From: Duncan Turnbull
To: Morissette, Rachel
Cc: Joseph V Rodricks
Subject: RE: GRAS notice for basic methacrylate copolymer
Date: Wednesday, July 05, 2017 3:42:17 PM
Attachments: image007.png
image008.png

Dr. Morissette:

I can confirm that there are no plans to use basic methacrylate copolymer in infant formula or products under the jurisdiction of the U.S. Department of Agriculture.

Sincerely,

Duncan Turnbull, DPhil, DABT
Senior Science Advisor
Toxicology

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dturnbull@ramboll.com

Ramboll Environ
4350 North Fairfax Drive
Suite 300
Arlington, VA 22203
USA
www.ramboll-environ.com

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Wednesday, July 05, 2017 11:03 AM
To: Duncan Turnbull <DTurnbull@ramboll.com>
Subject: GRAS notice for basic methacrylate copolymer

Dear Dr. Rodricks,

My name is Dr. Rachel Morissette and I am the Consumer Safety Officer assigned to handle your GRAS notice for basic methacrylate copolymer. Before I continue processing your notice, can you please confirm if your intended uses involve infant formula or products under the jurisdiction of the U.S. Department of Agriculture (i.e. meat, poultry, egg products, catfish)?

Sincerely,

Rachel Morissette, Ph.D.
Consumer Safety Officer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov


FDA
U.S. FOOD & DRUG
ADMINISTRATION

From: Duncan Turnbull
To: Morissette, Rachel
Cc: Joseph V Rodricks
Subject: RE: GRN 710 questions
Date: Monday, September 25, 2017 12:33:50 PM
Attachments: image009.png
image001.png
image007.png
image008.png
image019.png
Response to FDA.pdf
Annex 3.1_Adler 2, 2005.pdf
Annex 11.5_EFSA 2016.pdf
Annex 11.6_Reg. 2017_324, Specification change BMC, E 1205.pdf
Annex 11.3_Reg. 816_2013, Admission E1206 + 1207, Spec change E 1205.pdf
Annex 4.1_Eisele et al 2011-RegToxPharmacol.pdf
Annex 3.2_PSS calibration kit CoA.pdf
Annex 11.1_Reg. 231_2012, Specification of BMC, E 1205.pdf
Annex 9.1_BfR_2010_XXII Empfehlung Lebensmittelkontakt Initiator.pdf
Annex 10.1_USP-NF, Amino Methacrylate Copolymer.pdf
Annex 11.2_Specification of EUDRAGUARD protect.pdf
Annex 2.1_EFSA 2010.pdf
Annex 8.1_Ph.Eur. BBMC.pdf
Annex 8.2_INFO 7.1.pdf
Annex 11.4_Public summary BMC dossier 2014, Spec change.pdf
Annex 8.3_JPE_inoffTranslation_E_109215.pdf

Rachel:

The attached document, “Response to FDA.pdf” contains the non-confidential portions of the responses (along with several Annexes) to the FDA reviewers’ questions regarding GRN 710. There should be a total of 16 pdf files attached. Let me know if you have any problems with these.

As previously indicated, responses to two of the questions (#1 and #6) have been submitted to you directly by the polymer manufacturer, Evonik, and are considered by Evonik to contain Confidential Business Information.

Sincerely,

Duncan Turnbull, DPhil, DABT
Senior Science Advisor
Toxicology

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dturnbull@ramboll.com

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RAMBOLL ENVIRON

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, September 25, 2017 10:11 AM
To: Duncan Turnbull <DTurnbull@ramboll.com>
Subject: RE: GRN 710 questions

Dear Duncan,

I did receive an encrypted email from the company. However, this is not an encryption type that we've dealt with before and have not been able to open it yet. FDA has to be very careful with the types of files we accept. We would ask the company to either send the information unencrypted or they have the option to send it via carrier and someone at FDA can sign for it. The latter option will take longer obviously. I would remind the company that any information that bears on safety cannot be confidential, so we discourage companies from sending us confidential business information if at all possible.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Consumer Safety Officer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

From: Duncan Turnbull [mailto:DTurnbull@ramboll.com]
Sent: Friday, September 22, 2017 1:53 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Subject: RE: GRN 710 questions

Rachel:

You should have received an email from Uta Deiting of Evonik, the manufacturer of the copolymer that is the subject of GRN 710, containing detailed information on the composition and manufacturing details for the copolymer. Evonik considers that information to be Confidential Business Information. It addresses 2 of the questions (#1 and #6) you had sent to me. We will be responding to the other questions on Monday.

Sincerely,

Duncan Turnbull, DPhil, DABT
Senior Science Advisor
Toxicology

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RAMBOLL ENVIRON

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, September 11, 2017 2:05 PM
To: Duncan Turnbull <DTurnbull@ramboll.com>
Subject: RE: GRN 710 questions

Thanks!

Rachel

Rachel Morissette, Ph.D.
Consumer Safety Officer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

From: Duncan Turnbull [mailto:DTurnbull@ramboll.com]
Sent: Monday, September 11, 2017 1:42 PM
To: Morissette, Rachel <Rachel.Morissette@fda.hhs.gov>
Cc: Joseph V Rodricks <JRodricks@ramboll.com>
Subject: RE: GRN 710 questions

Thanks, Rachel. We'll get back to you as soon as possible.

Duncan

From: Morissette, Rachel [mailto:Rachel.Morissette@fda.hhs.gov]
Sent: Monday, September 11, 2017 1:32 PM
To: Duncan Turnbull <DTurnbull@ramboll.com>
Cc: Joseph V Rodricks <JRodricks@ramboll.com>
Subject: GRN 710 questions

Dear Dr. Turnbull,
Please see attached the questions FDA has for Ramboll Environ's GRAS notice GRN 710, which were summarized during our phone conference on Sept. 6. Please let me know if you have further questions at this time.

Best regards,

Rachel

Rachel Morissette, Ph.D.
Consumer Safety Officer

Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
U.S. Food and Drug Administration
rachel.morissette@fda.hhs.gov

Reply to FDA´s questions on GRN 710, Basic Methacrylate Copolymer:

1. On page 4 the substance's identity is written as follows: "Basic Methacrylate Copolymer is manufactured by Evonik Rohm GmbH and is designated by the International Union of Pure and Applied Chemistry (IUPAC) as follows: Poly[(dimethylaminoethyl methacrylate)-co-(methyl methacrylate)-co-(butyl methacrylate]. The molar ratio is 0.24: 0.34:0.25 and a weight ratio is 49:25:26." Using abbreviations, the substance is DMAEA-MMA-BMA copolymer. Based on a molar ratio of 0.24:0.34:0.25 (DMAEA: MMA:BMA), we calculate a different weight ratio of 35:32:33. Please clarify this discrepancy.

   Reference 1 (Eisele, J., et. al.) states: "The copolymer is described as poly(butylmethacrylateco-(2-dimethylaminoethyl)methacrylate-co-methyl methacrylate) 1:2:1 under IUPAC nomenclature." From this reference the molar ratio is 2:1:1 (DMAEA:MMA:BMA), which is a different molar ratio and weight ratio than that given in the notice.

   Since the molar ratios are a crucial attribute of a polymer's identity, additional information on the molar and weight ratios should be provided. What are the molar ratios and weight ratios of the monomers in the methacrylate copolymer? Does the substance always have the same molar ratios? Are the molar ratios finite or have a range? How are the molar ratios determined? How do you ensure that each batch of the methacrylate copolymer has the same molar ratios?

   The discrepancy in the molar and weight ratios was due to an error in the information available to EFSA which was quoted in the GRAS notice. Evonik is providing the correct information and detailed responses to the other questions above on composition directly to FDA as ***CONFIDENTIAL BUSINESS INFORMATION*** *(CBI), not releasable to the public.*

2. On page 2 the following is stated: "As described by ECHA (2008), basic methacrylate copolymer is a fully polymerized copolymer derived from acrylic and methacrylic acid esters. The substance is described as a cationic copolymer based on dimethylaminoethyl methacrylate and neutral methacrylic esters (butyl methacrylate and methyl methacrylate)." Please provide the ECHA (2008) reference or provide additional references describing the identity of your substance.

   By mistake, this does not cite the correct reference. Please replace "ECHA (2008)" with "EFSA (2010)" (Annex 2.1).

3. The **molecular weight** of the methacrylate copolymer is not provided in the notice. Molecular weight data is provided in References 1 (Eisele, J., et.al) and 2 (EFSA, 2010); however, only limited information is provided in these references.

   Like molar ratio, molecular weight is pivotal in identifying a polymer. Please provide the molecular weight values of the methacrylate copolymer. What analytical method(s) were used to determine the molecular weight? How were these analytical methods calibrated and validated? Ramboll Environ should provide evidence that the molecular weight of the methacrylate copolymer is consistent between different batches. Please provide molecular weight values of the methacrylate copolymer for at least three samples from non-consecutive batches.

   The mass average molecular weight (Mw) is approximately 47,000 g/mol and the number average molecular weight (Mn) is approx. 22,000 g/mol. These data have been obtained by gel permeation chromatography (GPC as described in Adler et al., 2005[1], Annex 3.1). For calibration purposes, a commercial calibration kit with polymer samples of known molecular weight and of similar composition and properties was used (see Annex 3.2 with an example CoA). The software for

[1] Adler M, Pasch H, Meier C, Senger R, Koban H-G, Augenstein M, Reinhold G, Molar mass characterization of hydrophilic copolymers, 2 Size exclusion chromatography of cationic (meth)acrylate copolymers, e-Polymers 2005, no. 057, 1-11 (2005)

molecular weight determination was also obtained by the same commercial provider (PSS, Polymer Standards Service, Mainz, Germany).

