone or in combination for 8 weeks. Patients in all treatment groups showed significant changes in their Disease Activity Score (DAS). The group receiving BCM-95® showed the highest improvement in DAS and American College of Rheumatology (ACR) criteria for reduction in tenderness and swelling of joint scores. Hematology, blood chemistry, C-reactive protein, antistreptolysin-O, rheumatoid factor, and blood sugar were monitored bi-weekly for safety evaluation. There were no major changes among groups in blood urea, serum creatinine, serum calcium, serum phosphorus, total bilirubin, direct bilirubin, serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT) and fetal bovine serum (FBS). The adverse events associated with BCM-95® included mild fever and throat infection. The authors concluded that BCM-95® was generally safe and well-tolerated in most subjects when administered for a period of up to 8 weeks.

2. Urinary Health

Hejazi et al. (2013) reported the results of a pilot clinical trial using BCM-95® as a radioprotector in patients with prostate cancer who had undergone radiation therapy. Forty prostate cancer patients undergoing external beam radiotherapy (EBRT) were randomly assigned to the BCM-95® group (3 g/day) or the placebo group for 20 weeks. Quality of life was assessed by the Persian version of the European Organization for Research and Treatment of Cancer prostate cancer-specific quality of life questionnaire (QLQ-PR25). The change in urinary symptoms across the 20-week period differed significantly between groups, and patients in the BCM-95® group experienced much milder urinary symptoms compared with the placebo group. No group differences were observed in any other domain of the QLQ-PR25. The authors conclude that curcumin can confer

radioprotective effect in patients with prostate cancer who undergo radiation therapy through reducing the severity of radiotherapy-related urinary symptoms.

3. Mood and Depression

Sanmukhani et al. (2014) reported the results of a randomized, observer masked clinical study, with 3 parallel treatment arms to compare the efficacy and safety of BCM-95® with the drug, fluoxetine, in patients with major depressive disorder (MDD). Sixty patients diagnosed with MDD were randomized in a 1:1:1 ratio for a 6-week treatment with fluoxetine (20 mg) or curcumin (1,000 mg) individually or in combination. Group I received fluoxetine 20 mg/day in the morning, group II received BCM-95®1,000 mg/day, while group III received fluoxetine 20 mg/day and BCM-95® 1,000 mg/day. Efficacy and safety were evaluated after two, four and six weeks by measuring the response rate according to the Hamilton Depression Rating Scale 17-item scale (HAM-D17). The secondary efficacy measures were mean change in HAM-D17 score at two, four and six weeks; remission rate according to HAM-D17 scale; response rate on the clinical global impression-improvement (CGI-I) assessment scale; score on clinical global impression-severity of illness (CGI-S) scale and global efficacy at the end of study. The proportion of responders as measured by the HAM-D17 scale was higher in the combination group (77.8%) than in either the fluoxetine (64.7%) or the BCM-95® (62.5%) groups; however, these data were not statistically significant. The mean change in HAM-D17 score at the end of six weeks was comparable in all three groups. The investigators' opinion on global efficacy was that there was no statistical difference in the 3 treatment groups---all 3 groups showed "excellent" or "good" efficacy of the study medication.

An unpublished protocol for an intended double-blind, placebo-controlled clinical study (no author) was provided. It will assess the antidepressant and anti-inflammatory effects of BCM-95® (1000 mg/day) on 40-60 adults with mild to moderate depression. Changes in depression, anxiety, and general health will be measured over an 8-week period. Levels of cortisol, kynurenine pathway metabolites (measure of inflammation), and oxidative stress markers will be assessed over time.

4. Cognitive Function

Baum et al. (2007) conducted a 6-month human trial on the effects of BCM-95® on blood lipid profiles. Elderly patients (n=31, aged 50 or over with progressive memory decline) were randomized to three oral, daily doses of BCM-95®: placebo, 1 g, or 4 g. Plasma curcumin and metabolites were measured at 1 month. At baseline, 1 month, and 6 months, blood samples were taken after an overnight fast to measure serum lipid and lipoprotein concentrations. To monitor safety, liver and kidney function parameters were measured, including sodium, potassium, urea, creatinine, protein, albumin, bilirubin, alkaline phosphatase, and alanine aminotransferase (ALT/GPT). Of these parameters,

only ALT/GPT differed among groups, which may have been due to an elevated baseline level of ALT/GPT in the 1 g/day dose group. At the end of the trial, mean ALT/GPT levels were 16.8 in the placebo group, 24.6 in the 1 g/day group, and 16.5 for the 4 g/day dose group. Therefore this change was not dose related. The plasma curcumin concentration reached a mean of 490 nmol/L for the 4 g dose and 270 nmol/L for the 1 g dose. Triacylglycerol, total cholesterol, LDL and HDL cholesterol levels were not affected by BCM-95® consumption at either dose. However, a positive and significant correlation between the concentrations of plasma curcumin and serum cholesterol was found. Adverse effects from BCM-95® consumption at 1 g or 4 g doses were mild, and included a case of dizziness, and increased delusions, constipation, and diarrhea. There were fewer adverse events reported at the 4 g dose than the 1 g dose. The results of the study suggest that daily administration of BCM-95® at a dose of 4 g/day for 6 months did not reveal any significant safety concerns.

5. Chemoprotection

Shakibaei et al. (2014) described an *in vitro* study regarding curcumin's role in enhancing chemosensitization. Current therapies for the treatment of colorectal cancer (CRC) mainly comprise 5-Fluorouracil-based (5-FU) chemotherapies. Previous studies have shown that combined treatment of curcumin with 5-FU induces more significant cytotoxicity in DNA mismatch repair (MMR)-deficient colorectal cancer (CRC) monolayer cultures compared to the agent individually. High density 3D cultures of CRC cell lines and their corresponding isogenic 5-FU-chemoresistant derivative clones were treated with 5-FU either without or with curcumin in time- and dose-dependent assays. Pre-treatment with curcumin significantly enhanced the effect of 5-FU on HCT116R and HCR116+ch3R cells, in contrast to 5-FU alone. Curcumin and/or 5-FU strongly affected MMR-deficient CRC cells in high density cultures, however, MMR-proficient CRC cells were more sensitive. Curcumin also exhibited the ability to effectively suppress cancer stem cell (CSC) pools as evidenced by a decreased number of CSC marker positive cells.

Goel and Aggarwal, (2010), in a review paper, outlined curcumin's role as a chemo resensitizer and protector. The paper provides a review of the literature while addressing curcumin's effect as a chemosensitizer in a large number of cancers including breast, colon, pancreas, gastric, liver, and prostate. Similar studies have also revealed that this agent can sensitize a variety of tumors to gamma radiation. The mechanism believed to be responsible for these effects is the downregulation of various growth regulatory pathways and specific genetic targets including genes for NF-κB, STAT3, COX2, Akt, antiapoptotic proteins, growth factor receptors, and multidrug-resistance proteins. Research also supports curcumin's effect in protecting normal organs from chemotherapy and radiotherapy-induced toxicity through its ability to induce the activation of NRF2 and induce the expression of antioxidant enzymes.

An unpublished protocol by C. R. Becerra addresses an ongoing colon cancer study at Baylor University for terminally ill patients (Becerra, 2013). The primary objective of the study is to confirm the clinical safety and to determine the maximum tolerable dose for curcumin. Secondary objectives are to test curcumin's chemo resistant clinical efficacy in combination with 5-FU and to retrospectively determine DNA methylation status of peripheral blood circulating tumor cells (CTC) pre-and post-curcumin treatment using archived blood from clinical responders and non-responders.

6. Studies in Progress

Clinical trials using BCM-95® are ongoing, and a search of the U.S. National Institutes of Health site ClinicalTrials.gov[2] yielded 5 current clinical studies using BCM-95®. These studies are summarized in Table 12.

Table 12. Current Clinical Studies Using BCM-95® (from ClinicalTrials.gov)

Condition	Dose	Duration	Number of Subjects	Design/Adverse Effects	Study Status
Multiple Sclerosis	500 mg BCM-95® (oral dose) 2x/day with subcutaneous Interferon Beta 1a	42 months (18 months of enrollments, 24 month treatment period)	80	Study to evaluate the efficacy, safety, and tolerability of BCM-95 in patients with relapsing multiple sclerosis by examining the difference between the proportion of subjects with active T2 lesions assessed by MRI.	Phase 2, Ongoing
Osteoarthritis	500 mg BCM-95® (Curamed) 3x/day	12 weeks	67 osteoarthritis patients in each group	Study the effects of BCM-95 (Curamed) in osteoarthritis compared to Curamin (500 mg, 3x/day) or Placebo. The effects will be measured by degree of joint pain and physical performance.	Not yet open for participant recruitment
Mucocitis	BCM-95® administered by ingested mouth rinse. There will be 3 participant at each of 4 does levels (0.33g, 1g, 2g, 3g) per rinse, three times daily	4-6 weeks	12-15 chemotherapy patients	To determine how safe curcumin is and how well it works to treat mucocitis in chemotherapy patients.	Phase 1, Phase 2, not yet recruiting

Condition	Dose	Duration	Number of Subjects	Design/Adverse Effects	Study Status
Prostate Cancer	500 mg BCM-95® 2x/day	6 months	600 males (Estimated)	Study to determine recurrence of prostate cancer by measuring serum prostate specific antigen.	Phase 2, Recruiting
Radioprotection	3 g BCM-95®/ day	7-8 weeks	40 males (Estimated)	Study to determine the radioprotective effects of BCM-95T in prostate cancer using magnetic resonance spectroscopy (MRS 1 week before radiation therapy and 3 months after radiotherapy completion. Also prostate specific antigen (PSA) rebound will be compared after 1 year.	Unknown

F. Toxicology Studies on Other Sources of Curcumin

1. Acute Study

The single-dose oral administration of 5 g curcumin/kg bw in rats did not result in any toxic effects (Wahlstrom and Blennow, 1978). In addition, oral toxicity studies using 2.5 g turmeric/kg bw or 300 mg/kg bw of an alcohol extracts of turmeric in guinea pigs, rats, and monkeys did not result in any toxicity (Shankar et al., 1980). The reported acute LD_{50} of curcumin oil in rats exceeds 5 g/kg and the acute oral LD_{50} of curcumin is greater than 2 g/kg (Opdyke and Letizia, 1983; Srimal and Dhawan, 1973).

Dadhaniya et al. (2011) performed acute and subchronic safety assessments of Longvida® (curcumin) in rats and mice. The oral LD_{50} in both rats and mice was found to be greater than 2000 mg/kg bw/day. In the subchronic toxicity study, the NOAEL for Longvida® was determined to be 720 mg/kg bw/day, the highest dose tested.

2. Short-Term Study

Short-term safety studies of curcumin in animals have been well-reviewed (Chianani-wu, 2003). Rats that were fed 1.8 g/kg bw/day for 90 days showed no adverse effects, as was the case with monkeys fed 0.8 mg/kg bw/day for 90 days (Majeed et al., 1995).

However, curcumin from turmeric has shown to cause hepatotoxicity in mice and in rats at high doses. A study in female Wister rats and Swiss mice fed 0%, 0.01, 0.1, 0.2, 1%, or 5% turmeric and 0%, 0.05%, and 0.25% ethanolic turmeric extract in the diet for 14 and another group of mice and rats was fed 0 or 5% turmeric extract for 90 days. Mice were more susceptible to the hepatotoxic effects of the extracts than rats. Histological effects (focal necrosis or focal necrosis with regeneration) were observed after consumption of 5% turmeric extract for 14 days in the diets of mice. These effects were also occasionally

observed for lower doses of turmeric extract and for both doses of ethanolic turmeric extract. In the 90-day study, mice showed significant reductions in body weight gain and significant increases in absolute and relative liver weight after consuming 5% turmeric in the diet. These effects were not observed in mice after 14 days, with the exception of a reduction in the relative liver weight for the 0.05% ETE group. The rats that were fed 5% turmeric for 90 days showed a reduction in body weight gain, significant decrease in liver weight (absolute only), and hepatotoxicity. The authors note that these changes have been observed at extremely high doses of turmeric, about 200-5,000 times the ADI of 0-2.5 mg/kg allocated by the JECFA. The authors also explain that human consumption for adults generally falls in the range of 0.2-0.6 g/person/day, and the toxic doses observed in these studies are at least 50 times higher than this and should not raise any alarm for human consumption (Deshpande et al., 1998).

Hepatoxicity was seen in another study where mice were fed whole turmeric at levels of 0.2%, 1%, or 5% or ethanolic turmeric extract (0.05% or 0.25%) for 14 days. Histopathological examination showed coagulative necrosis in the liver accompanied by a zone of regenerating hepatic parenchymal cells. The ultrastructural changes seen in liver parenchymal cells were non-specific reactions to injury. The authors concluded that mice seem to be a susceptible species for turmeric induced toxicity (Kandarkar et al., 1998).

3. Genotoxicity & Mutagenicity Studies

Curcumin exhibits both pro- and antimutagenic effects. It has been shown to reduce the number of aberrant cells in a chromosomal aberration assay in Wistar rats at 100 and 200 mg/kg bw (Shukla et al., 2002). Turmeric also prevents mutation effects of the powerful mutagen urethane (el Hamss et al., 1999). On the other hand, curcumin and turmeric have been shown to enhance gamma-radiation-induced chromosome aberration in the Chinese hamster ovary (Araujo et al., 1999). It also has been shown to not protect against hexavalent chromium-induced DNA strand break, and chromium and curcumin together have been shown to cause DNA breaks in human lymphocytes and gastric mucosal cells (Blasiak et al., 1999).

4. Reproductive Study

Ganiger et al. (2007) performed the final toxicology study on curcumin that was reviewed by the JECFA at the 61st meeting in 2003 (originally reviewed by JECFA as a 2002 unpublished report and subsequently published by Ganiger in 2007). The study assessed the two-generational reproductive toxicity of oral curcumin in Wistar rats. Three groups of rats were fed diets containing curcumin at concentrations of 1,500, 3,000 and 10,000 ppm. No adverse toxicological effects were observed in the parental animals. There was no effect of curcumin on reproductive parameters and the only effect on offspring was a small reduction in pre-weaning body weight gain in the F2 pups at the highest dose level. The

mean body weights of the F2 offspring were significantly decreased on postnatal days 1 and 7 at the intermediate dose, and on postnatal days 7, 14 and 21 at the highest dose. This trend was dose-related, but the effect was small, with average body weights being greater than 90% that of the control pups, and the changes were reported to be within the data for historical controls. There were no other effects on general health, body weight, pup survival and fertility in either generation. The effects at the intermediate dose were considered to be incidental; therefore, the dose of 250–320 mg/kg bw/day for the F1 generation was the NOEL. The authors concluded that the NOEL for reproductive toxicity of curcumin fed in the diet for two generations was 10,000 ppm, which is equivalent to 847 and 959 mg/kg bw/day for male rats and 1043 and 1076 for females for F_0 and F_1 generations, respectively. However, JECFA (2003) concluded that body weight reduction in F_2 pups at the highest dose prevented it from being regarded as a no adverse effect level. Therefore, the ADI for curcumin was changed to 0-3 mg/kg bw based on the intake of 250 - 320 mg/kg bw in the mid-dose group.

5. Human Studies

Many human studies using curcumin have been well reviewed in the literature (Chainani-Wu, 2003; Epstein et al., 2010) and have shown evidence of the safety of curcumin. As described in Sharma et al. (2005), Cheng et al. (2001) observed no toxic effects of curcumin when administered at a dose of up to 8,000 mg/day. In addition, five other clinical studies administered doses of curcumin ranging from 1,125 to 2,500 mg per day and noted the safety of curcumin (Deodhar et al., 1980; Satoskar et al, 1986; James, 1996; Lal et al., 1999; Lal et al., 2000). In addition, Arggarwal et al. (2003) reported there was no apparent toxicity of curcumin at a dose of 10,000 mg/day. Curcumin remains a topic of active research, and other clinical studies have been published following the issuance of the Chainani-Wu and Epstein reviews. The studies are summarized in 0.

G. Studies Conducted by National Toxicology Program on Curcumin

The studies conducted by NTP were reviewed by the NTP evaluation process, and it was concluded that the evidence for carcinogenicity in mice and rats was equivocal (NTP, 1993).

In a 13-week study, groups of 10 male and 10 female rats were fed diets containing 0, 1,000, 5,000, 10,000, 25,000 or 50,000 ppm turmeric oleoresin. These dietary levels of turmeric oleoresin were estimated to deliver about 50, 250, 480, 1,300 or 2,600 mg/kg bw to males and 60, 300, 550, 1,450, or 2,800 mg/kg bw to females, respectively. In males receiving 50,000 ppm, the final mean body weight was lower than that of the controls. Feed consumption in all groups was similar to the controls. The absolute liver weights of female rats and the relative liver weights in male rats receiving 5,000, 10,000, 25,000 and 50,000 ppm were significantly greater than the controls. No significant differences were

found in clinical or hematologic chemistry, and urinalysis parameters. In males and females receiving the 50,000 ppm dose, hyperplasia of the mucosal epithelium was observed in the cecum and colon. Clinical findings in treated animals included stained fur and discolored feces and urine.

In a 13-week mouse study, groups of 10 male and 10 female B6C3F mice were fed 0, 1,000, 5,000, 10,000, 25,000 or 50,000 ppm turmeric oleoresin. These dietary levels of turmeric oleoresin were estimated to deliver average daily doses of 50, 250, 480, 1,33 or 2,600 mg/kg bw to males and 60,0300,0550, 1,450 or 2,800 mg/kg bw in females, respectively. In males receiving 50,000 ppm, the rinal mean body weight was lowere than that of the controls. Feed consumption in all groups was similar to the controls. . The absolute liver weights of female rats and the relative liver weights of male rats recieing 5,000, 10,000, 25,000 or 50,000 ppm dose, hyperplasia of the mucosal epithelium was observed in the cecum and colon.

In a 13-week mouse study, grops of 10 male and 10 female B6C3F mice were fed 0, 1,000, 5,000, 10,000, 25,000 or 50,000 ppm turmeric oleoresin. These dietary levels of turmeric oleoresin were estimated to deliver average daily doses of 150, 750, 1,700, 3,850, 7,700 mg/kg bw to males and 200, 1,000, 1,800, 4,700 or 9,300 mg/kg bw in females, respectively. Thefeed consumption, final mean body weight gains, and final mean body weights were the same in treated groups as in controls. The absolute and relative liver weights of male mice recieivng 5,000 ppm and male and female mice that recieved 10,00, 25,00 and 50,000 ppm of turmeric oleoresin were significantly greater than the controls. There were no significant changes compare to controls in hematologic and clinical chemistry or urinalysis parameteres, nor were treatment-related histopathologic lesions observed. Clinical finds in treatment animals included stained fur and discoloration in the feces in rine.

In the 2-year NTP studies, groups of 60 male and 60 female B6C3F1 mice and F344/N rats received doses of 0, 2,000, 10,000 or 50,000 ppm turmeric oleoresin in the feed. Up to ten animals from each group were reserved for a 15-month interim examination. There were no differences in survival and feed consumption in rats or mice between the treated groups and the control group throughout the study. The estimated average daily turmeric consumption values in rats were 80, 460, or 2,000 mg/kg bw in males and 90, 440, or 2,400 mg/kg bw in females. In rats, there were no clinical findings that were related to toxicity. Male rats receiving 50,000 ppm had increased incidences of ulcers, hyperplasia, and hyperkeratosis of the forestomach and cecum. In addition, male and female rats receiving 50,000 ppm and male rats receiving 10,000 ppm had increased sinus ectasia of the mesenteric lymph node. In female treated rats, there were significant increases in clitoral gland adenoma in all dose groups, but, due to the similar incidence in all dose groups, there was a lack of correlation to dose. The investigators concluded that under the conditions of the 2-year feeding studies there was no evidence of carcinogenic activity

of turmeric oleoresin in male F344/N rats at any dose level. NTP concluded that there was equivocal evidence of carcinogenic activity of turmeric oleoresin in female rats based on the increase in clitoral gland adenoma.

In mice, the estimated average daily turmeric consumption values were 220, 520 or 6,000 mg/kg bw for males and 320, 1,620 or 8,400 mg/kg bw for females. Alkaline phosphatase values in males and females mice receiving 10,000 and 50,000 ppm turmeric were significantly higher than the controls. There were no other significant differences in hematologic or clinical chemistry in either males or females. At the 15-month interim evaluation, the absolute and relative liver weights of male and female mice in the 10,000 and 50,000 ppm dose groups were significantly greater than the controls, and hepatocellular neoplasms occurred in several treatment male and female mice but not in controls. At the end of the 2-year study, there were significantly increased hepatocellular adenomas in males and females receiving 2,000 or 50,000 ppm. The incidences of hepatocellular adenoma and carcinoma in all exposed groups of male mice exceeded the range for neoplasms in historical control male mice. In the small intestine, three male mice that received 2,000 ppm turmeric and three male mice that received 10,000 ppm turmeric had carcinomas of the small intestine, while no carcinomas were observed in the control or 50,000 ppm groups. Since there was no dose-response trend, the investigators were unsure if the neoplasms were treatment-related. In the forestomach and pituitary gland, the incidence of lesions was well within the range for the historical control mouse. The investigators concluded that in B6C3F1 mice, there was equivocal evidence of carcinogenic activity of tumeric oleoresin in males based on an increased incidence of hepatocellular adenoma at the 10,000 ppm level and the occurrence of carcinomas of the small intestine in the 2,000 and 10,000 ppm groups. NTP concluded that there was equivocal evidence of carcinogenic activity in female mice due to an increased incidence of hepatocellular adenoma in the 10,000 ppm group.

H. JECFA Review of Curcumin & Turmeric

Turmeric oleoresin, the product of solvent extraction of turmeric containing <90% of total coloring matter (curcuminoids), and curcumin were evaluated by JECFA at its 13th, 18th, 22nd, 24th, 26th, 30th, 35th, 39th, 44th, 51st and 57th meetings (WHO 1970, 1974, 1978, 1980, 1982, 1987, 1990, 1992, 1995, 2000, and 2002). The latest review at its 61st meeting (WHO, 2004) established an ADI of 0-3 mg/kg bw based on an updated reproductive study in rats (subsequently published as Ganiger et al., 2007). JECFA assigned a no observed effect level (NOEL) of 250 - 300 mg/kg based on this study. The highest doses tested (847 and 959 mg/kg bw/day for male rats and 1043 and 1076 for females in the F0 and F1 generations, respectively) in this study were used to determine the NOEL by the authors, however, JECFA concluded that body weight reduction in F2 pups at the highest dose prevented it from being regarded as a NOAEL. The ADI of 0-3 mg/kg bw was obtained by applying a 100-fold safety factor for extrapolation from animals

to humans. The test material in this study consisted of 80% curcumin or diferuloylmethane (1, 7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3, 5-dione) and 99% total curcuminoids. At the 61st meeting, JECFA reviewed two new clinical studies (Sharma et al., 2001; Cheng et al., 2001) but concluded that these clinical studies had little relevance to setting an ADI. Therefore, the previous ADI of 0-3 mg/kg bw was left unchanged.

In previous meetings, JECFA reviewed all other relevant studies which resulted in a tentative ADI of 0-1 mg/kg bw on the basis of chronic mouse and rat studies that were conducted by the National Toxicology Program (NTP, 1993) on turmeric oleoresin (curcumin content 79-85%). The key effect on liver weight in mice was used to establish the tentative ADI based on a NOEL of 220 mg/kg bw, and a 200–fold safety factor was used to give the 0-1 mg/kg bw ADI. JECFA expressed a willingness to recalculate the ADI after review of an adequately conducted animal study for reproductive effects (WHO, 1996).

JECFA closely examined the tumor incidence in the mouse and rat chronic study, along with studies on the mutagenic and other genotoxic activity of turmeric oleoresin and curcumin. JECFA concluded that the increased incidence in liver and clitoral gland tumors seen in some dose groups was not dose related and that there was no evidence that curcumin was genotoxic.

I. Safety Studies on Desmethoxycurcumin

Currently, no traditional toxicology studies are available on desmethosycurcumin in the scientific literature. A search of the literature using the Toxicology Data Network Database (TOXNET) on December, 2015 using the search term “Desmethoxycurcumin” yielded 8 results. One study indicated that desmethoxycurcumin and curcumin have time and concentration-dependent protective effects against DNA damage (Subramanian et al., 1994) and another examined the systemic bioavailability of curcumin (Marczylo et al. 2007). The other studies were less relevant including studies about dyes and pigmentation efficacy (Jentzsch et al., 1970; Racz et al., 1972). Other studies mentioned desmethoxycurcumin only as a component of curcumin and its efficacy in chemoprotective effects (Epelbaum et al., 2010) and anti-inflammatory effects (Jacob et al., 2007). The other two articles described preparation on curcumin niosomes and effects of curcumin on mosquitoes

J. Safety Studies on Bisdesmethoxycurcumin

No traditional toxicology studies on bisdesmethoxycurcumin surfaced in searching the scientific literature. A search of the literature using the Toxicology Data Network Database (TOXNET) on December 2015 using the search term “bisdesmethoxycurcumin” yielded 7 results. These 7 studies were identical to the studies listed above for dexmethoxycurcumin.

K. Other Studies on Turmerone

Nishiyama et al. (2005) investigated the effects of turmeric extracts on blood glucose levels in type 2 diabetic mice. These turmeric extracts were obtained by ethanol extraction (E-ext) to yield both, curcuminoids and sesquiterpenoids (including turmerones), hexane extraction (H-ext) to yield sesquiterpenoids, and ethanol extraction from hexane-extraction residue (HE-ext) to yield curcuminoids. The control group was fed a basal diet, while the other groups were fed a diet containing 0.1 or 0.5 g of H-ext or HE-ext/100 g of diet or 0.2 or 1.0 g of E-ext/100 g of diet for 4 weeks. Although blood glucose levels in the control group significantly increased ($P < 0.01$) after 4 weeks, feeding of 0.2 or 1.0 g of E-ext, 0.5 g of H-ext, and 0.5 g of HE-ext/100 g of diet suppressed the significant increase in blood glucose levels. Furthermore, E-ext stimulated human adipocyte differentiation, and these turmeric extracts had human peroxisome proliferator-activated receptor-gamma (PPAR-gamma) ligand-binding activity in a GAL4-PPAR-gamma chimera assay. Also, curcumin, demethoxycurcumin, bisdemethoxycurcumin, and Ar-turmerone had PPAR-gamma ligand-binding activity. PPAR-γ is a member of the nuclear receptor family of transcription factors, a large group of proteins that mediate ligand-dependent transcriptional activation and transrepression. PPAR-γ is highly expressed in adipose tissue and plays a crucial role in adipocyte differentiation. It is also expressed in a variety of other tissue and cell types where it plays key roles in the regulation of metabolism and inflammation. Induction of PPARγ activity by curcuminoids and the turmerones could be one of the mechanisms through which these compounds exert their anti-diabetic action. There were no adverse effects reported in any of the animals.

Liju et al. (2011) found that oral administration of turmeric oil (Ar-turmerone 61.8%, curlone 12.5%, ar-curcumene 6.1%) for one month to mice significantly increased superoxide dismutase, glutathione, and glutathione reductase enzyme levels in blood and glutathione-S-transferase and superoxide dismutase enzymes in liver. Turmeric oil showed significant reduction in paw thickness in carrageenan, dextran-induced acute inflammation, and formalin-induced chronic inflammation. No adverse effects were reported by the authors.

Several *in vitro* studies have been performed to demonstrate the efficacy of turmerone and to show that the combination of curcumin and turmerone could result in better bioavailability than curcumin alone. Lantz et al. (2005) reported that a combination of curcuminoids and turmeric oils produce a better anti-inflammatory effect than that produced by curcuminoids alone in HL-60 cells exposed to proinflammatory mediators. Similarly, Yue et al. (2012) found that a turmeric extract including curcumin and turmerones were transported in Caco-2 cells more readily than curcumin alone. Caco-2 cell monolayers are widely used as an *in vitro* model to study drug permeability because these cells are similar to the absorptive cells in the human intestine. Another study by Yue et al. (2010) demonstrated that turmeric extracts (including curcuminoids and volatile oil) had chemopreventive/antitumor properties in human breast cancer cell lines.

L. Allergenicity

A case report described the development of contact dermatitis on the hands and forearms in response to contact with food coloring in a 58-year-old woman who worked in a pasta factory Kieć-Swierczyńska and Krecisz (1998). When a patch test was conducted, a positive reaction to curcumin and curcuma was observed.

In another case report, a 54-year-old woman had a positive reaction to tetrahydrocurcumin (1% pet.), an ingredient of Avon age block cream (Avon Cosmetics Ltd. Northampton, UK), but had a negative reaction to the other constituents of the product (Lamb and Wilkinson, 2003).

A 53-year-old woman experience recurrent facial and eyelid swelling and a red scaly rash when she used Avon age block cream (Avon Cosmetics Ltd. Northampton, UK) (Thompson and Tan, 2006). When ingredients of the cream were tested individually, she showed a positive reaction only to tetrahydrocurcumin (1% pet.).

Fischer and Anger (2004) two cases of contact dermatitis that developed in one man 53-year-old man and one 56-year old woman after their skin was clean with yellow chlorhexidine solution. Patch testing showed that they were allergic to curcumin.

Liddle et al. (2006) described a case of contact urticaria following exposure to curcumin in a 44-year-old woman. They also described a case of a 20-year-old woman with no known history of contact urticaria or sensitivity to curcumin who was administered a prick test and developed a wheal at the site of application.

A study conducted by Futrell and Rietchel (1993) investigated the incidence of contact allergy to 12 spices found in traditional foods of New Orleans in individuals with suspected contact dermatitis. Study participants were 19 men and 36 women aged 2 to 76 years. The study participants were subjected to patch tests for turmeric, curry, cumin seed, ginger, nutmeg, oregano, cinnamon, sweet basil, cayenne pepper, coriander, clove, and sage. When two concentrations of curry, cumin seed, and turmeric were tested, the numbers of study participants who had positive reactions were 0, 1, and 0, respectively. There were 3, 3, and 2, positive reactions, respectively, in response to 25% concentration of curry, cumin seed, and turmeric.

A case of allergic dermatitis was described for a 31-year-old woman with a history of erythema on the dorsal surface of her hands for the previous year (Hata, 1997). The woman applied topical ointments including “Chuu-ou-kou” to the eruptions, but the lesions worsened. The woman had a positive response to the active ingredient, *Curcuma longa L.*at 2.5% (the amount in “Chuu-ou-kou”), 1.25%, and 0.25% pet. Although the essential oil, which includes turmerone, dihydroturmerone, zingiberene, d-α-phellandrone, and cinerol, produced a negative result, curcumin gave a positive result at 1%, 0.5%, and 0.1%

pet. A control study in which 30 individuals were treated with *Curcuma longa L.*(2.5%, 1.25%, and 0.25%), curcumin (1% pet.), curry powder (25% pet.), dried ginger (kankyo, 25% pet.), and vanilla essence 10% pet. showed no positive responses.

In summary, incidences of individuals who have experienced contact dermatitis or urticaria in response to dermal exposure to curcumin have been reported in the literature; however, no basis exists on which to expect a tendency for development of allergic responses to curcumin in foods.