A validation of the analytical method is not easily applicable to gel permeation chromatography. Instead, a system suitability test is performed with every analysis, confirming that the molecular weight of a control sample is within defined acceptable limits.

The following molecular weights of ten lots of basic methacrylate copolymer, manufactured with the former bulk process, were determined:

Lot number	Average molecular weight Mw [g/mol]	Molecular number Mn [g/mol]
G070331066	46,650	21,250
G070331065	47,600	23,750
G060931183	47,450	21,850
G060931166	47,300	21,750
G060731129	47,050	21,450
G060731128	46,400	21,450
G060431062	46,600	21,000
G060431060	48,300	21,900
G060331051	46,950	21,550
G060331050	48,000	21,950
Mean value	47,230	21,790
Standard deviation (SD)	620	752
Mean value +/- 4 SD	47,230 +/- 2,480	21,790 +/- 3,008

From these data an M_W of approximately 47,000 [g/mol] and an Mn of approximately 22,000 [g/mol] were deduced. This is reflected by the molecular weight of approximately 47 000 g/mol named in the Annex of Reg. (EU) No. 231/2012.

After changing to the new solupol process in 2013, the molecular weight of five batches of basic methacrylate copolymer produced with the new process was controlled and confirmed to be approximately 47 000 g/mol:

Lot number	Average molecular weight Mw [g/mol]
B130401503	47,200
B130401504	47,500
B130401505	46,300
B130401506	46,900
Product from solution polymerization (mean)	**47,000**

4. What fraction of the methacrylate copolymer has a molecular weight of less than 1000 Da? The notifier should provide data demonstrating the low molecular weight oligomer (LMWO) fraction of 3 samples from different non-consecutive batches.

The mean mass fractions of Basic Methacyrlate Copolymer with molecular weight less than 1000 Da is 0.0 %. The mean value had been determined out of 10 production batches. The molecular weight distribution as well as the mass fractions for all ten batches are published in Eisele, 2011 (J. Eisele et al., Regulatory Toxicology and Pharmacology 61 (2011) 32-43), Table 1 (Annex 4.1).

5. On page 11 it is stated that the micronutrients "were encapsulated using Basic Methacrylate Co-polymer, with or without hyaluronic acid as an additional stabilizing excipient, producing particles approximately 200 µm in diameter." Is this typically how the methacrylate copolymer is used in the final product? Are there other stabilizing agents other than hyaluronic acid used? Please describe how you process the methacrylate copolymer to encapsulate the micronutrients. Please include a list of any processing aids.

   Currently, the only excipient used in the production of the coated micronutrients, other than Basic Methacrylate Copolymer, is hyaluronic acid, a natural cellular component that is synthesized in the human body. Hyaluronic acid is also a common ingredient in dietary supplements, cosmetic preparations, and certain GRAS substances (e.g., GRN 491, Rooster Comb Extract[2]). Its presence in the products made using it is not expected to increase significantly the intake or body burden of hyaluronic acid, and not affect the safety of the foods made using it.

6. The notifier does not provide manufacturing information in the body of the notice. References 1 and 2 contain a summary of the manufacturing. However, sufficient details regarding the manufacturing process are not included in either reference. Sufficient details on the manufacturing process should be provided so that FDA can assess safety. Details on the identity of any initiators free radical donor initiator system dissolved in a small amount of propan-2-ol; later residual initiator decomposed, chain-modifying agents, solvents, and processing steps, charge amounts, time and temperature conditions, and cleaning steps should be provided.

   The response to this question will be provided as a separate Annex directly to FDA by the manufacturer, Evonik. The current Solupol process will be described, not the bulk process from the original EFSA dossier 2010. Please note, the information in that Annex is considered by the manufacturer to be ***CONFIDENTIAL BUSINESS INFORMATION*** *(CBI), not releasable to the public.*

7. In an EFSA report (2016) titled "Safety of the proposed amendment of the specifications for basic methacrylate copolymer (E 1205) as a food additive," it is described that the manufacturer changed the manufacturing process from bulk polymerization to solution polymerization.

   When providing details on the manufacturing process, please indicate if only one manufacturing process was used to produce the methacrylate copolymer. The manufacturing process provided should be representative of the process currently used to produce the final product.

   Evonik switched in 2013 from the former bulk process to the new Solupol process and informed EFSA in 2014 when all analytical data were available. Production process details as described in the reply to question 6 refer to this current Solupol process which was the only process in use since then, and is the process used to make the material that is the subject of this GRN.

8. Table 1 on page 5 shows specifications for monomers and solvents. The "Specification" column lists the following references: Ph. Eur., INFO 7.1, and JPE. Please provide these references.

   See Annexes 8.1 (Ph.Eur. monograph "Basic Butylated Methacrylate Copolymer"), 8.2 (INFO 7.1) and 8.3. (JPE monograph "Aminoalkyl Methacrylate Copolymer E").

9. Ramboll Environ should identify whether they expect any of the starting materials to remain with the final product, and if so, specification limits for residual levels should be provided. These impurities may include residual initiator, chain modifying agents, solvents, and processing agents.

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[2] https://www.accessdata.fda.gov/scripts/fdcc/index.cfm?set=GRASNotices&id=491

- The **initiator system** used in solution polymerization is listed in the BfR (German Federal Institute for Risk Assessment) recommendation XXII as suitable initiator for polyacrylates and polymethacrylates in food contact materials. It decomposes fully, as described for question No. 6.
- The **chain modifying agent** is approved in Germany for food contact according to BfR (German Federal Institute for Risk Assessment) recommendations XIV and XXII. The content of residual agent was evaluated by gas chromatography and found to be present only in traces in the final product. For details see answer to question No. 6.
- Residual **volatile components, e.g. solvents,** are removed during extrusion under vacuum.
- The **residual monomers and solvents** are regularly controlled and below specified parameters, as described for question No. 6.

10. In Table 1 on page 5 the specification results from 4 lots of the methacrylate copolymer are provided.

    Please provide details on how the residual levels were determined for the monomers and solvents. What analytical methods were used to determine the residual monomers and solvents? How were the analytical methods calibrated and validated?

    Ramboll Environ should identify the byproducts of the initiators and should state whether the byproducts will remain with the final product. If they expect the formation of initiator byproducts, they should provide specification levels and provide details on how the residual levels were determined. They should also provide details on the analytical methods used to determine residual levels and information on the calibration and validation of the analytical method.

    - **Residual monomers**: Analytical determination is performed according to USP/NF monograph for Amino Methacrylate Copolymer (NF) on 1 g basic methacrylate copolymer (Annex 10.1). According to USP-NF General Chapter <1225> entitled “VALIDATION OF COMPENDIAL PROCEDURES“, users of analytical methods described in USP–NF are not required to validate the accuracy and reliability of these methods.
    - **Residual solvents**: Internal methods are used by Evonik for analysis of residual solvents. Their suitability under actual conditions of use has been confirmed.
    - The **initiator** decomposes fully, as described for question No. 6. Other byproducts than by decomposition do not occur.

11. In Reference 2, the following is stated: “The panel notes that basic methacrylate copolymer will be used in food supplements and that according to Commission Regulation (EC) No 629/2008, the maximum levels of lead, mercury and cadmium in food supplements, as sold, should be 3.0 mg/kg, 0.1 mg/kg and 1mg/kg, respectively.”

    There are specifications for the methacrylate copolymer that are included in the EFSA paper that are not included in Table 1 on page 5 of the notice. Further, different specifications for the methacrylate copolymer are discussed in two EFSA reports (2010 and 2016).

    Ramboll Environ should provide all specifications for the methacrylate copolymer, including heavy metals.

    The specification cited in Table 1 on page 5 of the notice refers to the same polymer, basic methacrylate copolymer (BMC), used in pharmaceutical applications. The specifications for use as pharmaceutical excipient and as food additive differ slightly.

    The regulatory specification for BMC as food additive (E 1205) is listed in the annex of Reg. (EU) No. 231/2012 (Annex 11.1).

The commercial specification (Annex 11.2) for BMC as food additive is compliant with its regulatory specification in Reg. (EU) No. 231/2012. The commercial name of BMC as food additive is EUDRAGUARD® protect.

Originally, the regulatory specification for heavy metals in BMC, listed in the first issue of Reg. (EU) No. 231/2012, was as described in the EFSA opinion in 2010. In 2013, the heavy metal parameters and limits were corrected by Reg. (EU) No. 816/2013 (Annex 11.3) for reasons described in sections (7) to (9) of this regulation. In Evonik´s application for a specification change in 2014, the new heavy metal parameters and limits were named in the dossier; however they were not a target of the application for specification change. The specification change referred to the description of the manufacturing process and the particle size distribution only. The public summary of the application is given in Annex 11.4. Heavy metals were not mentioned in the resulting EFSA opinion in 2016 (Annex 11.5). The accepted specification change finally came into force by Reg. (EU) No. 2017/324 (Annex 11.6).

12. EFSA report (2016) "Safety of the proposed amendment of the specifications for basic methacrylate copolymer (E 1205) as a food additive" states that there is an amendment to the specifications of basic methacrylate copolymer. The amendment included a change of manufacturing process from a bulk polymerization process to a solution polymerization process and a change in the particle size specification. "The specifications were amended to the following: at least 95% of the particles have a size below 50 µm; at least 50% have a size below 20 µm; not more than 10% have a size below 3 µm." Please provide particle size specifications for your substance.

    The material used is that described by EFSA (2016).[3] The particle size distribution is specified as described above:

    < 50 µm at least 95 %
    < 20 µm at least 50 %
    < 3 µm not more than 10 %.