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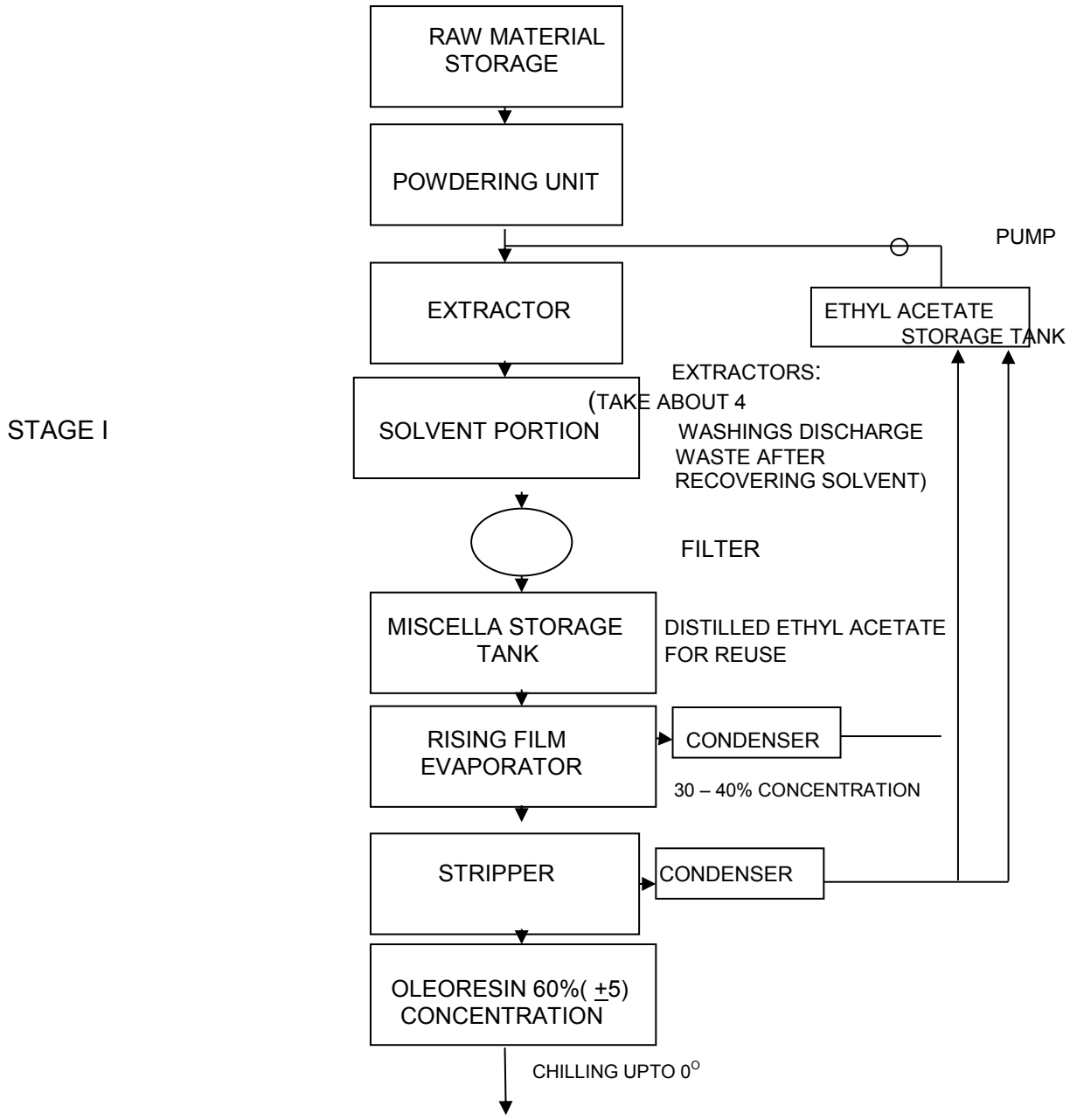
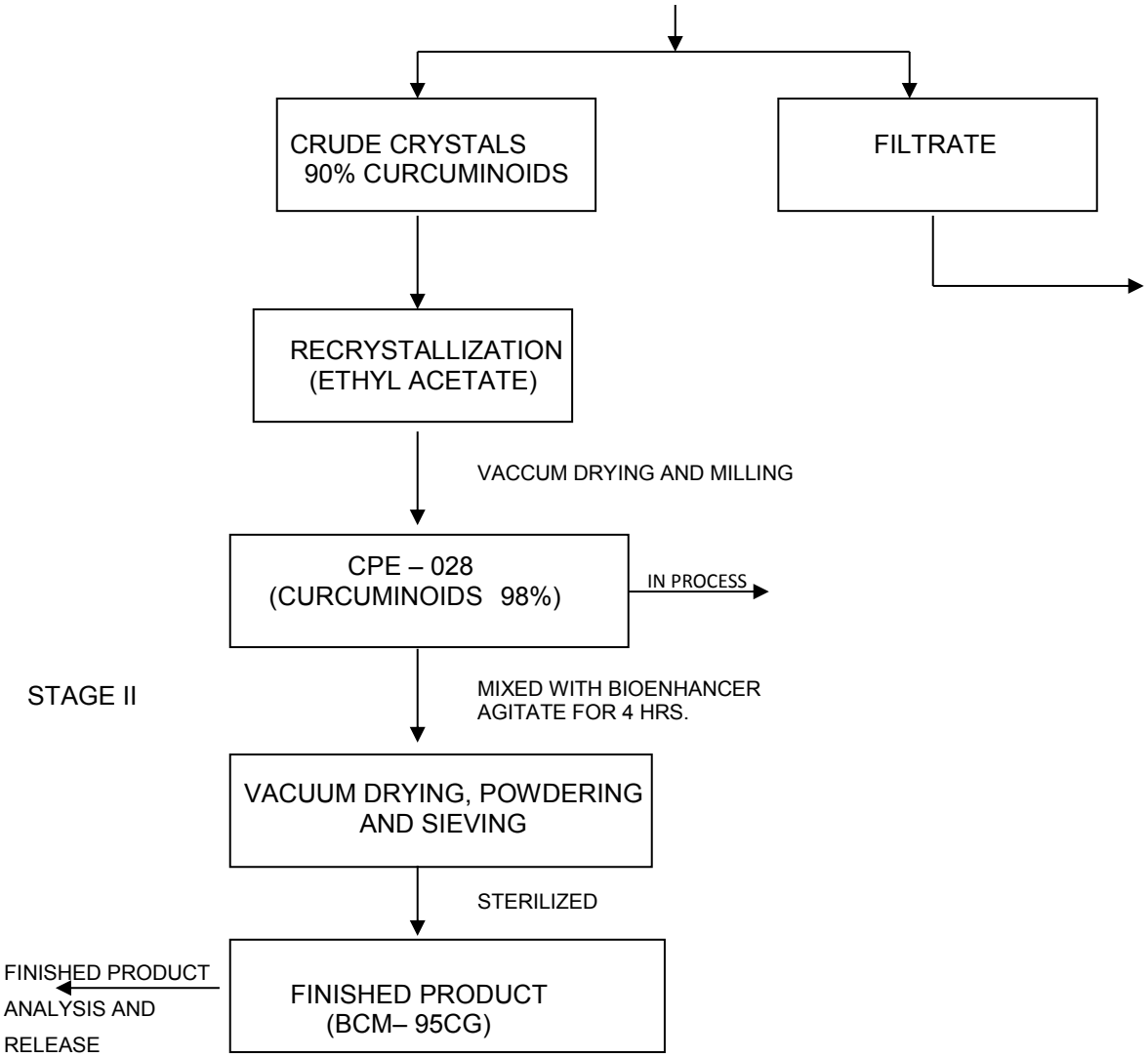
Appendix A Flow Chart Of Manufacturing Process For BCM-95®

PROCESS FLOWCHART: BCM – 95® CG





EVAPORATION AND
SOLVENT RECOVERY

Appendix B Certificates Of Analysis For Five Production Batches Of BCM-95®

Dolcas Biotech LLC
9 Lenel Road, Landing, NJ 07850
Ph: 973-347-1958 Fax: 973-347-0433
www.dolcas-biotech.com

CERTIFICATE OF ANALYSIS

Product Name:	BCM-95® (Bio-Curcumin®)	**Product Code:**	[redacted]
Botanical Name:	*Curcuma longa*	**Lot Number:**	[redacted]
Plant Part Used:	Rhizome	**Date of Manufacturing:**	September 2016
Country of Origin:	India	**Retest Date:**	September 2019

DESCRIPTION	SPECIFICATION	TEST METHOD	RESULTS
Identification	Pass	TLC	Complies
Color	Orange red	Visual	Complies
Appearance	Powder	Visual	Complies
Flavor	Characteristic	Organoleptic	Complies
Odor	Characteristic	Organoleptic	Complies
Analytical Assay			
Herb Extract Ratio	25:1	In House Specification	Complies
Solubility (in Acetone)	Soluble	IP	Complies
(In water)	Insoluble	IP	Complies
Moisture	NMT 2%	USP <921>	0.50%
Extraction Solvent	100% Ethyl Acetate	In House Specification	Complies
Particle Size	100% thru 30 mesh	USP <786>	Complies
Allergens	None detected	Elisa	Complies
Tap Density (g/ml)	NLT 0.60	USP <616>	0.77
Bulk Density (g/ml)	NLT 0.39	USP <616>	0.53
Pesticide Residue	Complies with USP	USP <561>	Complies
Excipients	None	In House Specification	Complies
Carriers	None	In House Specification	Complies
Residual Solvents			
Benzene	As per USP	USP <467>	Complies
Carbon Tetrachloride	As per USP	USP <467>	Complies
1,2-Dichloroethane	As per USP	USP <467>	Complies
1,1-Dichloroethene	As per USP	USP <467>	Complies
1,1,1-Trichloroethane	As per USP	USP <467>	Complies
Ethyl Acetate	As per USP	USP <467>	Complies
Ethanol	As per USP	USP <467>	Complies
Acetone	As per USP	USP <467>	Complies
Trace Metals			
Total Heavy Metals	NMT 10 ppm	ICP-MS	0.2685 ppm
Arsenic	NMT 1 ppm	ICP-MS	0.0716 ppm
Cadmium	NMT 1 ppm	ICP-MS	0.0285 ppm
Lead	NMT 0.5 ppm	ICP-MS	0.1684 ppm
Mercury	NMT 1 ppm	ICP-MS	BDL*
(*BDL: As – 0.02 ppb, Pb – 0.015 ppb, Hg – 0.02 ppb)			
Microbiological Assay			
Total Plate Count	NMT 1,000 cfu/g	AOAC, BAM	30 cfu/g
Yeast & Mold	NMT 100 cfu/g	AOAC, BAM	Not Detected
Salmonella	Absent / 25g	AOAC, BAM	Complies
E. coli	Absent / 10g	AOAC, BAM	Complies
Staphylococcus aureus	Absent / 10g	AOAC, BAM	Complies
Pseudomonas aeruginosa	Absent / 10g	AOAC, BAM	Complies
Aflatoxin	Absent	AOAC, BAM	Complies
Coliforms	Absent / 10g	AOAC, BAM	Complies
(**Microbial assay – detection limit – 10 cfu/g)			
Assay for Actives			
Volatile compounds of Turmeric	Present	UV-Vis	Complies
Total Curcuminoids Complex:	NLT 95%	HPLC	97.50%
*Consisting of **Curcumin, Desmethoxy Curcumin, Bis-Desmethoxy Curcumin** and **Volatile Oils** of Turmeric Rhizome*			
Total Curcuminoids	NLT 86%	HPLC	90.28%
Curcumin	NLT 65%	HPLC	71.63%

BCM-95® & Bio-Curcumin® are registered trademarks of Dolcas Biotech LLC
* Material is NON-ETO and NON-Irradiated
* GMO Free
* Store in a cool, dry place and away from direct sunlig(b) (6)
* Shelf Life: Retest 3 years from date of manufacturin

Approved By: _____ **Date:** 10/7/16

The above analytical information is analyzed and certified by Arjuna Naturals Extracts Ltd

STAR KOSHER CERTIFIED

Dolcas Biotech LLC
9 Lenel Road, Landings, NJ 07850
Ph: 973-347-1958 Fax: 973-347-0433
www.dolcas-biotech.com

CERTIFICATE OF ANALYSIS

Product Name:	BCM-95® (Bio-Curcumin®)	**Product Code:**	(b) (4)
Botanical Name:	*Curcuma longa*	**Lot Number:**	(b) (4)
Plant Part Used:	Rhizome	**Date of Manufacturing:**	January 2016
Country of Origin:	India	**Retest Date:**	January 2019

DESCRIPTION	SPECIFICATION	TEST METHOD	RESULTS
Identification	Pass	TLC	Complies
Color	Orange red	Visual	Complies
Appearance	Powder	Visual	Complies
Flavor	Characteristic	Organoleptic	Complies
Odor	Characteristic	Organoleptic	Complies
Analytical Assay			
Herb Extract Ratio	25:1	In House Specification	Complies
Solubility (in Acetone)	Soluble	IP	Complies
(in water)	Insoluble	IP	Complies
Moisture	NMT 2%	USP <921>	0.6%
Extraction Solvent	100% Ethyl Acetate	In House Specification	Complies
Particle Size	100% thru 30 mesh	USP <786>	Complies
Allergens	None detected	Elisa	Complies
Tap Density (g/ml)	NLT 0.60	USP <616>	0.73
Bulk Density (g/ml)	NLT 0.39	USP <616>	0.48
Pesticide Residue	Complies with USP	USP <561>	Complies
Excipients	None	In House Specification	Complies
Carriers	None	In House Specification	Complies
Residual Solvents			
Benzene	As per USP	USP <467>	Complies
Carbon Tetrachloride	As per USP	USP <467>	Complies
1,2-Dichloroethane	As per USP	USP <467>	Complies
1,1-Dichloroethene	As per USP	USP <467>	Complies
1,1,1-Trichloroethane	As per USP	USP <467>	Complies
Ethyl Acetate	As per USP	USP <467>	Complies
Ethanol	As per USP	USP <467>	Complies
Acetone	As per USP	USP <467>	Complies
Trace Metals			
Total Heavy Metals	NMT 10 ppm	ICP-MS	0.1784 ppm
Arsenic	NMT 1 ppm	ICP-MS	*BDL
Lead	NMT 0.5 ppm	ICP-MS	0.1427 ppm
Mercury	NMT 1 ppm	ICP-MS	0.0357 ppm
(*BDL: As – 0.02 ppb, Pb – 0.015 ppb, Hg – 0.02 ppb)			
Microbiological Assay			
Total Plate Count	NMT 1,000 cfu/g	AOAC, BAM	20 cfu/g
Yeast & Mold	NMT 100 cfu/g	AOAC, BAM	20 cfu/g
Salmonella	Absent / 25g	AOAC, BAM	Complies
E. Coli	Absent / 10g	AOAC, BAM	Complies
Staphylococcus aureus	Absent / 10g	AOAC, BAM	Complies
Pseudomonas aeruginosa	Absent / 10g	AOAC, BAM	Complies
Aflatoxin	Absent	AOAC, BAM	Complies
Coliforms	Absent / 10g	AOAC, BAM	Complies
(**Microbial assay – detection limit – 10 cfu/g)			
Assay for Actives			
Volatile compounds of Turmeric	Present	UV-Vis	Complies
Total Curcuminoids Complex:	NLT 95%	HPLC	97.31%
*Consisting of **Curcumin, Desmethoxy Curcumin, Bis-Desmethoxy Curcumin** and **Volatile Oils** of Turmeric Rhizome*			
Total Curcuminoids	NLT 86%	HPLC	90.31%
Curcumin	NLT 65%	HPLC	71.63%

BCM-95® & **Bio-Curcumin®** are registered trademarks of Dolcas Biotech LLC
* Material is NON-ETO and NON-Irradiated
* GMO Free
* Store in a cool, dry place and away from direct sunlight
* Shelf Life: Retest 3 years from date of manufa(b) (6)

Approved By: _____ **Date:** 2/1/16

The above analytical information is analyzed and certified by Arjuna Naturals Extracts Ltd

STAR KOSHER CERTIFIED

Dolcas Biotech LLC
9 Lenel Road, Landings, NJ 07850
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www.dolcas-biotech.com

CERTIFICATE OF ANALYSIS

Product Name:	BCM-95® (Bio-Curcumin®)	**Product Code:**	(b) (4)
Botanical Name:	*Curcuma longa*	**Lot Number:**	(b) (4)
Plant Part Used:	Rhizome	**Date of Manufacturing:**	April 2016
Country of Origin:	India	**Retest Date:**	April 2019

DESCRIPTION	SPECIFICATION	TEST METHOD	RESULTS
Identification	Pass	TLC	Complies
Color	Orange red	Visual	Complies
Appearance	Powder	Visual	Complies
Flavor	Characteristic	Organoleptic	Complies
Odor	Characteristic	Organoleptic	Complies
Analytical Assay			
Herb Extract Ratio	25:1	In House Specification	Complies
Solubility (in Acetone)	Soluble	IP	Complies
(in water)	Insoluble	IP	Complies
Moisture	NMT 2%	USP <921>	0.2%
Extraction Solvent	100% Ethyl Acetate	In House Specification	Complies
Particle Size	100% thru 30 mesh	USP <786>	Complies
Allergens	None detected	Elisa	Complies
Tap Density (g/ml)	NLT 0.60	USP <616>	0.83
Bulk Density (g/ml)	NLT 0.39	USP <616>	0.58
Pesticide Residue	Complies with USP	USP <561>	Complies
Excipients	None	In House Specification	Complies
Carriers	None	In House Specification	Complies
Residual Solvents			
Benzene	As per USP	USP <467>	Complies
Carbon Tetrachloride	As per USP	USP <467>	Complies
1,2-Dichloroethane	As per USP	USP <467>	Complies
1,1-Dichloroethene	As per USP	USP <467>	Complies
1,1,1-Trichloroethane	As per USP	USP <467>	Complies
Ethyl Acetate	As per USP	USP <467>	Complies
Ethanol	As per USP	USP <467>	Complies
Acetone	As per USP	USP <467>	Complies
Trace Metals			
Total Heavy Metals	NMT 10 ppm	ICP-MS	0.4451 ppm
Arsenic	NMT 1 ppm	ICP-MS	0.0096 ppm
Lead	NMT 0.5 ppm	ICP-MS	0.4355 ppm
Mercury	NMT 1 ppm	ICP-MS	BDL*
(*BDL: As – 0.02 ppb, Pb – 0.015 ppb, Hg – 0.02 ppb)			
Microbiological Assay			
Total Plate Count	NMT 1,000 cfu/g	AOAC, BAM	20 cfu/g
Yeast & Mold	NMT 100 cfu/g	AOAC, BAM	Not detected**
Salmonella	Absent / 25g	AOAC, BAM	Complies
E. coli	Absent / 10g	AOAC, BAM	Complies
Staphylococcus aureus	Absent / 10g	AOAC, BAM	Complies
Pseudomonas aeruginosa	Absent / 10g	AOAC, BAM	Complies
Aflatoxin	Absent	AOAC, BAM	Complies
Coliforms	Absent / 10g	AOAC, BAM	Complies
(**Microbial assay – detection limit – 10 cfu/g)			
Assay for Actives			
Volatile compounds of Turmeric	Present	UV-Vis	Complies
Total Curcuminoids Complex:	NLT 95%	HPLC	96.56%
*Consisting of **Curcumin**, **Desmethoxy Curcumin**, **Bis-Desmethoxy Curcumin** and **Volatile Oils** of Turmeric Rhizome*			
Total Curcuminoids	NLT 86%	HPLC	90.88%
Curcumin	NLT 65%	HPLC	71.83%

BCM-95® & **Bio-Curcumin®** are registered trademarks of Dolcas Biotech LLC
* Material is NON-ETO and NON-Irradiated
* GMO Free
* Store in a cool, dry place and away from direct sunlight
* Shelf Life: Retest 3 years from date of manufacture (b) (6)

Approved By: _____ **Date:** 5/5/16

The above analytical information is analyzed and certified by Arjuna Naturals Extracts Ltd

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Dolcas Biotech LLC
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www.dolcas-biotech.com

CERTIFICATE OF ANALYSIS

Product Name:	BCM-95® (Bio-Curcumin®)	**Product Code:**	(b) (4)
Botanical Name:	*Curcuma longa*	**Lot Number:**	(b) (4)
Plant Part Used:	Rhizome	**Date of Manufacturing:**	June 2016
Country of Origin:	India	**Retest Date:**	June 2019