13. In Reference 2, the following is stated: "The petitioner also indicates that, in general, different types of ionic interactions with food components/ingredients may appear between counter-charged functional groups. Thus, the cationic polymers (e.g. basic methacrylate copolymer) may form ionic interactions with anionic substances (e.g. active (pharmaceutical) ingredients, excipients, food ingredients, etc.). … The probability of complex formation depends on different factors, e.g. contact intensity, nature of the functional groups, steric hindrances, number of ionic groups and thus frequency of contact, processing (contact time and catalyzing factors like temperature and humidity). Please discuss if there could be interactions with different types of foods (e.g. acidic, aqueous foods).

    In general, ionic interactions may appear between counter-charged functional groups. This means that the cationic polymers (e.g. Basic Methacrylate Copolymer) may form ionic interactions with anionic substances (APIs, excipients, food ingredients, etc.). With regard to food, potential anionic partners for the formation of ionic interactions may be organic acids as citric acid or tartaric acid. As stronger acids generally replace the weaker ones in their salts, these ionic interactions will be dissolved in the gastrointestinal fluids and the Basic Methacrylate Polymers as such is present. Any such transitory interactions would not affect absorption of nutrients, or otherwise affect the safety of the polymer.

14. The notifier states that the methacrylate copolymer is approved for use as a coating in pharmaceutical products on the market. What is the expected exposure to the methacrylate

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[3] European Food Safety Authority (EFSA). 2016. Safety of the proposed amendment of the specifications for basic methacrylate copolymer (E 1205) as a food Additive EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS). EFSA Journal ;14(5):4490. (http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2016.4490/epdf).

copolymer from use in these pharmaceutical products? Please describe the pharmaceutical products that currently use the methacrylate copolymer.

The publicly available data on the use of Basic Methacrylate Copolymer as a coating in pharmaceutical products is limited. It is listed (as DIMETHYLAMINOETHYL METHACRYLATE - BUTYL METHACRYLATE - METHYL METHACRYLATE COPOLYMER) in FDA's Inactive Ingredients Database[4] as being present in 16 capsule, tablet, and suspension products at 1.63 to 214 mg, and Drugs.com[5] identifies it as being present (but not the quantity present) in the following drugs:

Alfuzosin Hydrochloride Extended Release 10 mg (Sun Pharmaceutical Industries Ltd.)
Atorvastatin Calcium 10 mg (Kremers Urban Pharmaceuticals Inc.)
Atorvastatin Calcium 20 mg (Kremers Urban Pharmaceuticals Inc.)
Atorvastatin Calcium 40 mg (Kremers Urban Pharmaceuticals Inc.)
Atorvastatin Calcium 80 mg (Kremers Urban Pharmaceuticals Inc.)
Clozapine (Orally Disintegrating) 12.5 mg (Teva Pharmaceuticals)
Clozapine (Orally Disintegrating) 25 mg (Teva Pharmaceuticals)
FazaClo 25 mg (Azur Pharma Inc.)
FazaClo 100 mg (Azur Pharma Inc.)
FazaClo 150 mg (Azur Pharma Inc.)
FazaClo 200 mg (Azur Pharma Inc.)
Metformin Extended-Release 750 mg (Torrent Pharmaceuticals)
Mirtazapine 15 mg (Teva Pharmaceuticals)
Mirtazapine 30 mg (Teva Pharmaceuticals)
Mirtazapine 45 mg (Teva Pharmaceuticals)
Natafort prenatal multivitamins with folic acid 1 mg (Mission Pharmacal Company)
Pantoprazole Sodium Delayed Release 20 mg (Actavis US)
Pantoprazole Sodium Delayed Release 40 mg (Actavis US)
Perphenazine 2 mg (Qualitest Pharmaceuticals Inc.)
Perphenazine 4 mg (Qualitest Pharmaceuticals Inc.)
Perphenazine 8 mg (Qualitest Pharmaceuticals Inc.)
Perphenazine 16 mg (Qualitest Pharmaceuticals Inc.)
Propranolol Hydrochloride Extended-Release 60 mg (Mylan Pharmaceuticals Inc.)
Propranolol Hydrochloride Extended-Release 80 mg (Mylan Pharmaceuticals Inc.)
Propranolol Hydrochloride Extended-Release 120 mg (Mylan Pharmaceuticals Inc.)
Propranolol Hydrochloride Extended-Release 160 mg (Mylan Pharmaceuticals Inc.)
Risperidone (Orally Disintegrating) 1 mg (Jubilant Cadista Pharmaceuticals Inc.)
Risperidone (Orally Disintegrating) 2 mg (Jubilant Cadista Pharmaceuticals Inc.)
Risperidone (Orally Disintegrating) 3 mg (Jubilant Cadista Pharmaceuticals Inc.)
Risperidone (Orally Disintegrating) 4 mg (Jubilant Cadista Pharmaceuticals Inc.)
Risperidone (Orally Disintegrating) 0.5 mg (Jubilant Cadista Pharmaceuticals Inc.)
Risperidone (Orally Disintegrating) 0.25 mg (Mylan Pharmaceuticals Inc.)
Risperidone (Orally Disintegrating) 0.5 mg (Mylan Pharmaceuticals Inc.)
Risperidone (Orally Disintegrating) 1 mg (Mylan Pharmaceuticals Inc.)
Risperidone (Orally Disintegrating) 2 mg (Mylan Pharmaceuticals Inc.)
Risperidone (Orally Disintegrating) 3 mg (Mylan Pharmaceuticals Inc.)
Risperidone (Orally Disintegrating) 4 mg (Mylan Pharmaceuticals Inc.)
Risperidone (Orally Disintegrating) 0.5 mg (Zydus Pharmaceuticals)
Risperidone (Orally Disintegrating) 1 mg (Zydus Pharmaceuticals)

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[4] https://www.fda.gov/Drugs/InformationOnDrugs/ucm113978.htm

[5] https://www.drugs.com/inactive/dimethylaminoethyl-methacrylate-butyl-methacrylate-methyl-methacrylate-copolymer-468.html

Thiola 100 mg (Mission Pharmacal Company)
Tranexamic acid 650 mg (Watson Laboratories, Inc.)
Venlafaxine Hydrochloride Extended Release 37.5 mg (Dr. Reddy's Laboratories Ltd.)
Venlafaxine Hydrochloride Extended Release 75 mg (Dr. Reddy's Laboratories Ltd.)
Venlafaxine Hydrochloride Extended Release 150 mg (Dr. Reddy's Laboratories Ltd.)
Zolpidem tartrate extended-release 6.25 mg (Watson Laboratories, Inc.)
Zolpidem tartrate extended-release 12.5 mg (Watson Laboratories, Inc.)

These represent only a tiny fraction of the drugs on the market. To provide a conservative estimate of the exposure from pharmaceutical use, we adopt the procedure used in the EFSA (2010) assessment of the copolymer. The average level of copolymer usage listed in the FDA IID is approximately 34 mg/oral dosage form. By comparison, EFSA considered usage at 30 and 100 mg/tablet or capsule. EFSA also assumed that adults consumed 6 tablets or capsules coated with the copolymer per day, and 2/day for children. Considering the small number of products identified in the IID and at Drugs.com as containing the copolymer, it seems unlikely that many individuals would consume as many as 6 capsules or tablets containing the copolymer per day. It is, therefore, reasonable to conclude that 6 capsules/day, each containing 30 mg of copolymer (a total of 180 mg/day) represents a reasonable worst case consumption level for adults from pharmaceutical products (60 mg/day for children).

By comparison, the intake from the proposed GRAS uses of the copolymer will vary depending upon which micronutrients are included and at what fraction of their RDA or AI. If all 12 micronutrients discussed in the GRAS notice were included at 100% of their RDA or AI, the total intake of the copolymer would be 2.3 g/day. More likely, usage would involve just Vitamin A, folic acid, and iron, resulting in an intake of the copolymer of 0.79 g/day. When combined with the conservative estimate of intake from pharmaceutical use, this would result in a total intake of approximately 0.97 g/day. For a 70 kg person, that intake would provide an MOE of 144. While the MOE would be smaller with more micronutrients encapsulated, even with all of the listed micronutrients at 100% of their RDA/AI, the MOE would still be more than 55-fold, which is adequate for a polymer like this that shows no adverse effects at any dose tested, including the six-month rat study with doses up to 2,000 mg/kg/day, which is double the usual OECD limit dose for repeat-dose toxicity studies.[6] The absence of any signs of toxicity with this extreme dose, and the very low levels of low molecular-weight components in the copolymer ensure that no adverse effects would be expected in humans consuming the proposed use levels of the copolymer.

15. The methacrylate copolymer is intended to encapsulate micronutrients, which will be released in the gut. When the methacrylate copolymer is in contact with gastric fluids, how will the methacrylate copolymer release the micronutrients? Will the methacrylate copolymer break down in the gastric fluids? If so, what are the likely byproducts from interaction with the gastric fluids?

    Due to the stable polyethylenic carbon backbone, a degradation of the polymer chains e.g. by hydrolysis can be excluded and has never been observed under normal storage and handling conditions. In acidic aqueous solutions basic methacrylate copolymer dissolves to give a clear to slightly cloudy solution. Therefore, it is concluded that the copolymer dissolves in the gastric fluid without breaking down.

    This is in line with the absorption study, which had been performed by applying radioactive labeled basic methacrylate copolymer (Eisele et al. 2011, Annex 4.1). After oral application the copolymer was not significantly absorbed (less than 0.02% of the administered dose) and was primarily excreted with the faeces, mostly occurring in the 48 h following dosing. This is basically due to the

[6] http://www.oecd-ilibrary.org/environment/test-no-408-repeated-dose-90-day-oral-toxicity-study-in-rodents_9789264070707-en

high molecular weight of the copolymer and the fact that no break down occurs. Both recovery rate and excretion time allow the conclusion that the polymer remains intact. A theoretical degradation of the backbone would result in smaller compounds which can be absorbed and metabolized by the body, which in turn would cause reduced recovery rates or longer body passage times of the radioactive labeling than observed, at least for the degraded portion of the substance. However, the observed data did not indicate any absorption by the body and thus any degradation.