DESCRIPTION	SPECIFICATION	TEST METHOD	RESULTS
Identification	Pass	TLC	Complies
Color	Orange red	Visual	Complies
Appearance	Powder	Visual	Complies
Flavor	Characteristic	Organoleptic	Complies
Odor	Characteristic	Organoleptic	Complies
Analytical Assay			
Herb Extract Ratio	25:1	In House Specification	Complies
Solubility (in Acetone)	Soluble	IP	Complies
(in water)	Insoluble	IP	Complies
Moisture	NMT 2%	USP <921>	0.2%
Extraction Solvent	100% Ethyl Acetate	In House Specification	Complies
Particle Size	100% thru 30 mesh	USP <786>	Complies
Allergens	None detected	Elisa	Complies
Tap Density (g/ml)	NLT 0.60	USP <616>	0.80
Bulk Density (g/ml)	NLT 0.39	USP <616>	0.56
Pesticide Residue	Complies with USP	USP <561>	Complies
Excipients	None	In House Specification	Complies
Carriers	None	In House Specification	Complies
Residual Solvents			
Benzene	As per USP	USP <467>	Complies
Carbon Tetrachloride	As per USP	USP <467>	Complies
1,2-Dichloroethane	As per USP	USP <467>	Complies
1,1-Dichloroethene	As per USP	USP <467>	Complies
1,1,1-Trichloroethane	As per USP	USP <467>	Complies
Ethyl Acetate	As per USP	USP <467>	Complies
Ethanol	As per USP	USP <467>	Complies
Acetone	As per USP	USP <467>	Complies
Trace Metals			
Total Heavy Metals	NMT 10 ppm	ICP-MS	0.2473 ppm
Arsenic	NMT 1 ppm	ICP-MS	0.0415 ppm
Lead	NMT 0.5 ppm	ICP-MS	0.1827 ppm
Mercury	NMT 1 ppm	ICP-MS	0.0231 ppm
(*BDL: As – 0.02 ppb, Pb – 0.015 ppb, Hg – 0.02 ppb)			
Microbiological Assay			
Total Plate Count	NMT 1,000 cfu/g	AOAC, BAM	20 cfu/g
Yeast & Mold	NMT 100 cfu/g	AOAC, BAM	Not detected
Salmonella	Absent / 25g	AOAC, BAM	Complies
E. coli	Absent / 10g	AOAC, BAM	Complies
Staphylococcus aureus	Absent / 10g	AOAC, BAM	Complies
Pseudomonas aeruginosa	Absent / 10g	AOAC, BAM	Complies
Aflatoxin	Absent	AOAC, BAM	Complies
Coliforms	Absent / 10g	AOAC, BAM	Complies
(**Microbial assay – detection limit – 10 cfu/g)			
Assay for Actives			
Volatile compounds of Turmeric	Present	UV-Vis	Complies
Total Curcuminoids Complex:	NLT 95%	HPLC	96.75%
*Consisting of **Curcumin**, **Desmethoxy Curcumin**, **Bis-Desmethoxy Curcumin** and **Volatile Oils** of Turmeric Rhizome*			
Total Curcuminoids	NLT 86%	HPLC	90.64%
Curcumin	NLT 65%	HPLC	71.96%

BCM-95® & **Bio-Curcumin®** are registered trademarks of Dolcas Biotech LLC
* Material is NON-ETO and NON-Irradiated
* GMO Free
* Store in a cool, dry place and away from direct sunlight
* Shelf Life: Retest 3 years from date of manufac (b) (6)

Approved By: _____ **Date:** 7/12/16

The above analytical information is analyzed and certified by Arjuna Naturals Extracts Ltd

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Dolcas Biotech LLC
9 Lenel Road, Landing, NJ 07850
Ph: 973-347-1958 Fax: 973-347-0433
www.dolcas-biotech.com

CERTIFICATE OF ANALYSIS

Product Name:	BCM-95® (Bio-Curcumin®)	**Product Code:**	(b) (4)
Botanical Name:	*Curcuma longa*	**Lot Number:**	(b) (4)
Plant Part Used:	Rhizome	**Date of Manufacturing:**	August 2016
Country of Origin:	India	**Retest Date:**	August 2019

DESCRIPTION	SPECIFICATION	TEST METHOD	RESULTS
Identification	Pass	TLC	Complies
Color	Orange red	Visual	Complies
Appearance	Powder	Visual	Complies
Flavor	Characteristic	Organoleptic	Complies
Odor	Characteristic	Organoleptic	Complies
Analytical Assay			
Herb Extract Ratio	25:1	In House Specification	Complies
Solubility (in Acetone)	Soluble	IP	Complies
(in water)	Insoluble	IP	Complies
Moisture	NMT 2%	USP <921>	0.5%
Extraction Solvent	100% Ethyl Acetate	In House Specification	Complies
Residual Solvents	As per USP	USP <467>	Residual Solvents
Particle Size	100% thru 30 mesh	USP <786>	Complies
Allergens	None detected	Elisa	Complies
Tap Density (g/ml)	NLT 0.60	USP <616>	0.77
Bulk Density (g/ml)	NLT 0.39	USP <616>	0.53
Pesticide Residue	Complies with USP	USP <561>	Complies
Excipients	None	In House Specification	Complies
Carriers	None	In House Specification	Complies
Trace Metals			
Total Heavy Metals	NMT 10 ppm	ICP-MS	0.4630 ppm
Arsenic	NMT 1 ppm	ICP-MS	0.1038
Lead	NMT 0.5 ppm	ICP-MS	0.3553 ppm
Mercury	NMT 1 ppm	ICP-MS	0.0039 ppm
Cadmium	NMT 1 ppm	ICP-MS	Complies
(*BDL: As – 0.02 ppb, Pb – 0.015 ppb, Hg – 0.02 ppb)			
Microbiological Assay			
Total Plate Count	NMT 1,000 cfu/g	AOAC, BAM	30 cfu/g
Yeast & Mold	NMT 100 cfu/g	AOAC, BAM	Not detected
Salmonella	Absent / 25g	AOAC, BAM	Complies
E. coli	Absent / 10g	AOAC, BAM	Complies
Staphylococcus aureus	Absent / 10g	AOAC, BAM	Complies
Pseudomonas aeruginosa	Absent / 10g	AOAC, BAM	Complies
Aflatoxin	Absent	AOAC, BAM	Complies
Coliforms	Absent / 10g	AOAC, BAM	Complies
(**Microbial assay – detection limit – 10 cfu/g)			
Assay for Actives			
Volatile compounds of Turmeric	Present	UV-Vis	Complies
Total Curcuminoids Complex:	NLT 95%	HPLC	96.64%
*Consisting of **Curcumin, Desmethoxy Curcumin, Bis-Desmethoxy Curcumin** and **Volatile Oils** of Turmeric Rhizome*			
Total Curcuminoids	NLT 86%	HPLC	90.80%
Curcumin	NLT 65%	HPLC	71.78%

BCM-95® & Bio-Curcumin® are registered trademarks of Dolcas Biotech LLC
* Material is NON-ETO and NON-Irradiated
* GMO Free
* Store in a cool, dry place and away from direct sunlight.
* Shelf Life: Retest 3 years from date of manufacturing.
* This material is manufactured without the use of any harmful solvents. (e.g., Benzene, Carbon Tetrachloride, 1,2-Dichloroethane, 1,1-Dichloroethene, 1,1,-Trichloroethane)

Approved By: (b) (6) **Date:** 9/19/16

The above analytical information is analyzed and certified by Arjuna Naturals Extracts Ltd

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Appendix C JECFA Specifications For Curcumin

TURMERIC OLEORESIN

Prepared at the 35th JECFA (1989), published in FNP 49 (1990) and in FNP 52 (1992). Metals and arsenic specifications revised at the 59th JECFA (2002). A temporary ADI established at the 30th JECFA (1986) was not maintained at the 35th JECFA (1989)

DEFINITION

Obtained by solvent extraction of turmeric (*Curcuma longa* L.). Only the following solvents may be used in the extraction: acetone, dichloromethane, 1,2-dichloroethane, methanol, ethanol, isopropanol and light petroleum (hexanes).

The selection of a turmeric oleoresin of a particular composition is based on the intended use in food. In general, all turmeric oleoresins contain colouring matter and most contain flavouring matter but some oleoresins are processed to remove aromatic compounds. Commercial products include oleoresins (per se) and formulations in which oleoresin is diluted in carrier solvents and which may contain emulsifiers and antioxidants. Purified extracts of turmeric containing more than 90% total colouring matter are subject to specifications for "Curcumin".
Turmeric Oleoresins are sold on the basis of "colour value" or "curcumin content", which generally means the total content of the curcuminoid substances: (I) curcumin, (II) demethoxycurcumin and (III) bis-demethoxycurcumin.

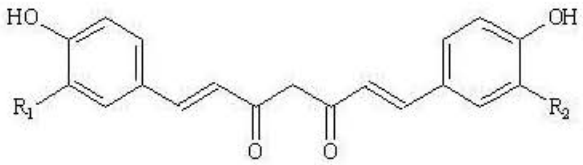
Chemical names

The principle colouring components are:
I. 1,7-Bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene- 3,5-dione
II. 1-(4-Hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-hepta-1,6-diene-3,5-dione
III. 1,7-bis(4-hydroxyphenyl)hepta-1,6-diene-3,5-dione

Chemical formula

Chemical formula
I. $C_{21}H_{20}O_6$
II. $C_{20}H_{18}O_5$
III. $C_{19}H_{16}O_4$

Structural formula



I. $R_1 = R_2 = -OCH_3$
II. $R_1 = -OCH_3$, $R_2 = H$
III. $R_1 = R_2 = H$

Formula weight

I. 368.39
II. 338.39
III. 308.39

Assay

Content of total colouring matter (curcuminoid content) not less than declared.

DESCRIPTION Turmeric Oleoresins, *per se*, are deep brownish-orange viscous oily fluids, pasty semisolids or hard amorphous solids containing 37-55% curcuminoids and up to 25% volatile oil. Diluted turmeric oleoresin formulations are, generally yellow solutions containing 6-15% curcuminoids and nil to 10% volatile oil.

FUNCTIONAL USES Colour, flavouring agent

CHARACTERISTICS

IDENTIFICATION

Solubility (Vol. 4) Insoluble in water

Colour in ethanol The ethanol-soluble fraction of the sample is characterized by its pure yellow colour and light green fluorescence; if this ethanol extract is added to concentrated sulfuric acid, a deep crimson is produced.

Boric acid test Treat an aqueous or dilute ethanolic suspension of the sample with hydrochloric acid until a slightly orange colour begins to appear. Divide mixture into 2 parts and add some boric acid powder or crystals to one portion. Marked reddening will be quickly apparent, best seen by comparison with the portion to which the boric acid has not been added. The test may also be made by dipping pieces of filter paper into an ethanolic suspension of the sample, drying at 100°, and then moistening with a weak solution of boric acid to which a few drops of hydrochloric acid have been added. On drying, a cherry red colour will develop.

PURITY

Residual solvents (Vol. 4) Acetone : Not more than 30 mg/kg
Methanol: Not more than 50 mg/kg
Ethanol: Not more than 50 mg/kg
Isopropanol: Not more than 50 mg/kg
Dichloromethane and 1,2-dichloroethane: Not more than 30 mg/kg, singly or in combination
Light petroleum (hexanes): Not more than 25 mg/kg

Arsenic (Vol. 4) Not more than 3 mg/kg

Lead (Vol. 4) Not more than 2 mg/kg
Determine using an atomic absorption technique appropriate to the specified level. The selection of sample size and method of sample preparation may be based on the principles of the method described in Volume 4, "Instrumental Methods."

METHOD OF ASSAY

Method I

Standard Preparation
Transfer about 250 mg of purified curcumin, accurately weighed, into a 100-ml volumetric flask, and record the weight as W, in mg. Dissolve in acetone, dilute to volume with acetone, and mix. Pipet a 1-ml portion of this solution into a second 100-ml volumetric flask, dilute to volume with acetone, and

mix. Finally, pipet a 5-ml portion of the last solution into a 50-ml volumetric flask, dilute to volume with acetone, and mix.

Sample Preparation
Transfer an accurately weighed amount of the sample, equivalent to about 250 mg of curcumin, into a 100-ml volumetric flask, and record the weight as w, in mg. Dissolve in acetone, dilute to volume with acetone, and mix. Pipet a 1-ml portion of this solution into a second 100-ml volumetric flask, dilute to volume with acetone, and mix. Finally, pipet a 5-ml portion of the last solution into a 50-ml volumetric flask, dilute to volume with acetone, and mix.

Procedure
Determine the absorbance of each solution in 1-cm cells at the wavelength of maximum absorption at about 421 nm with a suitable spectrophotometer, using acetone as the blank.

Calculate the percentage of curcumin in the sample by the formula:

$$100 \times \frac{W}{w} \times \frac{A_U}{A_S}$$

where
A_U = the absorbance of the Sample Preparation
A_S = the absorbance of the standard preparation.
(NOTE: The absorbance readings should be made as soon as possible after the solutions are prepared to avoid colour loss).

Method II
Accurately weigh (W) about 0.1 g of the sample in a 100-ml beaker. Add 50 ml of ethanol and extract the colour by vigorously stirring. Filter the solution into a 200-ml volumetric flask. Make up to volume with ethanol.
Take an aliquot of the colour solution and dilute with additional ethanol according to the estimated colouring matters content as follows:

Colouring matter content	*Dilution factor*
Less than 20%	20
Between 20 and 40%	50
More than 40%	100

Determine the absorbance (A) at 425 nm in a 1-cm cell.
Calculate the total colouring matters content of the sample by the formula:

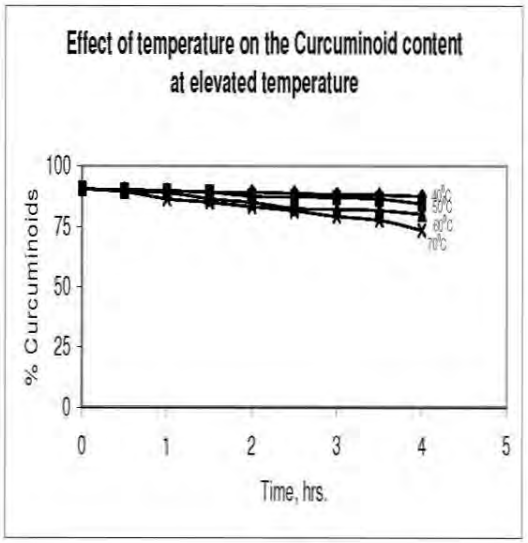
$$\frac{A \times 10000 \times D}{W \times 1607}$$

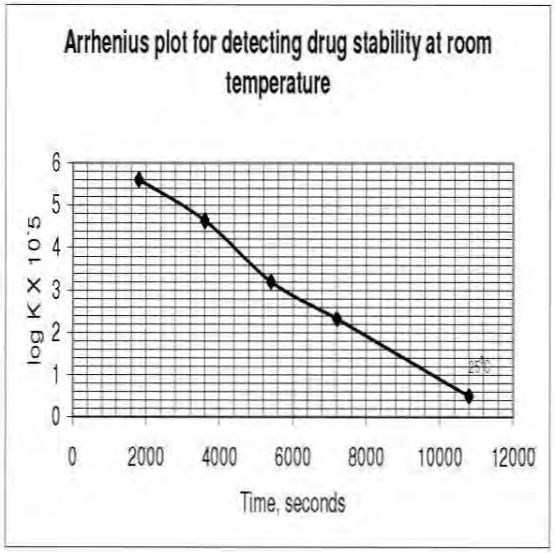
where
D = 0.4, 1 and 2 for dilution factors of 20, 50, and 100, respectively.

Appendix D Accelerated And Long-Term Stability Report For BCM-95®

ACCELERATED STABILITY STUDY :- BIO-CURCUMIN® (BCM 95CG®)

Bio-Curcumin® (BCM -95CG®) is a standardized extract of curcuminoids with not less than 95% total curcuminoid complex.





Report

Based on the accelerated stability study, the shelf life of the Bio - curcumin® (BCM 95 CG®) is 3 years and 5 months with respect to its curcuminoid content.

Reference:

Physical Pharmacy by Alfred Martin; 4 th Edition
Publisher : Lippincott Williams & Wilkins
A wolters Kluwer company.

LONG TERM STABILITY DATA: BIO-CURCUMIN® (BCM-95CG®)

(Reference ICH Guideline)

Bio-Curcumin® (BCM -95CG®) is a standardized extract of curcuminoids with not less than 95% total curcuminoid complex.

The Proposed Stability Specifications are :

Tests	Acceptance Criteria	Analytical Procedure
Colour & Appearance	Orange Red Powder	Visual
Moisture	NMT 2%	USP <616>
Assay	NLT 95% Total Curcuminoid Complex	HPLC
Microbial Assay		
Total Plate Count	<1000cfu/g	AOAC, BAM
Yeast & Mould	<100cfu/g	AOAC, BAM
E-coli	Absent/10g	AOAC, BAM
Salmonella	Absent/25g	AOAC, BAM

3

The Acceptance limits for these attributes remain the same as those used to confirm the quality of the finished product on batch release.