16. Please discuss if there are any degradation products formed (LMWOs or monomers) in the gastro-intestinal tract when the methacrylate copolymer is ingested. If yes, please identify them and discuss how they are metabolized and why they would not raise any safety concerns.

    As indicated above for question 15, no degradation or break down occurs in the gastrointestinal tract.

    We would also like to point out that the level of residual monomers in the copolymer are sufficiently low that they present no health hazard when the copolymer is ingested. EFSA (2010) noted:

    > "Using the worst case exposure, the calculated exposure to the residual monomers (MMA, BMA, and DMAEMA) present in the substance would be less than 50 µg/kg bw/day for adults and less than 32 µg/kg bw/day for children. The Panel noted that these figures were significantly below the group TDI established by the SCF of 0.1 mg/kg bw/day for MMA and BMA expressed as methacrylic acid. For DMAEMA, the SCF noted that residues of this substance could not be detected (at LOD: 10 µg/kg), suggesting that DMAEMA is not labile from the polymer matrix."

    With the copolymer intake level noted in the response to question 14 (2.35 g/day) when used on all 12 micronutrients listed in Table 3 of the GRN, plus 180 mg/day from pharmaceutical use, the maximum daily dose of MMA + BMA would be 0.08 mg/kg/day for a 60 kg adult, which is below the SCF group TDI for these methacrylate monomers. With the more likely usage involving just vitamin A, folic acid, and iron, the resulting maximum intake of the copolymer would be 0.79 g/day + 180 mg/day from pharmaceutical use, resulting in a maximum daily dose of MMA + BMA of 0.016 mg/kg/day. Furthermore, these estimates are based on the upper specification limit on monomer content (1,000 ppm each). Based on the analysis of four representative lots described in Table 1 of the GRN, the average concentration of MMA, BMA, and DMAEMA was just 14 ppm, 93 ppm, and 253 ppm, respectively, a total monomer concentration less than one-eighth of the specification limit, with a correspondingly lower potential exposure level, and greater margin of safety. More importantly, as discussed by EFSA (2010, 2016), DMAEMA does not migrate from the copolymer to food materials in contact with it, as demonstrted by the fact that it is not detectable at a detection limit of 0.01 mg/kg food (EFSA 2010, 2016). Since the copolymer is proposed for use only in coating micronutrients whose consumption is in the range of micrograms or milligrams/day, the quantity of DMAEMA available for absorption will be trivially low.

17. Please provide the entire citation for any references discussed in the notice. In several cases a partial reference was given, but the full reference could only be found buried within another citation. For example, on page 14 "Daniel and Cooper, 1979" is cited, but the full reference could only be found by searching a second reference, "Eisele, et al. 2011."

    Full references of documents cited in GRAS Notice as "as cited in Eisele et al. (2011):

    Bien, E., 2003. 28-Day oral toxicity study of Eudragit E PO in the dog. Harlan Bioservice for Science, Walsrode, Germany. Report No. 20-2-0145-02. Unpublished report, as cited in Eisele et al. (2011).

    Cinelli, S., 2000. In vivo micronucleus assay with Eudragit E PO. Research Toxicology Centre, Rome, Italy. Report No. 7782-M-02500. Unpublished report, as cited in Eisele et al. (2011).

    Daniel, J.W., Cooper, I.V., 1979. [14C] – Eudragit-E-100: The excretion and Tissue Distribution of Radioactivity after Oral Administration to Rats Life Science Research, Stock, Essex, UK. Report No. 79/RGC024/278. Unpublished report, as cited in Eisele et al. (2011).

Kaneto, H., 1970. Acute Toxicity of Eudragit E. Department of Pharmacology, Nagasaki University, Japan, Unpublished report, as cited in Eisele et al. (2011).

Kinkel, H. J., 1966. Determination of acute oral toxicity in rats. Battelle-Institute, Frankfurt (Main), Germany. Unpublished report, as cited in Eisele et al. (2011).

Leuschner, F., 1968. Experiments to determine the effect of 2577G and 2697 on pregnant rats and their foetuses. Laboratory for Pharmacology and Toxicology, Hamburg, Germany. Unpublished report, as cited in Eisele et al. (2011).

Leuschner, F., 1970. The acute toxicity of Preparation 2787 on oral administration to rats. Laboratory for Pharmacology and Toxicology, Hamburg, Germany. Unpublished report, as cited in Eisele et al. (2011).

Leuschner, F., 1973 6-Month toxicity of 2787 B in Sprague-Dawley rats with administration in the feedstuff. Laboratory for Pharmacology and Toxicology, Hamburg, Germany. Report No. 100692. Unpublished report, as cited in Eisele et al. (2011).

Mager, D., 2001. In vitro – 3T3 NRU Phototoxicity Test with Eudragit EPO. Bioservice Scientific Laboratories, Planegg, Germany, Report No. 001972A. Unpublished report, as cited in Eisele et al. (2011).

Miltenburger, H.G., 1985. Salmonella typhimurium/liver microsome test (Ames test) Laboratory for Mutagenicity Testing, Technical University of Darmstadt, Germany. Report No. LMP 124C. Unpublished report, as cited in Eisele et al. (2011).

Wollny, H.-E., 2000. Cell mutation assay at the thymidine kinase locus (TK+/-) in mouse lymphoma L5178Y cells with Eudragit E PO. RCC Cytotest Cell Research, Rossdorf, Germany, Report No. 663900. Unpublished report, as cited in Eisele et al. (2011).

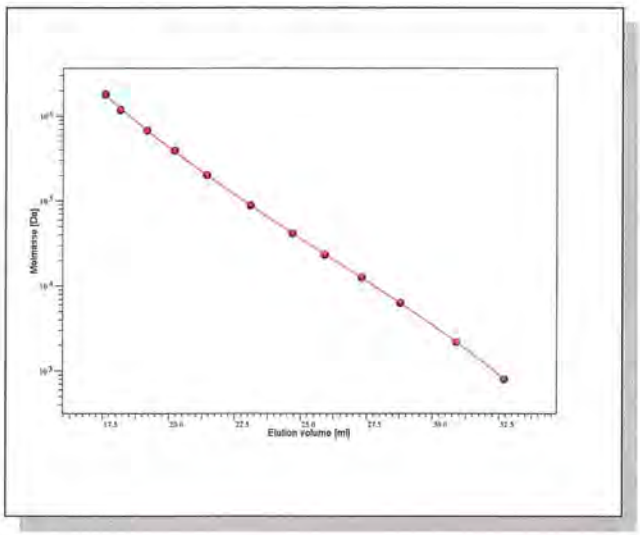
18. Figures 1 and 2 are indicated as confidential in the notice. Any information that bears on safety cannot be confidential in a GRAS notice per the general recognition requirement for GRAS. Since these figures were provided to FDA for review, please include a discussion explaining how these figures do not bear on safety and are not necessary to establish the general recognition of safety for your methacrylate copolymer.

    Figures 1 and 2 provide information on the efficacy of the copolymer for its proposed use (protecting micronutrients from degradation under conditions of prolonged heating or light exposure, and release of those micronutrients under the acidic conditions of the stomach), and do not directly bear on the safety of the copolymer. They are, therefore, not necessary to establish the general recognition of safety of the copolymer.

Certificate of Analysis

Kit type: ReadyCal-Kit Poly(methyl methacrylate)
Part No: PSS-mmkitr1
Lot No: mmkitr1-06n

GPC/SEC - Calibration Curve

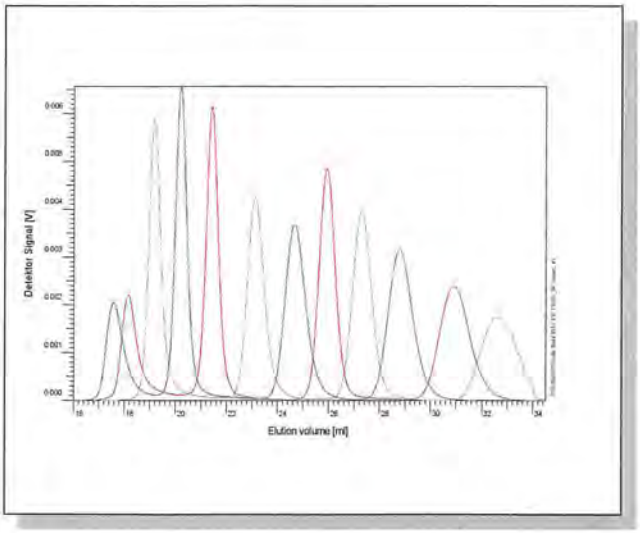


GPC/SEC - Calibration Table

Elution volume [ml]	Mp [Da]	Polymer Lot No:	Deviation [%]
17,5924	1600000	mm7091n	-2,5689
18,1582	1190000	mm300403	4,1763
19,1710	675000	mm24081n	0,5438
20,2154	392000	mm25081	-3,0458
21,4246	201000	mm240805	0,5849
23,1178	88500	mmg060808	-0,6775
24,6930	41400	mmg1079	1,2063
25,9242	23500	mmg15087	1,1006
27,3145	12600	mmg210603	-0,4332
28,7862	6370	mmg201102	-0,9710
30,9072	2200	mmg270704	0,0996
32,7102	800	mmg121202	0,1753

Note:
Mp = Molar mass at the peak maximum

GPC/SEC - Polymer Overlay



GPC/SEC - Calibration Conditions

Solvent	Tetrahydrofuran
Flow rate	1,00 ml/min
Precolumn [8 x 50 mm]	PSS SDV 5µm
Columns [8 x 300 mm]	PSS SDV 5µm 10e3Å / 10e5Å / 10e6Å
Temperature	23 °C
Inject volume	20 µl
Internal standard	Toluene at 37,19 ml
Data Acquisition Software	PSS WinGPC
Calibration by	S.Fugmann

Fit quality

Fit-type	PSS Poly 5
R	0,999973

Storage: Store the tightly recapped polymer standards in a dry, dark, cool area; e.g. a refrigerator (4 °C).
Expiration date: 5 years after purchase date provided standard is stored as described above.
Purchase date: 2012-02-16

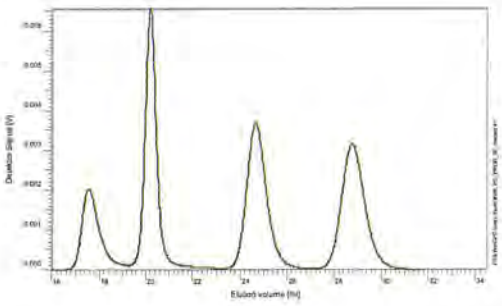
Manufacture and control according to PSS method of analysis

Dr. T. Hofe
production director

PSS Polymer Standards Service GmbH
In der Dalheimer Wiese 5 D-55120 Mainz
Tel.: +49 (0) 6131-96239-0 Fax: +49 (0) 6131-96239-11
Email: info@polymer.de www.polymer.de

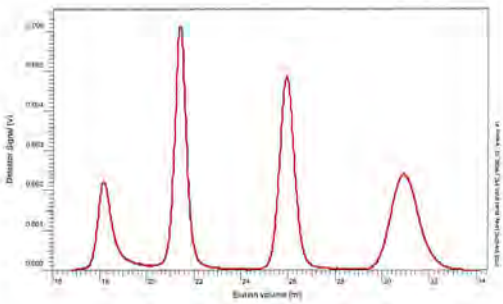
PSS Polymer Standards Service - USA Inc
160 Old Farm Rd, Suite A Amherst, MA 01002
Phone: +1 413-835-0265 Fax: +1 413-835-0354
Email: pssusa@pssgpcshop.com www.pssgpcshop.com

Product: ReadyCal-Kit Poly(methyl methacrylate)
Part No: PSS-mmkitr1
Lot No: mmkitr1-06n



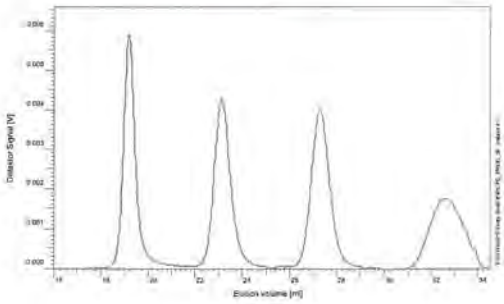
Colour code: Vial – clear / without label Cap – green

Mp [Da]	Mw [Da]	Mn [Da]	Mass [mg]	Lot No:
1 600 000	1 430 000	1 250 000	0.75*	mm7091n
392 000	380 000	372 000	1.50	mm25081
41 400	40 300	38 100	1.50	mmg1079
6 370	6 270	5 880	1.50	mg201102



Colour code: Vial – clear / without label Cap – red

Mp [Da]	Mw [Da]	Mn [Da]	Mass [mg]	Lot No:
1 190 000	1 100 000	1 010 000	0.75*	mm300403
201 000	199 000	195 000	1.50	mm240805
23 500	23 200	22 500	1.50	mmg15087
2 200	2 180	1 980	1.50	mmg270704



Colour code: Vial – clear / without label Cap – white

Mp [Da]	Mw [Da]	Mn [Da]	Mass [mg]	Lot No:
675 000	655 000	634 000	1.50	mm24081n
88 500	86 700	83 700	1.50	mmg060808
12 600	12 500	12 100	1.50	mmg210603
800	831	730	1.50	mmg121202

For exact determination of sample concentration, we recommend to add the solvent volume precisely.

Level of eluent	full	half	quarter
Volume of eluent	1.5 ml	0.75 ml	0.375 ml
Concentration	1 g/l resp. 0,5 g/l*	2 g/l resp. 1 g/l*	4 g/l resp. 2 g/l*

Note: Please use suitable caps and septa for high -temperature applications.

PSS Polymer Standards Service GmbH
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55120 Mainz | Germany
Phone +49 6131 96239-0
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160 Old Farm Rd, Suite A
Amherst | MA 01002 | USA
Phone +1 413 835-0265
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E-Mail usa@pss-polymer.com
Web www.pss-polymer.com

Eudragit®
An Evonik product.

Technical Information

EUDRAGIT® E 100, EUDRAGIT® E PO and EUDRAGIT® E 12,5

Specification and Test Methods

Ph. Eur.	Basic Butylated Methacrylate Copolymer
USP/NF	Amino Methacrylate Copolymer - NF
JPE	Aminoalkyl Methacrylate Copolymer E

1 Commercial form

EUDRAGIT® E 100

Solid substance

EUDRAGIT® E 100 is described in the monographs quoted above.

EUDRAGIT® E PO

Solid substance obtained from EUDRAGIT® E 100.

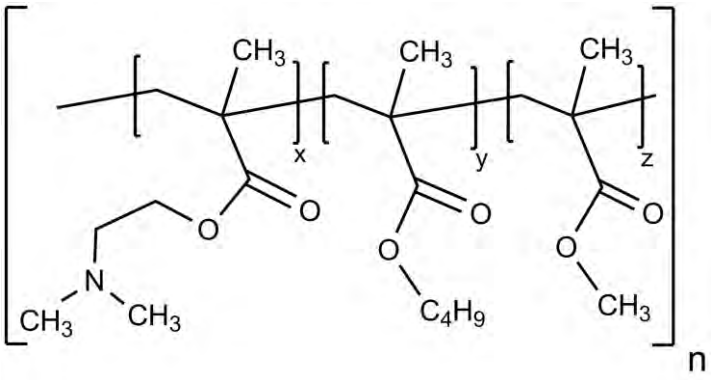
EUDRAGIT® E PO is described in the Ph. Eur. and JPE monographs quoted above.
The polymer conforms to the USP/NF monograph quoted above.

EUDRAGIT® E 12,5

Solution of EUDRAGIT® E 100 with 12.5 % (w/w) dry substance in a mixture of 60 % (w/w) Isopropyl Alcohol Ph. Eur. / USP and 40 % (w/w) Acetone Ph. Eur. / NF.

2 Chemical structure

EUDRAGIT® E 100 is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate with a ratio of 2:1:1.



The monomers are randomly distributed along the copolymer chain. Based on SEC method the weight average molar mass (Mw) of EUDRAGIT® E 100; EUDRAGIT® E PO and EUDRAGIT® E 12,5 is approximately 47,000 g/mol.

3 Characters

Description

EUDRAGIT® E 100: colourless to yellow tinged granules with a characteristic amine-like odour.
EUDRAGIT® E PO: white powder with a characteristic amine-like odour.
EUDRAGIT® E 12,5: light yellow liquid of low viscosity, clear to slightly cloudy with a characteristic odour of the solvents.

Solubility

1 g of EUDRAGIT® E 100 or EUDRAGIT® E PO dissolves in 7 g methanol, ethanol, isopropyl alcohol, acetone, ethyl acetate, methylene chloride or 1 N hydrochloric acid to give clear to slightly cloudy solutions. EUDRAGIT® E 12,5 is mixable with these solvents and with petroleum ether in a ratio of 1:1.

The solid substance is practically insoluble in petroleum ether and water. The polymer is precipitated from EUDRAGIT® E 12,5 when mixed with water in a ratio of 1:1.

4 Tests

Test solution

Either EUDRAGIT® E 12,5 is used for the Test solution, or a corresponding solution of EUDRAGIT® E 100 or EUDRAGIT® E PO: 12.5 % (w/w) dry substance is dissolved in a mixture of 60 % (w/w) isopropyl alcohol and 40 % (w/w) acetone.

Particle size

EUDRAGIT® E PO: Dv50 < 50 µm
The particle size is determined by laser light diffraction according to Ph. Eur. 2.9.31 / light diffraction measurement USP <429>.

Film formation

When the Test solution is poured onto a glass plate, a clear film forms upon evaporation of the solvents.

Dry substance / Residue on evaporation

EUDRAGIT® E 100 / EUDRAGIT® E PO: not less than 98.0 %
The test is performed according to Ph. Eur. 2.2.32 d.
1 g is dried in an oven for 3 hrs at 110°C.

EUDRAGIT® E 12,5: 11.9 - 13.1 %
The test is performed according to Ph. Eur. 2.2.32 d. 20 g quartz sand are mixed with 1 g of the solution and dried in an oven for 5 hrs at 110°C.

Loss on drying

EUDRAGIT® E 100 / EUDRAGIT® E PO: max. 2.0 % according to "Dry substance / Residue on evaporation".

Assay

Dimethylaminoethyl (DMAE) groups on dry substance (DS): 20.8 - 25.5 %
Alkali value: 162 – 198 mg KOH per g DS

The assay is performed according to Ph. Eur. 2.2.20 "Potentiometric titration" or USP <541>. 0.2 g EUDRAGIT® E 100 / EUDRAGIT® E PO or 1.6 g EUDRAGIT® E 12,5 are dissolved in 96 ml glacial acetic acid and 4 ml water. 0.1 N perchloric acid is used as the titrant. 1 mL of 0.1 N perchloric acid is equivalent to 7.21 mg of dimethylaminoethyl groups.

The alkali value (AV) states how many mg KOH are equivalent to the basic groups contained in 1 g dry substance (DS).

$$\text{AV (mg KOH / g DS)} = \frac{\text{ml 0.1 N } HClO_4 \cdot 561}{\text{sample weight (g)} \cdot \text{DS (\%)}}$$

DMAE groups (%) = AV (mg KOH / g DS) · 0.1286

JPE: EUDRAGIT® E 100 / EUDRAGIT® E PO: 4.0 - 6.0 % Nitrogen on dry substance
The test is performed according to JP method “Nitrogen determination”.