Study Conducted On :-2/1/2006
Duration Of Study :- 3 Years

Stability Protocol

Strength	Container/Closure	Conditions	Sample Times	Batches
1Kg x15	HM-HDPE	Temperature 30^0C(+/-2) and Humidity 65%(+/-2)	0,3,6,9,12,18,24,30,36 months	(b) (4) (b) (4)
1Kg x15	HM-HDPE	Temperature 30^0C(+/-2) and Humidity 65%(+/-2)	0,3,6,9,12,18,24,30,36 months	(b) (4)
1Kg x15	HM-HDPE	Temperature 30^0C(+/-2) and Humidity 65%(+/-2)	0,3,6,9,12,18,24,30,36 months	(b) (4)

4

(b) (4) [redacted]

Parameters	Month : 0	Month: 3	Month:6	Month : 9	Month: 12	Month:18	Month : 24	Month: 30	Month:36
Colour & Appearance	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder
Moisture	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.3%	0.3%
Curcumino d complex	95.5%	95.4%	95.4%	95.4%	95.4%	95.4%	95.4%	95.3%	95.3%
Total plate count	40 Cfu/G	50 Cfu/G	50 Cfu/G	50 Cfu/G	50 Cfu/G	50 Cfu/G	60 Cfu/G	60 Cfu/G	60 Cfu/G
Yeast and Mould	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
E-coli	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Salmonella	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative

5

(b) (4) [redacted]

Parameters	Month : 0	Month: 3	Month:6	Month : 9	Month: 12	Month:18	Month : 24	Month: 30	Month:36
Colour & Appearance	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder
Moisture	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.4%	0.4%	0.4%
Curcumino d complex	95.7%	95.7%	95.7%	95.6%	95.6%	95.6%	95.5%	95.5%	95.4%
Total plate count	50 Cfu/G	50 Cfu/G	50 Cfu/G	60 Cfu/G	60 Cfu/G	60 Cfu/G	70 Cfu/G	70 Cfu/G	70 Cfu/G
Yeast and Mould	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
E-coli	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Salmonella	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative

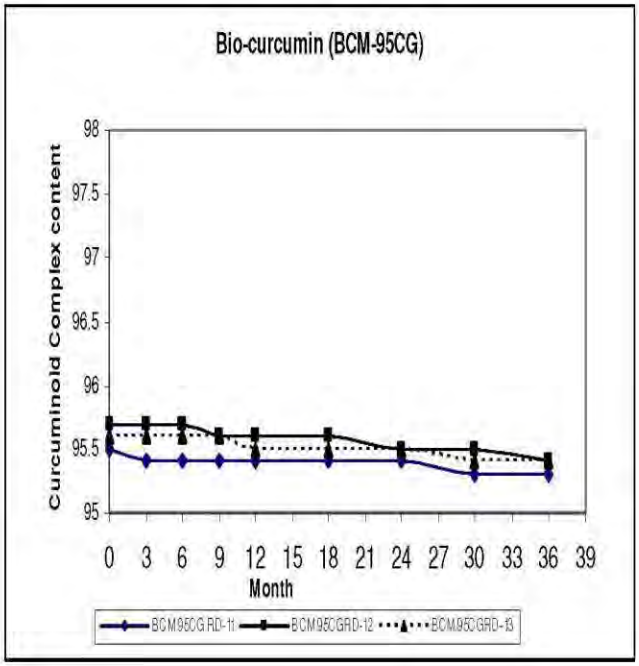
6

(b) (3) (B) [redacted]

Parameters	Month : 0	Month: 3	Month:6	Month : 9	Month: 12	Month:18	Month : 24	Month: 30	Month:36
Colour & Appearance	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder
Moisture	0.2%	0.2%	0.2%	0.2%	0.2%	0.3%	0.3%	0.3%	0.3%
Curcumino d complex	95.6%	95.6%	95.6%	95.6%	95.5%	95.5%	95.5%	95.4%	95.4%
Total plate count	40 Cfu/G	40 Cfu/G	40 Cfu/G	40 Cfu/G	50 Cfu/G	60 Cfu/G	60 Cfu/G	60 Cfu/G	60 Cfu/G
Yeast and Mould	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected	Not detected
E-coli	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative
Salmonella	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Negative

7

Graphical Representation Of Long Term Stability Data



Report

Based on the long-term stability study **at Temperature 30^{0}C(+/-2) and Humidity 65%(+/-2), Bio-curcumin® (BCM 95CG®) is found to be stable up to 3 years of study period.**

Reference:-

ICH Q1A(R2) Stability Testing of New Drug Substances and Products.

Appendix E Elevated Temperature Stability Report

(Temperatures: 40^0C, 50^0C, 60^0C)

1

STABILITY DATA: BIOCURCUMIN® BCM-95 CG

Scope of the Study:

To check the thermal stability of total curcumoids and Ar- turmerone content (w.r.t volatile oil) of the Biocurcumin® BCM-95 CG

Product Description

Biocurcumin® BCM-95 CG is a standardized with 95% total curcuminoid + volatile components of turmeric.

Conditions for the Study

For the study the 100 gms of sample is taken inside a glass bottle. Sample is kept inside water bath set at 30°C, through the time of the study. Simillarly sample is also kept at 40°C ,50°C ,& 60°C

Sampling pattern

Biocurcumin® BCM-95 CG is placed in the water bath. It is planned to take sample at different hours 0 ,2 ,4 ,6 ,12, and 24 for the analysis of Total curcuminoid content , Moisture and Ar-turmerone (w.r.t volatile oil)

The Proposed Stability Specifications are :

Tests	Acceptance Criteria	Analytical Procedure
Colour & Appearance	Yellowish orange red powder	Visual
Total Curcuminoid + Volatile componets	NLT 95%	HPLC
Ar-turmerone (w.r.t Volatile oil)	NLT 45%	GC

The Acceptance limits for these attributes remain the same as those used to confirm the quality of the finished product on batch release.

Stability At 30°C

Parameters	Hour - 0	Hour -2	Hour -4	Hour -6	Hour -12	Hour -24
Colour & Appearance	Orange Red	Orange Red	Orange Red	Orange Red	Orange Red	Orange Red
Total Curcuminoid + Volatile componets	95.9%	95.8%	95.8%	95.7%	95.7%	95.7%
Ar-turmerone (w.r.t Volatile oil)	46.1%	46.1%	46.1%	46.1%	46.1%	46.1%

Stability At 40°C

Parameters	Hour - 0	Hour -2	Hour -4	Hour -6	Hour -12	Hour -24
Colour & Appearance	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder
Total Curcuminoid + Volatile componets	95.8%	95.8%	95.8%	95.7%	95.7%	95.6%
Ar-turmerone (w.r.t Volatile oil)	46.1%	46.1%	46.1%	46.1%	46.1%	46.1%

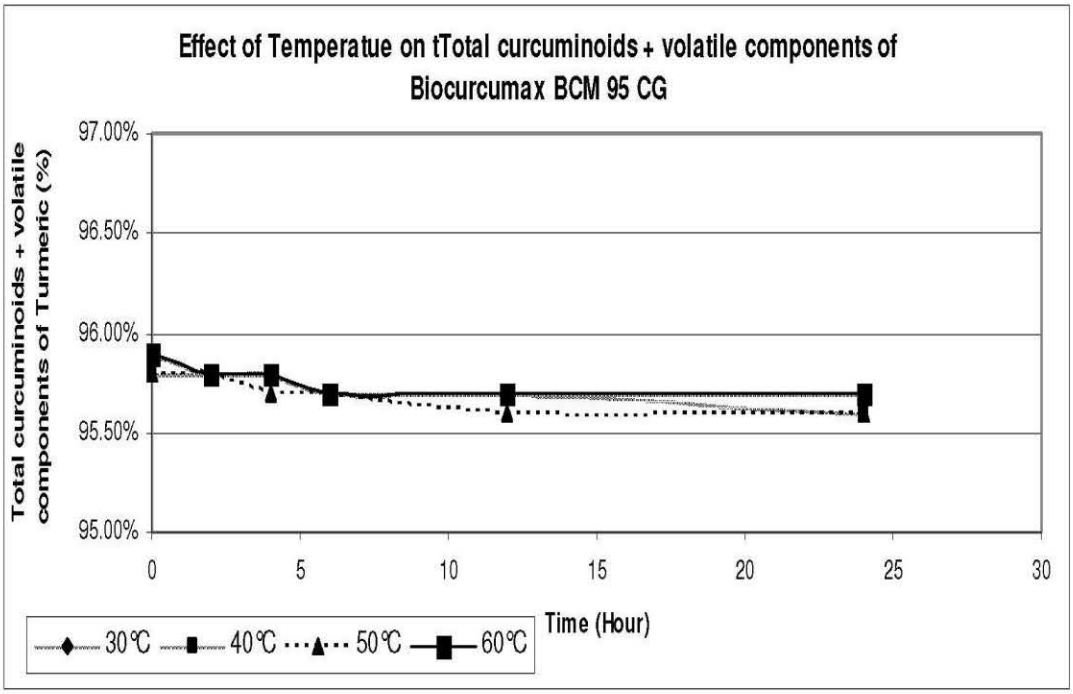
Stability At 50°C

Parameters	Hour - 0	Hour -2	Hour -4	Hour -6	Hour -12	Hour -24
Colour & Appearance	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder
Total Curcuminoid + Volatile componets	95.8%	95.8%	95.7%	95.7%	95.6%	95.6%
Ar-turmerone (w.r.t Volatile oil)	46.1%	46.1%	46.1%	46.05%	46.05%	46.05%

4

Report Stability At 60°C

Parameters	Hour - 0	Hour -2	Hour -4	Hour -6	Hour -12	Hour -24
Colour & Appearance	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder	Orange Red Powder
Total Curcuminoid + Volatile componets	95.9%	95.8%	95.8%	95.7%	95.7%	95.7%
Ar-turmerone (w.r.t Volatile oil)	46.1%	46.1%	46.0%	46.0%	46.0%	46.0%



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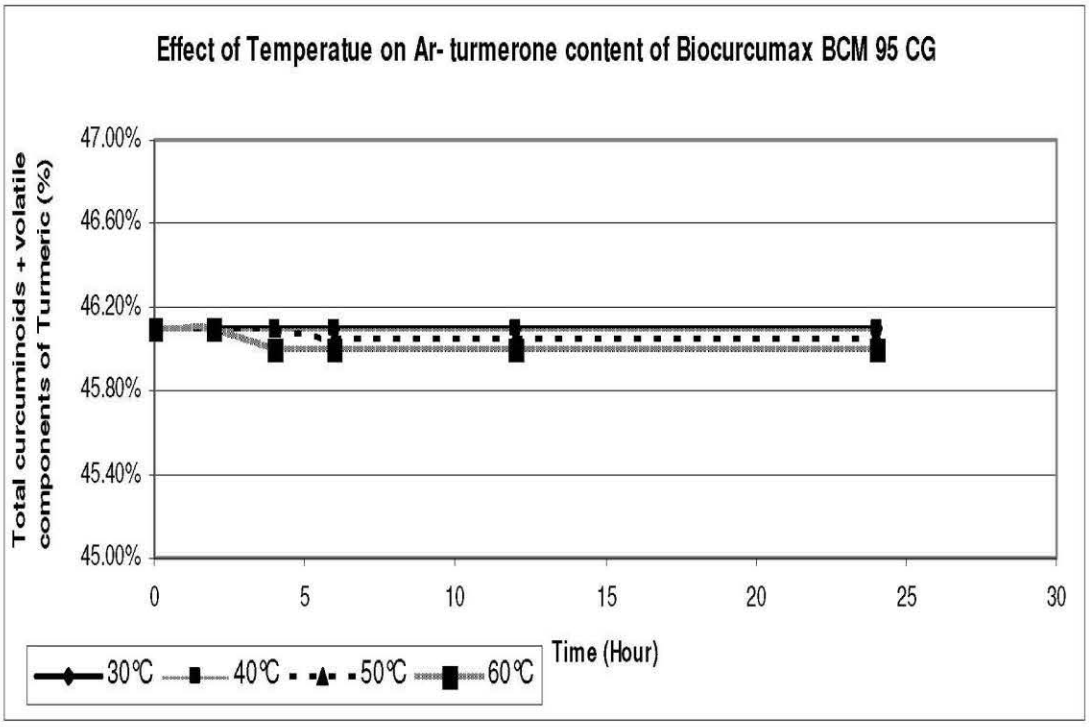

Result :

Based on the stability study at different temperatures, **Biocurcumin® BCM-95 CG** is found to be stable at elevated temperatures

Appendix F Human Studies on Other Curcumin Preparations

Lao et al. (2006) performed a dose escalation study to determine the maximum tolerated dose and safety of a single dose of uniformly milled curcumin extract (C3 Complex™, Sabinsa Corporation) in humans. The test preparation contained a minimum 95% concentration of three curcuminoids: curcumin, bisdemethoxycurcumin, and demethoxycurcumin. Twenty-four healthy subjects were administered escalating doses of the extract from 500 to 12,000 mg. No curcumin was detected in the serum of subjects administered 500, 1,000, 2,000, 4,000, 6,000 or 8,000 mg. Two subjects administered 10,000 or 12,000 had low levels of curcumin in serum. Seven subjects experienced minimal toxicity that did not appear to be dose-related. Adverse effects included diarrhea, headache, rash, and yellow stool. No other adverse events were reported, and the authors concluded that the tolerance of curcumin in single doses up to 12,000 mg is excellent.

Other human clinical studies using oral curcumin have not reported any major signs of toxicity. In patients with rheumatoid arthritis in India, the administration of 1.2 to 2.1 g of oral curcumin daily did not produce any major adverse effects (Deodhar et al., 1980). In a high-dose oral curcumin study in Taiwan, up to 12 g of curcumin were administered daily for 3 months in patients with pre-invasive malignant or high risk pre-malignant conditions. No resulting toxicity was reported in this study with daily administration up to 8 g. The 12 g/day dose was not acceptable to the patients due to the bulky volume of the tablets (Cheng et al., 2001). Curcumin was well-tolerated in a clinical study in the UK at all dose levels up to 3.6 g daily for 4 months in patients with advanced colorectal cancer. However, two types of gastrointestinal adverse events were reported by patients. One patient consuming 0.45 g daily developed diarrhea one month into the study and one patient consuming 3.6 g daily developed diarrhea four months into the study. Another patient consuming 0.9 g curcumin daily experienced nausea. In blood tests, a rise in serum alkaline phosphatase level was observed in four patients, and serum lactate dehydrogenase increased to more than 150% of pre-treatment values in three patients. The authors concluded that these effects may be more related to the progression of disease rather than treatment (Sharma et al., 2004).

Joshi et al. (2003) conducted a 3-month clinical trial to study the safety and tolerance of turmeric oil in humans. Volunteers were administered 0.6 mL of turmeric oil three times a day in capsule form for 1 month and 1 mL in 2 divided doses for 2 months. The composition of turmeric oil was as follows: 59% Turmerone and Ar-Turmerone, 25% zingiberene, 1% cineole, 15 d-phellandrene, 0.6% d-sabinene, and 0.5% borneol. There were no acute tolerability side effects on day one, and there was no effect of turmeric oil on weight, blood pressure, clinical, hematological, renal or hepatic toxicity at 1 month and 3 months. One volunteer had an allergic skin reaction to the turmeric oil preparation and another volunteer had reversible hypertriglyceridemia. No other adverse reactions were observed.

Das et al. (2010) evaluated the efficacy of turmeric and turmeric oil in patients with oral submucous fibrosis (OSMF), a chronic disease of the oral mucosa with a high incidence of malignancy. Forty-eight patients who were clinically and histopathologically confirmed as having OSMF were divided into three groups. Group 1 received 1 g curcumin in capsules, group II received 600 mg turmeric oil (from a dropper) and group III received control multinal (1 g) tablets daily for three months. After the treatment period and follow-up, there was a significant improvement in clinical signs and symptoms of patients treated with curcumin and turmeric oil compared to the control. There were also positive changes in the histological examination of treatment groups, including a reduction in inflammatory cells. All of the patients tolerated the treatment and there were no allergic or adverse effects from the treatment.