Colour

Absorbance (A): max. 0.300
The test is performed according to Ph. Eur. 2.2.25 or USP monograph.
The yellow colour of the test solution is determined against water at 420 nm in a 1 cm cuvette.

Viscosity / Apparent viscosity

3 - 6 mPa · s
The viscosity of the Test solution is determined by means of a Brookfield viscometer (UL adapter / 30 rpm / 20°C).
The test is performed according to Ph. Eur. 2.2.10 or USP <912> method II.

Viscosity / Kinematic viscosity

JPE: EUDRAGIT® E 100 / EUDRAGIT® E PO: 2.5 - 5.5 mm^2 / s
The test is performed according to the JPE monograph.

Refractive index

n_D^{20}: 1.380 - 1.385
The refractive index of the Test solution is determined according to Ph. Eur. 2.2.6.

Relative density

d : 0.811 - 0.821
The relative density of the Test solution is determined according to Ph. Eur. 2.2.5.

5 Purity

Sulphated ash / Residue on ignition

Max. 0.1 %
The test is performed according to Ph. Eur. 2.4.14 or USP <281>.
1 g EUDRAGIT® E 100, EUDRAGIT® E PO or EUDRAGIT® E 12,5 is used for the test.

Heavy metals

Max. 20 ppm
The test is performed according to Ph. Eur. 2.4.8 method C or USP <231> method II.
1 g EUDRAGIT® E 100, EUDRAGIT® E PO or EUDRAGIT® E 12,5 is used for the test.

Arsenic

JPE: EUDRAGIT® E 100 / EUDRAGIT® E PO: max. 2 ppm
The test is performed according to JP Method 3.
1.0 g EUDRAGIT® E 100 or EUDRAGIT® E PO is used for the test.

Monomers

EUDRAGIT® E 100 / EUDRAGIT® E PO total of monomers: < 2500 ppm
Butyl methacrylate: < 1000 ppm
Methyl methacrylate: < 500 ppm
Dimethylaminoethyl methacrylate: < 1000 ppm

EUDRAGIT® E 12,5: total of monomers max. 0.04 %

The test is performed according to the Ph. Eur., USP/NF or JPE monograph on 1 g EUDRAGIT® E 100 / EUDRAGIT® E PO or 8 g EUDRAGIT® E 12,5.

Residual Solvents

EUDRAGIT® E 100 / EUDRAGIT® E PO:
Contains small amounts of 2-Propanol with concentration below 0.5 %.
Small amounts of Methanol may be detectable in the product within the minimum stability period. The concentration remains below 0.1 %.
Small amounts of n-Butanol may be detectable in the product within the minimum stability period. The concentration remains below 0.5 %.
The test is performed according to Ph. Eur. 2.4.24 sample preparation 2 or USP <467> for water-insoluble substances.

EUDRAGIT® E 12,5:
The product is a solution of polymer in 2-Propanol and Acetone.

20
20

Microbial count

Total aerobic microbial count (TAMC): max. 10^3 CFU / g
Total combined yeasts and moulds count (TYMC): max. 10^2 CFU / g
(Acceptance criteria according to Ph. Eur. 5.1.4 / USP <1111>)
The test is performed according to Ph. Eur. 2.6.12 or USP <61>.

6 Identity testing

First identification

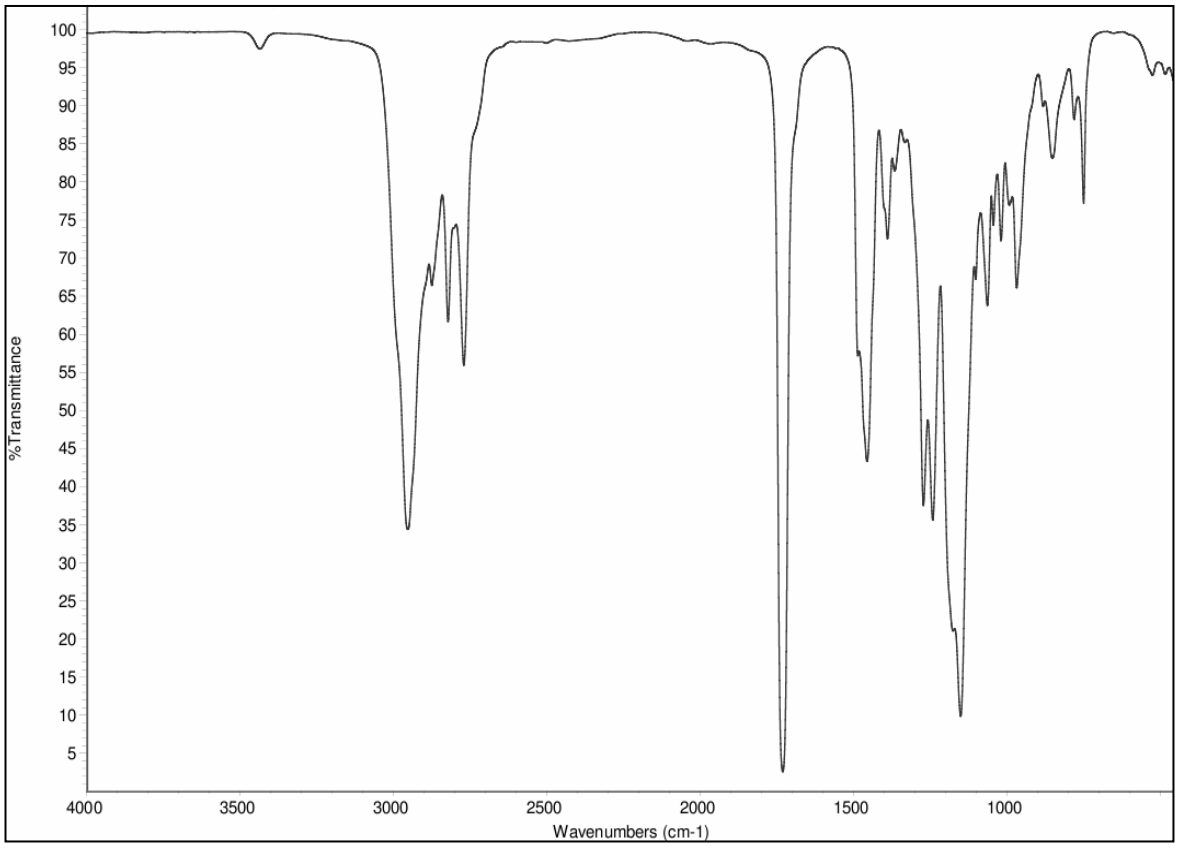
The material must comply with the tests for "Assay" and "Viscosity / Apparent viscosity."

Second identification

IR spectroscopy on a dry film approx. 15 µm thick. To obtain the film, a few drops of the Test solution are placed on a crystal disc (KBr, NaCl) and dried in vacuo for about 2 hours at 70°C.

The figure on page 5 shows the characteristic bands of the ester groups at 1,150 - 1,190, 1,240 and 1,270 cm^{-1}, as well as the C = O ester vibration at 1,730 cm^{-1}. In addition, CH_X vibrations can be discerned at 1,385, 1,450 - 1,490 and 2,950 cm^{-1}. The absorptions at 2,770 and 2,820 cm^{-1} can be assigned to the dimethylamino groups.

EUDRAGIT® E 100 / EUDRAGIT® E PO / EUDRAGIT® E 12,5



7 Detection in dosage forms

The dosage forms are extracted using the solvents listed under “Solubility,” if necessary after crushing. Insoluble substances are isolated by filtration or centrifugation. The clear filtrate is boiled down and the residue identified by IR spectroscopy.

8 Storage

EUDRAGIT® E 100: Protect from warm temperatures (USP, General Notices). Protect from moisture. Any storage between 8°C and 25°C fulfils this requirement. EUDRAGIT® E 100 tends to form lumps at warm temperatures (≥ 30°C). This has no influence on the quality. The lumps are easily broken up again.

EUDRAGIT® E PO: Store at temperatures up to 25°C. Protect from moisture. Any storage between 8°C and 25°C fulfils this requirement. Temperatures above 25°C will cause caking of EUDRAGIT® E PO.

EUDRAGIT® E 12,5: Protect from warm temperatures (USP, General Notices). Store in tightly closed containers.

9 Stability

Minimum stability dates are given on the product labels and batch-related Certificates of Analysis. Storage Stability data are available upon request.

July 2015

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Evonik. Power to create.

XXII. Acryl- und Methacrylsäureesterpolymerisate und deren Mischpolymerisate sowie Mischungen mit Polymerisaten

Stand vom 01.01.2010

Gegen die Verwendung von Acrylsäure- und Methacrylsäurepolymerisaten und deren Mischpolymerisaten sowie Mischungen mit Polymerisaten bei der Herstellung von Bedarfsgegen-
ständen im Sinne von § 2 Abs. 6 Nr. 1 des Lebensmittel- und Futtermittelgesetzbuches bestehen keine Bedenken, sofern die Bedarfsgegenstände sich für den vorgesehenen Zweck eignen und folgende Voraussetzungen erfüllt sind:

1. Hinsichtlich der Verwendung der Ausgangsstoffe für Acrylsäure- und Methacrylsäure-polymerisate und deren Mischpolymerisate gelten die Bestimmungen der Verordnung (EU) Nr. 10/2011.