Table 13. Summary of Select Curcumin Studies

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Deodhar et al., (1980)	18 patients with rheumatoid arthritis	double-blind crossover	1200 mg/day *Curcuma longa L*.in 3 divided doses	Two weeks (14 days)	Only a mild improvement in symptoms was evident	Small dose and short duration
Srimal and Dhawan (1985)	Individuals with osteoarthritis	1,500 mg/day curcumin		4 weeks	No adverse effects	
Satoskar et al. (1986)	40 patients who had recently had surgery for inguinal hernia	1,200 mg/day curcumin (n=13) Placebo (n=13), phenylbutazone, (n=14) Randomized, double-blind, placebo-controlled, parallel group	Not specified	5 days	Curcumin resulted in a significant reduction in tenderness at site, cord edema, cord tenderness, and pain at the operation site compared with baseline. Placebo only improved pain at site and cord tenderness	Small study
Thamlikitkul et al. (1989)	116 individuals with dyspepsia syndrome	2,000 mg curcumin (n=39) Placebo (n=41) Flatulence(n=36) randomized, double-blind, placebo-controlled, multicenter study	8 capsules /day *Curcuma domestica* Val (250 mg dried rhizome powder, containing 0.2 mL of volatile oil and 24 mg total curcuminoids)	7 days	The curcuma group had significantly more study participants with a favorable outcome than the placebo group. Frequency of side effects was not different for the three groups. Side effects were mild and self-limiting.	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Soni and Kuttan (1992)	10 healthy men and women	500 mg/day curcumin Single group study	98% pure curcumin (Bombay Oil Industries, Ltd., Angamali)	7 days	Curcumin decreased serum peroxides and serum cholesterol, increased HDL cholesterol, no effect on serum triglycerides or body weight. No toxic effects such as nausea, vomiting, headaches, or unusual bowel movements observed	Small study
Kositchaiwat et al. (1993)	60 patients with gastric ulcer, 18-80 years old	750 mg dried *Curcuma longa L.*in capsules split over three doses in one day (250 mg/dose) randomized, controlled	*Curcuma longa L.*rhizome cut into small pieces and dried then crushed into powder for encapsulation	Six weeks (42 days); patients with ulcer improvement during study continued for an additional six weeks.	Complete ulcer healing was observed in 33.3 % of patients, 51.9 % patients had improved ulcers. After 12 weeks, 70.6 % patience had complete ulcer healing.	Variation in ulcer size
James (1996)	40 individuals with HIV	625 mg, 4 times per day		56 days	Well-tolerated	
Hastak et al. (1997)	32 individuals with oral submucous fibrosis	3,000 mg/day turmeric extract (n=10) 600 mg turmeric oleoresin/day in 3,000 mg of turmeric extract (n=13) 600 mg turmeric oil + 3,000 mg of turmeric extract /day (n=16) Random, parallel group study	Turmeric oil and turmeric oleoresin were prepared by Kancor Flavours and Extracts Limited (Kochin, Kerala, India) and alcohol turmeric extract	3 months	The product reduced the number of micronuclei in oral submucous fibrosis patients. It also educed the number of micronuclei that were induced by benzo[a]pyrene.	Small study
Ramirez-Boscá et al. (1997)	30 healthy volunteers	20 mg/day curcumin extract Non-controlled trial	2 tablets/day each containing 10 mg if a hydroalcoholic extract of *Curcuma longa L.*(A.S.A.C. Pharmaceutical International)	60 days	Curcumin extract reduced high levels of peroxidation of HDL and LDL in individuals with high baseline levels of these substances. Liver biochemistry parameters were all in the normal rang. No toxic effects reported including nausea, diarrhea, or constipation	Small study, placebo, no control group

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Rasyid and Lelo (1998)	12 healthy individuals	20 mg curcumin Randomized, double- blind, placebo-controlled, crossover study	Curcumin (Merck Schudschardt)	2 days at least one week apart	Curcumin increased gallbladder contraction compared with placebo	Small study
Van Dau et al. (1998)	130 patients with duodenal ulcer	6 g *Curcuma longa L.*in tablets per day double-blind, two center study	*Curcuma longa L.*rhizome cut into small pieces and dried then crushed into powder for compression into tablets	Eight weeks (56 days)	Turmeric did not offer an improvement to ulcer healing over placebo Authors stated that the majority of the symptoms were related to ulcer disease and that *Curcuma longa L.*and the placebo were both well-tolerated	Potentially inadequate dosage
Lal et al. (1999)	32 men and women with chronic anterior uveitis	1,125 mg/day curcumin (n=18) Curcumin+antituber cular treatment (n=14) Non-controlled study	375 mg curcumin administered 3 times/day as gelatin capsules. >95% pure curcumin isolated from rhizomes of *C. longa*	12 weeks, evaluations at 2-week intervals	Efficacy of curcumin is comparable to that of corticosteroid therapy, the standard treatment and lacks side effects of corticosteroids. There was no recurrence of symptoms observed. No side effects	Small study, no placebo control group
Heng et al. (2000)	40 individuals with psoriasis	1% curcumin gel 10 individuals with psoriasis			Reduction in PhK activity, keratin transferrin receptor expression, parakeratosis, and density of epidermal CD8+T cells	
Lal et al. (2000)	5 individuals with idiopathic orbital pseudotumors	1,125 mg/day curcumin		6 to 22 months	4 of the 5 individuals who completed the study had a complete recovery, No recurrence of symptoms at follow up. No side effects were reported	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Ramirez-Boscá et al. (2000a)	8 healthy individuals with abnormally high levels of plasma fibrinogen	20 mg/day curcumin Non-controlled trial	2 tablets/day containing a hydroalcoholic extract of *C. longa* (A.S.A.S Pharmaceutical International, A.I.E., Alicante Spain)	15 days	Curcumin treatment significantly reduced fibrinogen levels No side effects including nausea, diarrhea or constipation were reported.	Small group, no placebo control
Ramirez-Boscá et al. (2000b)	12 healthy men with high LDL-C values (>150 mg/dl)	20 mg/day curcumin Non-controlled trial	2 tablets/day containing a hydroalcoholic extract of *C. longa* (A.S.A.S Pharmaceutical International, A.I.E., Alicante Spain)	1 month (30 days)	Curcumin treatment was associated with a reduction in LDL-C and apo B and an increase in HDL-C and apo A. No side effects including nausea, diarrhea or constipation were reported.	Small study, no placebo, no control group
Cheng et al. (2001)	25 study participants who had undergone surgery for bladder cancer, had arsenic Bowen's disease of the skin, uterine cervical intraepithelial neoplasm, oral leukoplakia, intestinal metaplasia of stomach	Phase I clinical trial 500, 1,000, 2,000, 4,000, 8,000 and 12,000 mg/day curcumin		3 months	Some individuals developed frank malignancies. Some beneficial effects of curcumin were observed. Curcumin is not toxic to humans at a dose of up to 8,000 mg/day. The 12,000 mg/day dose was not acceptable because of bulkiness.	
Prucksunand et al. (2001)	45 individuals with suspected peptic ulcer	5 600 mg/day turmeric Phase II clinical trial	Turmeric prepared from crude powder of dried rhizome of *Curcuma longa L.*Linn	12 weeks for ulcer patients and 4 weeks for non-ulcer patients	By week 12, 19 of 25 individuals with ulcers were healed. There were no changes in hematological measurements and liver and renal function.	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Sharma et al. (2001b)	15 individuals with advanced colorectal cancer refractory to chemotherapy	440, 880, 1320, 1760, and 2,200 mg/day *Curcuma* extract	Capsules contained 20 mg curcuminoids (18 mg curcumin and 2 mg desmethoxycurcumin) in 200 mg essential oils from *Curcuma* spp (Phytopharm plc. (Godmanchester, UK)	Up to 4 months Treated lasted until disease progression or withdrawal from the study	5 individuals had stable disease after 2 to 4 months of treatment. Consumption of curcumin is safe up to a 2,200 mg/day or 180 mg/d curcumin. Nausea in 1,320 mg dose and diarrhea in in 880 mg dose and 1 at 2,200 mg dose, but authors stated curucmi well-tolerated and no dose-limiting toxicity	
Joshi et al. (2003)	9 healthy volunteers	0.6 mL turmeric oil 3 times a day for one month, then 1 mL in 3 divided doses for 2 months.	Gelatin capsules containing turmeric oil	12 weeks	There were no effects of turmeric oil on weight, blood pressure, symptoms or safety parameters. One subject dropped out due to allergic skin rash, which disappeared after discontinuation of turmeric oil.	
Bundy et al. (2004)	166 individuals with self-reported irritable bowel syndrome (IBS) for at least 3 months	72 mg (1 tablet) or 144 mg (2 tablets) of curcumin extract uncontrolled, randomized, partially blinded pilot study	Cynara™ Turmeric, Lichtwater Pharma (UK) Ltd., Marlow, UK	8 weeks	Curcumin treatment significantly reduced IBS by 53% for the 72 mg/day dose group and 60% for the 144 mg/day dose group. Adverse effects included flatulence and dry mouth. The authors reported no major side effects of curcumin treatment	
Sharma et al. (2004)	15 patients with advanced colorectal cancer	Dependent on dose level, patients consumed 1, 2, 4, or 8 capsules (containing 450, 900, 1800, or 3600 mg of curcumin) once daily	C3 Curcuminoid capsules(Sabinsa CorpNJ). Each capsule contained 500 mg curcuminoids (450 mg curcumin 40 mg of desmethoxy-curcumin, 10 mg of bisdesmethoxy-curcumin)	4 months	Systemic activity and compliance trial. A daily dose of 3.6 g curcumin was advocated for Phase II evaluation.	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Durgaprasad et al. (2005)	20 individuals with tropical pancreatitis	500 mg/day curcumin	500 mg/day curcumin +5 mg/day piperine	6 weeks	Significant reduction in red blood cell levels of malonyldialdehyde and increase in red blood cell GSH levels.	
Holt et al. (2005)	5 individuals with ulcerative proctitis 5 individuals with Crohn's Disease	550 mg, 2-3 times/day for 60 days 360 mg curcumin 3x/day and 4 times/day		60 days 30 days 60 days	Reduced proctitis symptoms symptoms and need to take medication in 4 of 5 study participants 100% reduction in CDAII scores.	
Shoskes et al. (2005)	45 cadaveric kidney recipients	480 mg curcumin + 20 mg quercetin 960 mg curcumin +40 mg quercetin	Each tablet of Oxy-Q contained 480 mg curcumin + 20 mg quercetin	1 month	Oxy-Q improved renal function. Well-tolerated with minimal side effects.	
Cruz-Correa et al. (2006)	5 individuals with familial adenomatous polyps	1,440 mg/day curcumin and 40 mg/day quercetin	3 doses of Oxy-Q/day (480 mg curcumin + 20 mg quercetin 3 times/day)	mean of 6 month (3 to 9 months)	Side effects were limited and no laboratory anomalies were noted	
Lao et al. (2006)	24 healthy adults	500, 1000, 2000, 4000, 8000, 10000, 12000 mg curcumin in escalating doses	Standardized powdered extract (*C3 Complex*, Sabinsa Corporation), Containing: curcumin between 70% and 80%, demethoxycurcumin between 15% and 25%, and bisdemethoxycurcumin between 2.5% and 6.5%	Single dose at each dose level	Seven subjects experienced minimal toxicity (yellow stool, headache) that was not dose-related. High single doses of curcumin were well-tolerated.	Single dose

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Hanai et al. (2006)	89 patients with quiescent ulcerative colitis	2 g curcumin/day randomized, placebo controlled, multicenter, double-blind	2 x 1g doses of curcumin/day Curcumin prepared by API Co, Ltd (Gifu, Japan) contained 50% curcumin, 42.5% microcrystalline cellulose, 7.5% malitol and the composition of the placebo was 25% microcrystalline cellulose, 29.6% dextrin, 10% cornstarch, 35% malitol, 0.15% FD&C Yellow No. 5, 0.04% FD & C Yellow No. 6, and caramel color	6 months (180 days)	Fewer relapses; improved clinical activity index. Mild, transient side-effects such as abdominal bloating that may not have been due to curcumin.	2 g, large sample size, long duration
Ng et al. (2006)	1,010 non-demented elderly Asian subjects (epidemiological study)	Curry consumption	Curry	Age 63-90 years Never or rarely, occasionally or often	Better Mini-Mental State Examination scores	
Chainani-Wu et al. (2007)	33 patients with oral lichen planus	2 g/day randomized, double-blind	Curcumim C3 Complex (Sabinsa Corp, Piscataway, NJ) Containing: curcumin between 70% and 80%, demethoxycurcumin between 15% and 25%, and bisdemethoxycurcumin between 2.5% and 6.5%	7 weeks (49 days)	No difference between treatment group and control. Study was ended after first interim analysis. Dose was well-tolerated	2 g, small sample size, short duration;

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Baum et al. (2007)	36 adults with progressive decline in memory and cognitive function	1 g or 4 g/day curcumin preparation randomized, double-blind	Packets of curcumin were provided by Kancor Flavors, Kerala India, and curcumin capsules were provided by Arjuna Natural Extracts, Kerala, India	6 months (180 days)	No effect on triacylglycerols, total LDL and HDL cholesterol; positive significant correlation of serum cholesterol to plasma curcumin No severe adverse events observed.	Up to 4 g, small sample size but long duration. Given the lack of adverse effects in studies using this dose, this study is choses as basis for the OSL for supplemental curcumin.
Di Mario et al. (2007)	25 individuals with *H. pylori* infections and functional dyspepsia	Twice daily treatment with a combination of 30 mg curcumin, 100 mg bovine lactoferrin, 600 mg N-acetylcysteine, and 20 mg pantoprazole	Curcumin	7 days	Significant reduction in overall symptom severity ($P<0.001$) and serum pepsinogen I ($P=0.02$) and serum pepsinogen II ($P\leq0.001$). No significant effect on IgG and gastrin-17.	
Johnson and Muktar (2007)	12 individuals who were scheduled to undergo surgery	450, 1800, or 3,600 mg of curcumin/day Phase I clinical trial	Curcumin	7 days	Only the 3,600 mg curcumin dose was at the level of detection. Increased M1G adducts possibly due to surgery.	
Dhillon et al. (2008)	21 patients with advanced pancreatic cancer Original n=25	8 g/day curcumin Non-randomized, open label, phase II trial	1 g caplets from Sabinsa, each containing 1 g curcuminoids (900 mg curcumin, 80 mg desmethoxycurcumin, and 20 mg bisdesmethoxycurcumin)	8 weeks	Two study participants showed clinical effects. Blood tests and renal and hepatic function tests were conducted. Curcumin was well-tolerated, no toxicity occurred	
Kurd et al. (2008)	8 Patients with chronic psoriasis vulgaris	4.5 g/day curcuminoid C3 Complex Phase II, single-arm, single-dose, non-controlled	Capsules contained 95% curcuminoids (Sabinsa Corp., Piscataway, NJ)	16 weeks	Dose was well-tolerated and safe in psoriasis patients. Low response rate to the curcumin treatment. Adverse events reported for 10/12 study participants. Mild adverse events considered likely related to curcumin treatment:GI upset/ heat	Low subject number

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
					intolerance/flashes.	
Antony et al. (2008)	11 healthy volunteers	4x500 mg BCM-95™ in one group, control curcumin in second group	BCM-95 (Biocurcumax™. Arjuna Natural Extracts). Control curcumin capsules (Life Extension, USA)	Single dose to determine bioavailability	Short-term Bioavailability of BCM-95™ was 6.37 relative to that of a curcumin-lecithin-piperine combination. No adverse events were reported.	
Usharani et al. (2008)	72 diabetic patients	300 mg/day NCB-02 randomized, parallel-group	NCB-02 described as an encapsulated preparation of standardized curcuminoids	8 weeks (56 days)	Favorable effect on endothelial dysfunction. The authors stated that no serious adverse events were reported.	600 mg, large sample size, short duration.
Baum et al. (2008)	34 probable or possible Alzheimer's disease (AD) patients	1 g or 4 g/day curcumin preparation randomized, placebo-controlled, double-blind	Curcumin capsules (Arjuna Natural Extracts, Kerala, India) and curcumin packets for combining with food (Kancor Flavours, Kerala, India)	6 months (180 days)	Curcumin increased vitamin E, but had not effect on Amyloidβ $_{40}$. No change in sodium, potassium, urea, creatinine, protein, albumin, bilirubin, alkaline phosphatase, and alanine aminotransferase (ALT)/glutamic-pyruvic transaminase between baseline and 6 months. Number of adverse events: 4g curcumin=2, 1g curcumin=6, 0 g curcumin, =7. No severe adverse events observed.	Up to 4 g, small sample size but long duration. Supports OSL selected above.
Golombick et al. (2009)	26 patients with Monoclonal Gammopathy of Undefined Significance, which can precede multiple myeloma	4,000 mg/day oral curcumin Single blind, randomized, crossover, pilot study	C3 curcuminoids from alley finger turmeric, each tablet including 1,000 mg curcuminoids, (900 mg curcumin, 80 mg desmethoxycurcumin, and 20 mg of bisdesmethoxycurcumin	3 months	Curcumin reduced the paraprotein load in individuals with a paraprotein level of >20g/l	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Deepa Das et al. (2010)	48 patients with oral submucous fibrosis	1 g curcumin/day or turmeric oil containing 600 mg curcumin placebo-controlled	Not well-specified	3 months	Significant improvement in clinical signs and symptoms in patients treated with curcumin and turmeric oil. Treatment was well-tolerated.	Small study number
Epelbaum et al. (2010)	17 individuals with advanced pancreatic cancer	8,000 mg/day curcumin Open label, phase, II clinical trial	C3 Curcuminoids Complex® as two 4,000 mg doses/day (Sabinsa Corp, Piscataway, NJ) and1,000 mg/m^2 gemcitabine via i.v. for 3 of 4 weeks.	Median duration= 2 weeks Administered until death, disease progression, toxicity	Median time to tumor progression=2.5 months, range=1-12 months; median survival time =5 months, range 1-24 months 7 patients had GI toxicity-abdominal fullness and pain, mild hematological toxicity (neutropenia and cytopenia, n=2)	
Gota et al. (2010)	Healthy individuals and individuals with late stage osteosarcoma	650 mg Longvida™ Optimized Curcumin	Longvida™ Optimized Curcumin (130 to 195 mg curcumin)	Single dose	Good tolerability	
Koosirirat et al. (2010)	36 chronic gastritis patients	700 mg turmeric tablet 3 times per day (2100 mg/day)	Each tablet contained 40 mg curcumin	Six weeks (47 days)	Curcumin alone had little effect on *H. pylori* infection in gastritis patients in comparison to patients receiving standard therapy (Omeprazole, Amoxicillin, and Metronidazole)	Only single dose turmeric used
Agarwal et al. (2011)	50 patients following laparoscopic cholecystecto my	500 mg capsule curcumin every 6 h Randomized, double-blind, prospective	Curcumin supplied by Indsaff Inc. (India)	3 weeks post surgery	Lower mean pain and fatigue scores Patients able to decrease analgesics and increased pain relief.	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Carroll et al. (2011)	44 smokers with 8 or more Abnormal Crypt Foci on screening colonoscopy	Stage 1: 2 g curcumin once daily, n=20 subjects Stage 2: 4g (16 capsules), n=20 subjects Nonrandomized, open label, Phase IIa clinical trial	98.0 curcumin powder, Sabinsa corp, East Windsor, NJ	30 days	No significant changes in PGE_2 or 5-hydroxyeicosatetraenoic acid following curcumi consumption. Neither dose of curcumin resulted in a clinically significant elevation in liver function measurements Curcumin was well-tolerated.	
Kanai et al. (2011)	Patients with advanced pancreatic cancer	8 g/day curcumin	Sabinsa Corporation (Piscataway, NJ, USA) in microbead form. C3 complex) consisted of Curcumin (73%), demethoxycurcumin (22%), and bisdemethoxycurcumin (4%).	Dose-limiting toxicity	None of the surviving patients had a complete or partial response, 5 had stable disease (28%). None of the study participants withdrew due to intolerability of curcumin. No cumulative toxicity of curcumin was observed. Authors stated that combined therapy with curcumin and gemcitabine is safe and well-tolerated.	
Golombick et al. (2012)	19 patients with MGUS and 17 patients with smouldering multiple myeloma	4,000 mg/day curcumin 8,000 mg/day curcumin Randomized, double blind, placebo controlled crossover study	Each C3 curcuminoid granule stick pack (Sabinsa Corporation, Piscataway, NJ) contained 3600 mg of curcumin, 320 mg of desmethoxycurcumin, and 80 mg of bisdesmethoxycurcumin.	25 treated with 4,000 mg for 3 months 18 treated with 8 mg for 3 months after 3 months of treatment with 4,000 mg Curcumin	Curcumin was associated with a reduction in serum creatinine, free light – chain ratio and difference in clonal and nonclonal light chain and involved free light chain. There was also a reduction in a marker of bone resorption.	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Kanai et al. (2012)	6 healthy individuals	150 mg Theracumin and 210 mg Theracurmin	Theracurmin (Theravalues Corporation, Tokyo, Japan), 105 curcumin, 2% other curcuminoids, such as demethoxycurcumin, and bisdemethoxycurcumin, 46% glycerin, 4% gum ghatti, and 38% water.	Single oral doses two weeks apart	One report of grade I diarrhea, but not other toxic effects were observed	
Ringman et al. (2012)	30 patients with mild or moderate probable AD	0, 2 g or 4 g/day curcumin preparation randomized, double-blind	Curcumin (n=12/dose group) as Curcumin C3 Complex®	24 weeks (68 days) (open label study extended to 48 weeks)	No clinical or biochemical benefit Tolerability parameters monitored including hematocrit, glucose levels, lipid profile, chemistry panel, TSH. No significant changes out of normal range No serious adverse effects observed. Minor GI complaints, but not statistically significant compared to placebo.	Up to 4 g, small sample size, and relatively long duration. Safety parameters monitored and no serious adverse effects observed. Supports OSL selected above.
Chainani-Wu et al. (2012)	20 patients with oral lichen planus	6 g/day (n=10) randomized, double-blind	Curcumin C3 complex in 3 divided doses (Sabinsa Corporation), Piscataway, NJ	12 days	Improvement in signs and symptoms of oral lichen planus. Safety parameters monitored (blood counts; liver enzymes; C-reactive protein; and interleukin-6 level); no significant difference in blood counts and liver enzymes between groups. Curcumin was well-tolerated with no significant difference in adverse events between groups, including diarrhea, constipation, abdominal pain, heartburn, or nausea, (P=0.33) or change in liver enzymes (AST, ALT, and alkaline phosphatase), P=0.16.	6 g/day, small sample size

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Pinsornak and Niempoog (2012)	38 individuals with primary knee osteoarthritis	1 g/day curcumin Double blind randomized prospective trial	Curcumin manufactured by the Govt. Pharmaceutical corporation of Thailand Curcumin was administered with 75 mg/day diclofenac	3 months (120 days)	Looked atperfomance on the Knee injury and Osteoarthritis Outcome Score and the pain visual analog score. No clinical benefit Renal function deterioration (2/37) and facial swelling (1/37) in the control group and 1/36 hair falling out in the experimental group.	1 g, small sample size; moderate duration "High number of dropouts
Chuengsamarn et al. (2012)	240 prediabetic patients, 237 allocated to groups	1.5 g/day curcumin preparation Randomized, double-blind, placebo-controlled trial	Curcumin consumed as 6 capsules/day, each containing 250 mg curcumin manufactured by the Government Pharmaceutical Organization of Thailand and made from an ethanol extract of the ground rhizomes of *C. longa* Linn	9 months (270 days)	Prevented T2DM development. Improved β cell function; higher adiponectin., increased HOMA-β, reduced C-peptide compared with placebo, no effect on proinsulin/insulin ratio. No significant difference between groups was observed for AST, ALT, creatinine, and BMD, there were no signs of edema. No significant adverse events occurred. There was reports of itching (n=1), constipation (n=2), and vertigo (n=1) in the curcumin group.	1.5 g, large sample size, long duration.
Golombick et al. (2012)	36 patients with monoclonal gammopathy of undetermined significance and smoldering multiple myeloma	4 g/daycurcumin followed by open label extension at 8 g/day Placebo containing no curcumin randomized, double-blind placebo-controlled, crossover study	4g "C3" curcuminoid granule stick packs from Sabinsa Corporation (Psicataway, NJ) each containing 4,000 mg curcuminoids (3,600 mg curcumin, 320 mg desmethoxycurcumin, and 80 mg of bisdesmethoxycurcumin	3 months (90 days) Option for open label extension for a further 3 months	Decreased free-light chain ration, reduced difference between clonal and nonclonal light change. Decreased bone resorption marker. Serum creatinine were more reduced I the 4g curcumin dose group and serum parathyroid hormone was reduced b 19.8% (P=0002),which the authors stated warrants further study..	Smal number of study participants and short duration

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Panahi et al. (2012a)	96 male patients with sulphur-mustard induced pruritus, 80 completed the study	1 g/curcumin randomized, double-blind, placebo-controlled, two-center trial	Curcumin C3 Complex® capsules containing 500 mg curcuminoids and 5 mg Bioperine® (Sami Labs Limited)	4 weeks (28 days)	Improved antioxidant status, reduced pruritis severity, greater improvement in QoL. Six dropouts in the curcumin group due to gastrointestinal side effect (n=3), fear of side effects (n=1), inability to return to the clinic due to distances (n=1), and unknown reason (n=1). 10 dropouts in placebo group due to no treatment response or worsening symptoms (n=7), gastrointestinal side effects (n=2), and inability to return to the clinic (n=1).	1 g; large sample size, short duration
Panahi et al. (2012b)	96 male patients with sulphur-mustard induced pruritus, 80 completed the study	1 g/curcumin randomized, double-blind, placebo-controlled, two-center trial	Curcumin C3 Complex® capsules (Sami Labs Limited)	4 weeks (28 days)	Greater reductions in serum IL-8 and hs-CRP for the curcumin group compared with the placebo ($P<0.001$), significant reduction in serum CGRP for the curcumin group ($P< 0.001$), but not the placebo group, and no effect on serum IL-6. Significant correlations between changes in calcitonin-related gene peptide (CGRP) and IL-6 ($P = 0.011$) and between Dermatology Life Quality Index (DLQI) and IL-8 ($P = 0.026$) for the curcumin group. Changes in serum IL-8 concentrations were identified as significant predictors of DLQI scores ($P= 0.026$). Six dropouts in the curcumin group due to	1 g; large sample size, short duration

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
					gastrointestinal side effect (n=3), fear of side effects (n=1), inability to return to the clinic due to distances (n=1), and unknown reason (n=1). 10 dropouts in placebo group due to no treatment response or worsening symptoms (n=7), gastrointestinal side effects (n=2), and inability to return to the clinic (n=1).	
Chandran and Goel (2012)	45 patients with Rheumatoid Arthritis (RA)	500 mg curcumin or 50 mg diclofenac sodium (50 mg) or the combination randomized, single-blinded	Curcumin was in the form of BCM-95 (Arjuna Natural Extracts, India)	8 weeks	The curcumin group showed the highest degree in the improvement of RA symtpoms with minimal adverse events.	Short-term trial
DiSilvestro et al. (2012)	38 healthy subjects	400 mg/day curcumin preparation (80 mg curcumin, with vegetable stearic acid dextrin, hydroxypropylmehyl cellulose (vegetarian capsule), soy lecithin, ascorbyl palmitate, and silicon dioxide) placebo-controlled	Longvida® Optimized Curcumin	4 weeks (28 days)	Lowering of plasma triglyceride values, salivary amylase levels, plasma beta amyloid protein concentrations plasma sICAM readings, plasma alanine amino transferase activities; raising of salivary radical scavenging capacities, plasma catalase activities plasma nitric oxide; increased plasma myeloperoxidase without increased c-reactive protein levels. No adverse events reported.	400 mg, relatively small sample size, short duration argue against the use of this study for identification of an OSL
Volak et al. (2012)	8 healthy individuals	8 g curcuminoids and 48 mg piperine/day. Other treatments were midazolam, flurbiprofen, and paracetamol, or matched placebo. Randomized,	4 g curcuminoids+ 24 mg piperine administered orally 2 times/day (Sabinsa Corporation, Piscataway, NJ)	2 days	No clinically significant effect on CYP3A. CYP2C9, or paracetamol conjugation enzymes. The authors did not mention adverse effects.	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
		placebo-controlled, crossover study				
Irving et al. (2013)	Individuals who were planning to undergo endoscopic biopsy or colonic resection	2.35 g/day	5 x 470 mg capsules, Curcumin C3 Complex® (Sabinsa Corporation, Utah) with 470 mg curcumin C3 complex comprising 80% curcumin and 20% desmethoxycurcumin and bisdesmethoxycurcumin	14 days	Curcumin was present in the mucosa for up to 40 hours after it was administered. 13 adverse events were reported, but they were not serious.	
Irving et al (2013)	Individuals who were planning to undergo endoscopic biopsy or colonic resection	2.35 g/day	5x 470 mg capsules, Crucumin C3 Complex® (Sabinsa Corporation, Utah) with 470 mg curcumin C3 complex comprising 80% curcumin and 20% desmethoxycurcumin and bisdesmethoxycurcumin	14 days	Curcumin was present in the mucosa for up to 40 hourse after it was administered. 13 adverse events were reported , but they were not serious.	
Kanai et al. (2013)	16 individuals with pancreatic or biliary tract cancer	Theracurmin 2 g and 4 g containing 200 mg curcumin (n=10) and 400 mg curcumin (n=6), respectively	Theracurmin® (liquid type, CR-011L):10% curcumin, 2% other curcuminoids, including demethoxycurcumin and bisdemethycurcumin, 46% glycerin, 4% gum ghatti (primarily polysaccharides)	Curcumin consumed daily orally along with gemcitabine therapy	Maximum plasma levels were 324 ng/mL, for the 200 mg curcumin dose and 440 ng/mL for the 400 mg curcumin dose. No unexpected adverse events. 3 study participants continued to consume Theracurmin® for 9 months without adverse events attributable to Theracurmin®.	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
			and 38% water			
Kizhakkedath (2013)	28 individuals with osteoarthritis of the knee joint	350 mg *Curcuma longa L.*extract (BCM-95®)	BCM-95® containing 70% curcumin, 17% demethoxycurcumin, 3.5% bisdemethoxycurcumin and 7/5% turmeric essential oils and 150 mg *Boswellia serrate* extract containing 75% boswellic acids and 10% AKBA (both Arjuna Natural Extracts, Aluva, Kerala, India)	12 weeks	No adverse effects on vital signs, hemogram liver and kidney function tests. The treatment was safe, was not associated with dose-related toxicity or adverse effects, and was well-tolerated.	
Klickovic et al. (2013)	10 healthy men with different (GT)n length polymorphisms in promoter region of hemo oxygenase HO-1 gene	12 g curcumin Open label, uncontrolled, Phase I, pilot study	12 capsules containing Curcumin C3 Complex® powder	Single dose	Curcumin was not detected in plasma before or after administration of Curcumin C3 Complex®. Curcumin does not affect HO-1 mRNA or protein level in peripheral blood monuclear cells. Complete blood counts, blood, dialysate, and urine chemistry were measured. No clinically relevant safety effects of administration of Curcumin C3 Complex®.	
Morimoto et al. (2013)	24 healthy individuals	30 mg/100 mL Single dose, double-blind, 4-way crossover study	Theracurmin® (Theravalues Corporation)	Single doses to study pharmacokinetics	Theracurmin had a higher absorption efficiency that other. No adverse effects of any curcumin drink.	
Sahebkar et al. (2013)	30 obese individuals	1 g/day randomized, double-blind crossover	Two doses/day of 0.5 g Curcumin C3® Complex with 5 mg bioperine®, (Sami Labs, Ltd. Bangalore, India)	30 days	Reduced oxidative stress parameters pro-oxidant-antioxidant balance (P=0.044). No significant effect on weight, BMI, antiHsp27, or anti-oxLDL. The investigators did not mention adverse effects in this study.	1 g; small sample size; short duration.

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Ryan et al. (2013)	30 breast cancer patients with radiation dermatitis	6 g/day curcumin randomized, double-blind, placebo-controlled	Curcumin C3® complex (Sabinsa Corporation (Payson, Utah). At least 95% curcuminoids (390 mg curcumin, 75 mg desmethoxycurcumin, 12.5 mg bisdemethoxycurcumin) and excipients 2 g curcumin 3 times/day	4-7 weeks (28-49 days)	Reduced severity radiation dermatitis No significant adverse events observed	6 g, small sample size, short duration. Lack of clinically relevant safety outcome measures argue against this study for identification of an OSL
Kim et al. (2013)	60 subjects with mild to moderately elevated alanine transaminase (ALT) levels between 40 IU/L and 200 IU/L	3 g/day fermented turmeric (0.79 mg/curcumin/g),final n=26 Or placebo (final n=22) randomized, double-blind, placebo-controlled	Fermented turmeric powder	12 weeks (84 days)	Reduction in ALT levels AST levels There were no observed severe adverse events or abnormalities observed on blood glucose, total protein, albumin, blood urea nitrogen (BUN), and creatinine levels. Authors concluded that fermented turmeric powder at the doses administered is safe and generally well-tolerated.	2.37 g curcumin, modest sample size; modest duration; supports the OSL selected above.
Sugawara et al. (2012)	45 sedentary, postmenopausal women	150 mg/day curcumin Curcumin (n=11) Curcumin+exercise (n=12) Placebo (n=11) Placebo+exercise (n=11) Randomized, double-blind, placebo-controlled, parallel design study	6 capsules/day, each containing 25 mg highly absorptive curcumin dispersed with colloidal nanoparticles (Theracurumin, Theravalues, Tokyo, Japan)	8 weeks (56 days)	Aortic systolic blood pressure and heart rate-corrected aortic AP and the central arterial augmentation index (AIx) decreased when curcumin combined with exercise intervention, but did not change with exercise or curcumin alone. The authors stated that no adverse effects of curcumin ingestion reported.	150 mg/day. Small sample size; short duration.