Die im Folgenden gegebene Bewertung bezieht sich auf Polymere aus den folgenden monomeren Ausgangsstoffen:

a) Ester der Methacrylsäure und Acrylsäure mit
einwertigen und mehrwertigen aliphatischen gesättigten Alkoholen C_1-C_{18}, soweit sie in der Positivliste der Verordnung (EU) Nr. 10/2011 berücksichtigt sind
Benzylalkohol
Dimethylaminoethylmethacrylat

b) Styrol und α-Methylstyrol

c) Acrylsäure
Methacrylsäure
Maleinsäure
Itaconsäure
Amide der Acryl- und Methacrylsäure
N-Methylolamide der Acryl- und Methacrylsäure
Von den genannten Monomeren dürfen insgesamt höchstens 8 % verwendet werden. Sofern jedoch eine Vernetzung durch nachträgliche Behandlung sichergestellt ist, darf der Anteil dieser Monomeren bis zu höchstens 25 % betragen.
Der Anteil an Säureamiden, die eine Verbesserung der Wasserlöslichkeit und Emulgier fähigkeit bewirken, darf 12 % - bezogen auf das Gesamtpolymere - nicht überschreiten.

d) Acrylnitril und Methacrylnitril

e) Butadien

f) Vinylidenchlorid

g) Allylester der Methacrylsäure

Der Anteil an Estern der Acrylsäure und Methacrylsäure muss überwiegen.

2. Neben den gemäß der Verordnung (EU) Nr. 10/2011 bereits zugelassenen Additiven unter den dort genannten Beschränkungen dürfen bei der Herstellung und Aufarbeitung der Polymerisate nur die im folgenden aufgeführten Fabrikationshilfsmittel verwendet werden. Deren Reste und Umwandlungsprodukte dürfen sowohl im unverarbeiteten Rohstoff als auch im Fertigerzeugnis nur in den im folgenden angegebenen Mengen enthalten sein:

a) Reste der Umwandlungsprodukte folgender Katalysatoren:

Azodiisobuttersäurenitril Benzoylperoxid Peroxide von geradzahligen gesättigten einwertigen aliphatischen Carbonsäuren der Kettenlänge C_8-C_{18} Di-isopropyl-percarbonat Acetylcyclohexansulfonylperoxid Alkyl(C_1-C_4)ester der Azodiisobuttersäure tert-Butylperbenzoat tert-Butylperpivalat tert-Butylperoxy-(2-ethylhexanoat) Cumylhydroperoxid	insgesamt höchstens 0,2 %
tert-Butyl-per-3,5,5-trimethylhexanoat tert-Butylperneodecanoat Monotert-butylperoxymaleinat	insgesamt höchstens 0,5 %

2,2-Bis-(tert-butylperoxy)butan, höchstens 0,3 %

b) Reste folgender Emulgatoren:

Dinonylphosphat, höchstens 0,1 % Alkylsulfonate C_{12}-C_{20} Polyvinylalkohol (Viskosität der 4%igen wässrigen Lösung bei 20 °C mindestens 20 cP) Dodecyliertes Diphenylether-disulfonsaures Natrium, höchstens 1,5 %, jedoch nur für Polymere, die zur Herstellung von Mischpolymeren gemäß Nr. 2 e der Empfehlung II für weichmacherfreies Polyvinylchlorid und seine Mischpolymerisate verwendet werden. Der Anteil an Polymeren gemäß dieser Empfehlung in den Mischpolymerisaten gem. Empfehlung II darf 5 % nicht überschreiten.	insgesamt höchstens 2,5 %

c) Polymerisationsregler[1]:
Mercaptoethanol
Mercaptoessigsäure, sowie deren Ester mit ein- und mehrwertigen aliphatischen Alkoholen
Normale und tert. Mercaptane der Kettenlänge C_{10}-C_{14}
Methyl-3-mercaptopropionat

3. Der Gehalt an flüchtigen organischen Bestandteilen im unverarbeiteten Rohstoff und im Fertigerzeugnis darf 0,5 % nicht überschreiten[2].

4. Die Fertigerzeugnisse dürfen keine positive Reaktion auf Peroxide geben[3].

[1] Diese Stoffe werden bei der Polymerisation vollständig in das Polymerisat eingebaut.
[2] Die Bestimmung ist nach der in der 19. Mitteilung über die Untersuchung von Kunststoffen bekanntgegebenen Methode durchzuführen, Bundesgesundheitsblatt 14 (1971) 265.
[3] s. 58. Mitteilung zur Untersuchung von Kunststoffen, Bundesgesundheitsblatt 40 (1997) 412

Eudraguard
An Evonik product.

Technical Information

EUDRAGUARD® protect

Specification

EU food additive list, Annex II (Regulation (EC) No 1333/2008)	E 1205, Basic methacrylate copolymer (in food category 17.1, Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms, at a level of up to 100,000 mg/kg (10 %))
GRAS status (according to Section 201(s) of the FDC Act)	Self affirmed (June 2012), at a level of up to 10 wt % in unit dosage

The analytical parameters and limits are compliant with the specification for E 1205, Basic methacrylate copolymer, as listed in Regulation (EU) No. 231/2012.

1 Commercial form / Description

Solid substance: white powder

2 Definition

EUDRAGUARD® protect is a cationic copolymer based on dimethylaminoethyl methacrylate, butyl methacrylate, and methyl methacrylate with a ratio of 2:1:1.

Chemical name
Poly(butyl methacrylate-*co*-(2-dimethylaminoethyl)methacrylate-*co*-methyl methacrylate) 1:2:1

Chemical formula
Poly[(CH_2:$C(CH_3)CO_2(CH_2)_2N(CH_3)_2$)-co-($CH_2$:$C(CH_3)CO_2CH_3$)-co-($CH_2$:$C(CH_3)CO_2(CH_2)_3CH_3$)]

The weight average molar mass (Mw) of EUDRAGUARD® protect determined by GPC is approximately 47,000 g/mol.

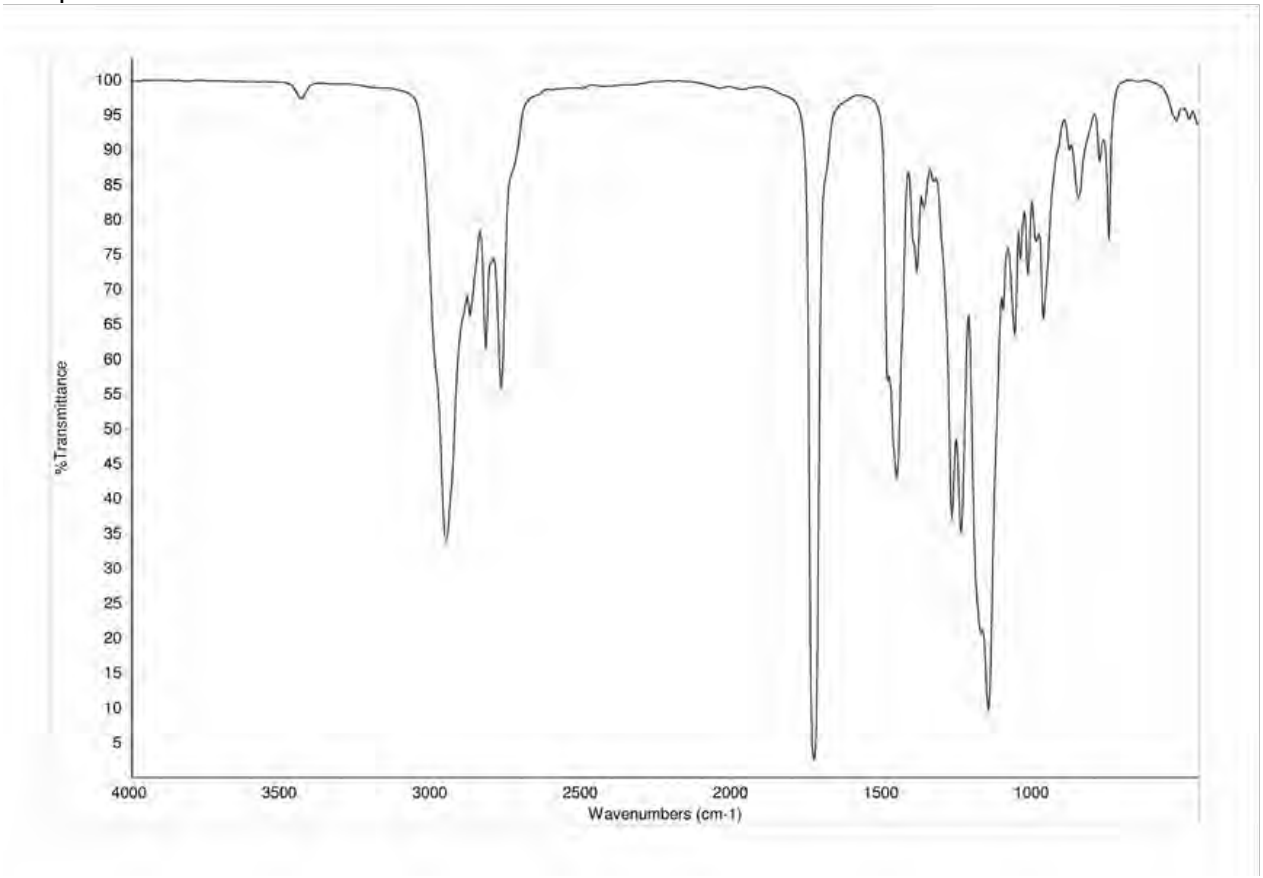
Particle size

< 50 µm	at least 95 %
< 20 µm	at least 50 %
< 3 µm	not more than 10 %

Assay
Dimethylaminoethyl (DMAE) groups on dry substance (DS): 20.8 - 25.5 %

3 Identification

IR Spectroscopy
complies



Viscosity of the test solution
3 - 6 mPa·s

Refractive index of the test solution
n_D^{20}: 1.380 - 1.385

Solubility

1g dissolves in 7 g methanol, ethanol, propan-2-ol, dichloromethane, aqueous hydrochloric acid 1N. Not soluble in petroleum ether.