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Na et al. (2013)	100 obese/diabetic patients	300 mg/day curcuminoids randomized, double-blind, placebo-controlled	Each curcumin capsule included 36.06% curcumin, 18.85% demethoxycurcumin, and 42.58% bisdemethoxycurcumin and two 150 mg capsules were taken each day (Hebei Food Additive Co., Shijiazhuang, Hebei, China).	3 months (90 days)	Decreased fasting blood glucose, HbA1c, insulin resistance index, serum total free fatty acids, triglyercides; increase in lipoprotein lipase. There were significant effects of curcuminoids on blood biochemical measures and liver enzyme markers. The authors did not mention any adverse effects in this study.	300 mg; large sample; short duration.
Mohammadi et al. (2013)	30 obese patients	1 g/day curcumin randomized, double-blind crossover	C3 Complex® capsules (Sami Labs, Ltd., Bangalore, India) Each tablet contained 500mg curcuminoids + 5 mg Bioperine. Two tablet consumed/day	30 days	Reduced serum triglycerides. No changes in total cholesterol, LDL-C, or HDL-C, or serum hs-CRP. Monitored anthropometric parameters, lipid profiles and CRP Adverse events after curcumin consumption were constipation (n=2), diuresis (n=2), and elevated volume and duration menstrual blood loss (n=1). Individuals in the placebo groups reported constipation (n=1), and feeling bloated (n=3)	1 g, small sample size, short duration. argue against the use of this study for identification of an OSL
Bergman et al. (2013)	40 patients with first episode of depression	500 mg/day curcumin Randomized, double-blind, placebo-controlled clinical	500 mg/day curcumin (Curcumin Forte Balance, Extracts H. Plant, Ra'anana, Israel)	5 weeks (35 days)	No difference between curcumin and placebo treatments in improvement of symptoms of depression. The authors reported that study participants did not complain of any adverse	Up to 500 mg. Small sample size; short duration; argue against the use of this study for identification of an OSL

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
					effects.	
Belcaro et al. (2013)	80 chemotherapy and 80 radiotherapy patients	500 mg curcumin preparation (100 mg curcumin) Placebo-controlled trial		60 days	A consistent improvement of the side-effect profile from both chemo- and radiotherapy was observed in the treatment group. No adverse events reported	
Elad et al. (2013)	Children undergoing doxorubicin-containing chemotherapy	Dose was 10 to 30 drops per day, tailored to body weight (rinse was twice/day) Study design comparable to a case series	Curcumall (Tumron Health Products, Jerusalem, Israel) 95% curcumin C3, turmeric and ginger, dissolved with glycerin and 0.4% alcohol	21 days	No oral adverse events reported. One individual developed stomach upset. The authors stated that curcumin mouthwash was safe and well-tolerated	Small study, study design change from placebo controlled study to one analagous to a case series, no control group, study completer had lowere mucositis scores than normally seen in the literature
Mazzolani and Togni (2013)	12 patients with chorioretinopathy	240 mg curcumin/day	Norflo tablets (EyePharma Co., Italy) containing Meriva® (Indena, Milan, Italy)	12-month follow-up study	After 12 months, no eyes showed further reduction in visual acuity, 39% showed stabilization, and 61% showed statistically significant improvement. Test material was well-tolerated	Small patient population
Abidi et al. (2014)	70 individuals with mild-to-moderate bronchial asthma	1 g/day curcumin + standard asthma therapy (Formonide Resicaps BD German Remedies) Standard asthma therapy Open label, randomized, single center study	CUR-500 (0.5 g Cap Curcumin) twice/day (M/s Indsaff and Chark Intl. Private Ltd, O/s Pahari Gate, Batala, Punjab)	30 days	Curcumin reduced airway obstruction as shown by improved FEV1 values. No clinically significant adverse events	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Ganjali et al. (2014)	37 subjects with BMI ≥ 30	1 g/day curcumin plus piperine randomized, double-blind crossover	C3 Complex Formula (Sami Labs Ltd., Bangalore, India) which contains curcumin, demethoxycurcuminand bisdemethoxycurcumin	4 weeks (30 days)	Serum IL-1β, IL-4 and VEGF reduced. No effects on IL-1α, IL-2, IL-6, IL-8, IL-10, interferon γ (IFNγ), epidermal growth factor (EGF), monocyte chemoattractant protein-1 MCP-1, and TNF-α No adverse effects reported.	1 g. small sample size; short duration; lack of control of diet, argue against the use of this study for identification of an OSL
Chuengsamarn et al. (2014)	240 patients with Type 2 diabetes	1,500 mg/day curcumin divided into two doses randomized, double-blind, placebo-controlled study	6 capsules/day each capsule with 250 mg curcumin. Dried rhizomes ground into powder and ethanol extracted. Total curcuminoid content was between 75-85%; made by the Govt/ Pharmaceutical Organization of Thailand	6 months (180 days)	Curcumin significantly lowered artherogenic risk parameters in diabetic patients, such as a reduction in pulse-wave velocity, increased serum adiponectin, decreased leptin, and reduced HOMA-IR, triglyceride and uric acid and abdominal obesity . Minor symptoms reported including hot flash (n=1), constipation (n=12), and nausea (n=1) in the curcumin group and hot flash, constipation, vertigo, and itching in the placebo group (n=1 each). Level of ALT significantly lower than placebo group (P=0.026), no significant difference in systolic/diastolic blood pressure, creatinine, and AST between groups, no development of new Cad or edema Authors stated that curcumin was well-tolerated with few adverse effects.	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Belcaro et al. (2014)	124 patients with osteoarthritis of the knee	500 mg Curcumin Phospholipids /day with glucosamine	Curcumin Phospholipids (Meriva®),	4 months	Patients experienced improved outcomes with Meriva® combined with glucosamine	Lack of randomization
Drobnic et al, (2014)	20 healthy males to test the effects of curcumin on delayed onset muscle soreness after exercise.	Curcumin Phospholipids, 1 g/day (corresponding to 400 mg curcumin/day) randomized, placebo-controlled, single-blind pilot trial	Curcumin Phospholipids Meriva®, Indena, Milan, Italy	4 days total: Supplementation was initiated 48 hours prior to a downhill running test and continued for 24 hours after test	Subjects reported less pain in the lower limb after exercise compared to placebo. Markers of muscle damage and inflammation were lower in curcumin group.	Up to 500 mg. Short duration; argue against the use of this study for identification of an OSL
Cox et al. (2014)	60 healthy adults (60-85)	400 mg curcumin preparation (80 mg curcumin), n=30 Placebo, n=30 randomized, double-blind, parallel-groups	Longvida® Optimized Curcumin, is curcumin in a solid lipid formulation	4 weeks (28 days)	Improved working memory, alertness and mood; reduced total and LDL cholesterol No effect on hematological safety measures. Well- tolerated	Short duration; argue against the use of this study for identification of an OSL
Hejazi et al. (2014)	40 prostate cancer patients undergoing external beam radiotherapy with hormone ablation	3 g/day curcumin preparation randomized, double blinded, placebo-controlled	6 capsules containing BCM-95® (Biocurcumin), Arjuna Natural Extracts, Ltd. (n=20) Contained 440 mg curcuminoids (347 mg curcumin, 84 mg desmethoxycurcumin, and 9 mg bisdesmethoxycurcumin) Placebo (n=20)	9 weeks (63 days)	Improved urinary symptoms. Adverse effects not reported. Exclusion criteria included adverse effects to curcumin.	Up to 3 g, relatively long duration, but diseased nature of population, relatively small sample size, lack of clinically relevant safety outcome measures argue against use of this study for identification of an OSL.

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Kuptniratsaikul et al. (2014)	331 primary knee osteoarthritis patients who met the American Rheumatism Association criteria for osteoarthritis, had a pain rating of ≥5 out of 10, and were age 50 years or older	1,500 mg/day *C. domestica* extracts (final n=171 study participants, 11 lost to follow up) 1,200 mg/day ibuprofen (final n=160 study participants, 14 lost to follow up) multicenter double-blind, randomized controlled trial	Two capsules after meals, three times per day for 4 weeks. The curcumin treatment was prepared from dried ground rhizomes of *C. domestica* made into a powder and extracted with ethanol from which oleoresin was removed.	4 weeks	Similar effectiveness of curcumin extract and ibroprofen for treatment of knee osteoarthritis. Similar adverse effects for the curcumin and the placebo groups, but curcumin group had significantly fewer GI effects.	
Nakagawa et al. (2014)	41 patients with osteoarthritis	Curcumin preparation (180 mg curcumin) randomized, double-blind, prospective	Theracurmin (180 mg curcumin), 6 capsules/day	8 weeks (56 days)	Improvement in knee pain; One report of sensation of tachycardia and hypertension on day 50; one report of redness of the tongue on day 5; No serious adverse events were observed.	0.4 g, moderate sample size and moderate duration; lack of clinically relevant safety outcome measures argue against use of this study for identification of an OSL
Panahi et al. (2014a)	80 patients with solid tumors	900 mg curcumin preparation (180 mg/day curcumin) randomized double-blind		8 weeks (56 days)	Improvement in QOL; reductions in inflammatory markers. Mild GI effects reported in curcumin group	0.9 g, moderate sample size and moderate duration; lack of clinically relevant safety outcome measures argue against use of this study for identification of an OSL
Panahi et al. (2014b)	87 patients with solid tumors	900 mg curcumin preparation (180 mg/day curcumin) randomized double-blind		8 weeks (56 days)	Greater elevation in the activities of SOD and CAT, and concentrations of GSH; significantly reduced serum TBARS; QoL scores improved. Adverse events were not reported. Exclusion criteria included adverse effects to curcumin.	
Panahi et al. (2014c)	89 patients with chronic pulmonary complications from sulphur mustard intoxication	1.5g/day, 500 mg/day three times/day randomized, double-blind , placebo-controlled	C3® complex capsules (SamiLabs Ltd. Bangalore, India)	4 weeks	Improved spirometric parameters curcuminoids had a greater effect than placebo in improving FEV1/FVC (p=0.002), inflammatory mediators, IL-6, TNFα, TGFβ, hs-CRP, CGRP, MCP-1 (all P<0.001), IL8 (P=0.035) and substance P	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
					(P=0.016). Authors describe as being safe and well-tolerated. No report of severe adverse evemnts resulting from medication in study. In curcumin group abdominal pain, and constipation (n=4), headache (2), unpleasant aroma (n=3), and large size of capsules (n=1).	
Panahi et al. (2014d)	40 patients with knee osteoarthritis	1.5 g/day curcumin randomized, double-blind		6 weeks (42 days)	Reductions in pain indices No adverse effects observed	1.5 g/day; small sample size; short duration.
Pajardi et al. (2014)	180 patients with carpal tunnel syndrome scheduled for surgery	1000mg curcumin/day split into 2 doses and as part of a combination product, Axin C	Axin C (Agave Farmaceutici srl, Prato, Italy) oral combination of alpha-lipoic acid, curcumin phytosome, and B-group vitamins	6 months total (3 months before surgery, 3 months post-surgery)	Treatment was effective in reducing pre and post-surgery symptoms. Treatment was well-tolerated.	Combination product tested only
Rahimnia et al. (2014)	40 individuals with mild-to-moderate degree osteoarthritis	1,500 mg/day C3 Complex®, Sami Labs Ltd. Bangalore, India Randomized, double-blind placebo-controlled trial	3 divided doses of C3 Complex® Each capsule contained 500 mg curcuminoids and 5 mg/bioperine (n=19, original n=27) Matched placebo (n=21, original n=)	6 weeks	No significant difference between groups for serum IL-4, IL-6, hs-CRP. TNF- α, TGF-β and erythrocyte sedimentation rate	
Lopresti et al. (2014)	56 individuals with major depressive disorder	1000 mg/day curcumin as BCM-95®, n=28 Placebo (cellulose), n=28 Randomized, placebo-controlled double blinded	Curcumin as BCM-95® (Arjuna Natural Extracts, India) containing 88% total curcuminoids	8 weeks (56 days)	Improved several mood-related symptoms as measured by the IDS totoal (P=0.026) and IDSm (P=0.020) and in STAIt anxiety scores for weeks 4-8 in the curcumin group. Authors reported greater efficacy in a subgroup with atypical depression. Adverse events were described as minor and one person in curcumin group withdrew because of adverse events. This individual had previously complained of stomach bloating and pain. Therewere not significant differences in adverse events between the placbo and curcumin groups.	No significant difference between groups in adverse effects.

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Lopresti et al. (2015)	47 individuals with major depressive disorder	1000 mg/day curcumin as BCM-95, final n=22 Placebo (cellulose), N=25 randomized Randomized double blinded, placebo-controlled	Curcumin as BCM-95 (Arjuna Naturals Extracts, India) containing 88% total curcuminoids	8 weeks (56 days)	Elevated levels of plasma endothelin-1 and leptin in individuals who were treated with curcumin were associated with a greater decrease in he Inventory of Depressive Symptomatology (IDSSR30) score. Placebo was associated with reduction in aldosterone and cortisol (P<0.05 for both) Curcumin treatment was associated with increased substance P (P<0.001), and urinary thromboxaneB2 (P<0.05). There was no association between biomarker changes and treatment outcome	Small sample size, No adverse effects discussed.
Sanmukhani et al(2014)	51 individuals with major depressive disorder	1,000 mg/day BCM-95 (2x500 mg BCM-95) Randomized observe-blinded with 3 parallel treatment arms	Two times/day, 500 mg capsule (BCM-95™, Arjuna Natural Extracts, Kochi, Kerala, India). Each containing total curcuminoids 88% (curcumin, bisdemethoxycurcumin, demethoxycurcumin) and volatile oils 7% from rhizomes of C. longa Linn	6 weeks	No significant difference between groups in number of responders	No placebo group few study participants
Schiborr et al. (2014)	23 healthy individuals	500 mg curcuminoids with Single-blind, randomized, crossover study	410 mg curcumin, 80 mg demethoxycurcumin and 10 mg bisdemethoxycurcumin as native powder (Jupiter Leys, Cochin, Kerala State, India), micronized powder with 25% by wt curcumin powder (RAPS gmBH and Co. KG, Kulmbach Germany), or liquid micelles with 17.2% curcumin powder,	Single dose	No significant differences in serum concentrations of Tot-C, LDL-C, HDL-C, TAG, and liver and kidney function markers between treatment groups. All values were all in the normal ranges.	

Study	Study Population	Dosage and study design	Preparation Description	Duration (days)	Key Observations	OSL Considerations
Yang et al. (2014)	65 patients with metabolic syndrome	1890 mg/day curcumin extract/day (3 doses of 630 mg curcumin extract) Randomized, double-blind, placebo-controlled	Capsules contained 630 mg curcumin extract (95% curcuminoids) with curcumin, demethoxycurcumin, and bisdemethoxycurcumin and other constituents	12 weeks (84 days)	Lipid lowering effect. Mild diarrhea, nausea in two individuals who were treated with curcumin. The test material was well-tolerated	Small sample size
Bayet-Robert et al. (2015)	9 patients with advanced and metastatic breast cancer	Curcumin doses: 500 mg/day (n=1), 1,000 mg/day (n=1), 2,000 mg/day (n=1), 4,000 (n=2), 6,000 mg/day (n=4), and 8,000 mg/day (n=5) Docetaxel (100 mg/m^2 administered as 1 h.i.v. infusionevery 3 weeks on day 1 for 6 cycles) Phase 1 dose escalation trial	No details provided	7 consecutive days/dose	Multiple adverse events occurred. Dose limiting toxicities included one grade 3 diarrhea at 6,000 mg/day, and at 8,000 mg/day, one grade IV neutropenia and one grade III diarrhea. The authors set a recommended dose for Phase II trials of 6,000 mg/d	
Maccio et al. (2015)	One patient with Myelofibrosis	4 g/day curcumin	Multi-targeted treatment containing oral L-carnitine 2 g/d, celecoxib 100 mg/d, curcumin (Meriva®, Indena, Milan, Italy) 4 g/d, lactoferrin 0.2 g/d, and subcutaneous re-combinant human EPO (rHuEPO)-a 30000 UI/w	1 year	After one year of treatment, all myelofibrosis symptoms were in remission	Single patient case
Storka et al. (2015)	Healthy men and women	Intravenous administration of 10, 20, 40, 80, 120, 180, 240, 320, and 400 mg/m^2 Lipicur™ (liposomal curcumin) (n=24) Placebo (n=26) Randomized, double-blind placebo-controlled, dose escalation, phase I clinical trial	Synthetic curcumin synthesized by Sami Labs, Ltd. Bangalore, India	Single dose	Plasma curcumin and tetrahydrocurcumin increase with increasing dose. Authors said that liposomal curcumin was well-tolerated but observed transient red blood cell echinocyte and increased mean cellular volume of red blood cells	Small study

Bonnette, Richard

From: Bonnette, Richard
Sent: Tuesday, January 03, 2017 8:09 AM
To: 'cheryld@dolcas-biotech.com'
Subject: FW: your submission to the FDA GRAS notification program for curcumin

Hello Cheryl,
I have the submission on my desk. I had previously tried by email and voicemail (unsuccessfully) to reach KG Rao in November, who was listed as the contact for the submission. There is a missing administrative component that is preventing it's filing. I've forwarded the email for your information below. Once I receive the statements, the submission will then move forward.
Regards,
Richard

From: Bonnette, Richard
Sent: Thursday, November 03, 2016 9:58 AM
To: 'grao@dolcas-biotech.com'
Subject: your submission to the FDA GRAS notification program for curcumin

Dear Mr. Rao,
We received your submission dated Oct.25, 2016 regarding GRAS uses of curcumin. As part of a pre-filing review, it was noted that the submission is missing a required component that will prevent its filing. It seems the submission is missing a required statement described in Subpart E of Part 170. Particularly the certification statement from 170.225(c)(9). As described in 170.225(c)(1), please also note that you're submitting a GRAS notice in accordance with Subpart E of Part 170. You may provide these statements as a separate letter and provide it either via email to me or in hardcopy to my attention at our address below. After receiving the information, I'll append it to the submission and it will then be able to be processed further.

Regards,
Richard

Richard E. Bonnette, M.S.
Consumer Safety Officer
Division of Biotechnology and GRAS Notice Review
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U.S. FDA, Center for Food Safety and Applied Nutrition

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Division of Biotechnology and GRAS Notice Review
Office of Food Additive Safety
U.S. FDA, Center for Food Safety and Applied Nutrition

RE: Certification Statement per 170.225(c)(9)

DolCas Biotech is submitting a GRAS notice in accordance with Subpart E of Part 170, FDA GRAS Notification.

DolCas Biotech certifies that, to the best of our knowledge, our GRAS notice is a complete, representative, and balanced submission that includes unfavorable information, as well as favorable information, known to us and pertinent to the evaluation of the safety and GRAS status of the use of the substance, BCM-95® curcumin complex (also known as Biocurcumax™ and Biocurcumin™).

DolCas has concluded that the notified substance, BCM 95® (also known as Biocurcumax™ and Biocurcumin™ and commonly referred to as curcumin) is GRAS and that the safety standards, per 21 CFR Part 170.30 Subpart E, of reasonable certainty of no harm, based on scientific procedures and common knowledge as described herein, are met. This conclusion is based on the in-depth review of the collective generally available scientific data regarding the safety of BCM 95® curcumin, common knowledge and general consensus among qualified experts corroborated by the written GRAS conclusion of an independent Expert Panel of qualified persons whom reviewed all publicly available referenced safety data.

We certify that this GRAS notification is complete and is a balanced representation of all data available.

(b) (6)

K G Rao, President
DolCas Biotech, LLC
9 Lenel Rd.
Landing, NJ 07850

SUBMISSION END