4 Purity

Loss of drying
NMT 2.0 %

Alkali value
162 – 198 mg of dried substance

Sulphated ash
NMT 0.1 %

Residual Monomers

Butyl methacrylate:	< 1000 mg/kg
Methyl methacrylate:	< 1000 mg/kg
Dimethylaminoethyl methacrylate:	< 1000 mg/kg

Residual Solvents

Propan-2-ol	< 0.5 %
n-Butanol	< 0.5 %
Methanol	< 0.1 %

Heavy Metals

Arsenic	NMT 1 mg/kg
Lead	NMT 3 mg/kg
Mercury	NMT 0.1 mg/kg
Cadmium	NMT 1 mg/kg

5 Storage

Store at temperatures up to 25°C. Protect from moisture. Temperatures above 25°C will cause caking of EUDRAGUARD® protect.

6 Stability

Minimum stability dates are given on the product labels and batch-related Certificates of Analysis.

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EVONIK
POWER TO CREATE

Request for a modification of the specification of the food additive Basic methacrylate copolymer, E 1205

– Public summary –

Within the meaning of Regulation (EC) No 1331/2008 of the European Parliament and of the Council establishing a common procedure for food additives, food enzymes and food flavourings

Submitted by EVONIK Industries AG,

64293 Darmstadt, Germany

Date of submission: November 21, 2014

Public Summary

With date of August 20, 2008 Evonik Röhm GmbH submitted a dossier requesting the authorization of a new food additive Basic methacrylate copolymer within in the meaning of Council Directive 89/107/EEC. This dossier was carefully evaluated by EFSA and a scientific opinion was published by the EFSA September 2010 (Reference 02, Scientific Opinion on the use of Basic Methacrylate Copolymer as a food additive of 8 September 2010; EFSA Journal 2010; 8(2):1513). As a result the authorzation was granted for Basic methacrylate coplymer in 2012 by the EU commission and the number E 1205 was assigned. E 1205 became listed in Annex II to Regulation (EC) No 1333/2008 and a specification for E 1205 was defined in COMMISSION REGULATION (EU) No 231/2012 of 9 March 2012, and updated with COMMISSION REGULATION (EU) No 816/2013 of 28 August 2013.

With this submission Evonik Industries AG, the legal successor of Evonik Röhm GmbH requests for a modification of the specification of E 1205.

This request suggests for two modifications in the specification of Basic methacrylate copolymer:

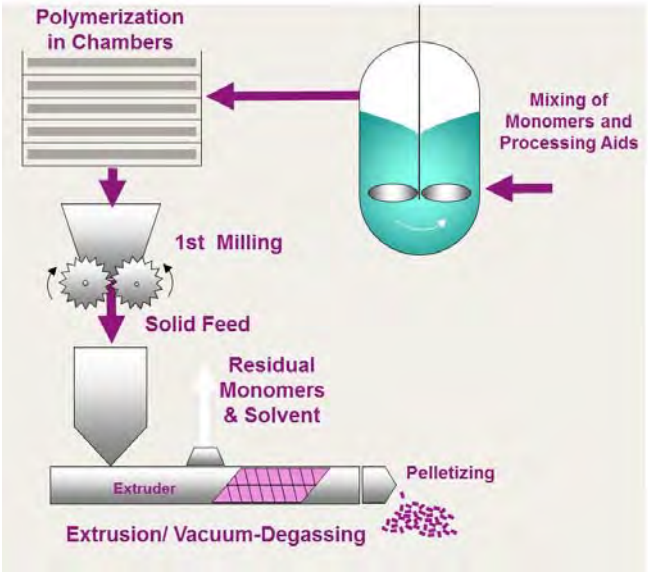
1. A modification of the definition, with regard to the short description of the manufacturing process
2. A modification of the definition, with regard to particle size of powder.

The modification request results from

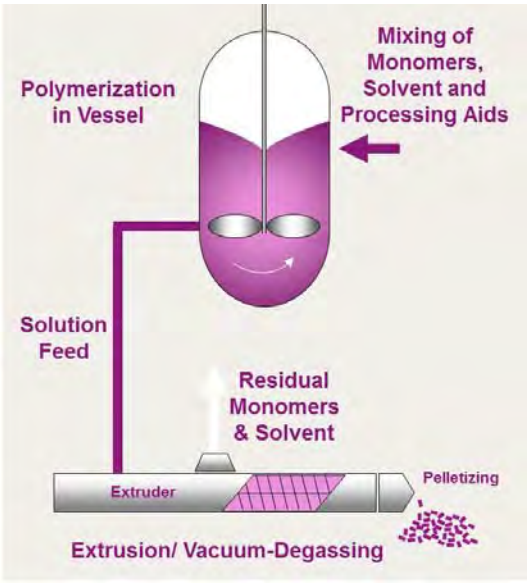
1. A modernization of the manufacturing process of Basic methacrylate copolymer as lined out below and described in detail in Chapter 4 of the submission; and
2. A thorough review of the specification of the particle size. This review revealed that the current specification is and was never met by the powder form of Basic methacrylate copolymer. As lined out below in Chapter 3.2.1 of the submission Evonik assumes that the specification was the result of a misinterpretation of data supplied to the commission during the elaboration of this specification.

The manufacturing process of Basic methacrylate copolymer / E 1205 was modified in 2013 from a bulk polymerization process to a solution polymerization process. The bulk polymerization process was developed decades ago, and at that time mainly intended for industrial quality bulk polymers. It was later adapted for minimal compliance with current bulk pharmaceutical excipient guidelines (IPEC GMP) and food manufacturing expectations.

In order to meet current compliance requirements for both pharmaceutical excipients and food additives, Evonik has established a state-of-the-art production facility. The newly installed solution polymerization equipment and process meets quality, regulatory and environmental requirements for the manufacture of food additives as well as for the manufacture of pharmaceutical excipients.



Previous bulk polymerization



Modern solution polymerization

Basic methacrylate copolymer / E 1205 continues to be manufactured by a temperature induced and thermic controlled radical polymerization process of the monomers methyl methacrylate (MMA), butyl methacrylate (BMA) and dimethylaminoethyl methacrylate (DMAEMA, dissolved in 2-propanol). The new solution polymerization process continues to use propan-2-ol as solvent and a free radical donor initiator system. After completion of polymerization, the intermediate product is a viscous polymer solution, which is fed directly into the extruder avoiding open processing. During the extrusion, volatile substances like the solvent propan-2-ol and residual monomers are removed.

In the extrusion process, solid granules of Basic methacrylate copolymer / E 1205 are formed. These granules can be micronized to a powder in a milling step.

As a result of the modernized process the wording of the defintion of Basic methacrylate copolymer has to be adjusted as given in the Table 1.

It is important to note that the essential chemical synthesis of the manufacturing process remains unchanged and is still based on radical polymerization. This applies accordingly to all key product properties of the copolymer. The product from the solution polymerization process meets the existing specifications for E 1205/EUDRAGUARD™ BMC and provides equivalent functionality. This is

confirmed by analytical data from the validation lots that are included in the submission.

As per the particle size of powder, Evonik only observed after the publication of the specification for E 1205 that the COMMISSION REGULATION (EU) No 231/2012 had introduced a limit of <0.1 µm 5.1 – 5.5 % for the powder of Basic methacrylate copolymer / E 1205. This limit seems to be based on data provided by Evonik to by EFSA December 21, 2009 (Annex 01 and Annex 02), however the data were partly misinterpreted. Evonik's evaluation confirmed that this specification is not met and was never met by the commercial product. Actually the current EU specification for E 1205 requests a defined percentage of nanoparticles in the powder. These were in effect neither intended nor observed by Evonik Industries AG. With the submission Evonik provides supporting data in Chapter 3.2.1, and suggests a revised limit for particle size as given in Table 1 below.

Evonik confirms that all other data such as specifictions, characteristics, stability and functionality remain unchanged compared to the first submission of 2008. This is also true for the chapters addressing methods for analysis in food, stability of substance and fate in food, case of need and proposed uses and exposure assessment.

Table 1: Suggested modification to the specification of E 1205

Definition	Basic methacrylate copolymer is manufactured by thermic controlled polymerisation of the monomers methyl methacrylate, butyl methacrylate and dimethylaminoethyl methacrylate, (dissolved in propan-2-ol) by using a free radical donor initiator system. An alkyl mercaptane is used as chain modifying agent. The ~~solid~~ polymer solution is ~~milled (first milling step) and~~ extruded and granulated under vacuum to remove residual volatile components. The granules resulting are commercialized as such or undergo a ~~second~~ milling step (micronisation).
Particle size of powder (when used forms a film)	~~< 50 µm more than 50 %~~ ~~< 0,1 µm 5,1-5,5 %~~ < 50 µm at least 95 % < 20 µm at least 50 % < 10 µm at least 10 %

Eighty pages have been removed in accordance with copyright laws. The removed reference citations with corresponding Annex numbers are:

Annex	Citation
Annex 2.1	Scientific Opinion on the use of Basic Methacrylate Copolymer as a food additive of 8 September 2010; EFSA Journal 2010; 8(2):1513
Annex 3.1	Adler M, Pasch H, Meier C, Senger R, Koban H-G, Augenstein M, Reinhold G, Molar mass characterization of hydrophilic copolymers, 2 Size exclusion chromatography of cationic (meth)acrylate copolymers, e-Polymers 2005, no. 057, 1-11 (2005)
Annex 4.1	Eisels, Characterisation and toxicological behaviour of Basic Methacrylate Copolymer for GRAS evaluation, Regulatory Toxicology and Pharmacology 61(2011) 32-43.
Annex 8.1	European Pharmacopoeia 9.0 p. 1798-1799
Annex 8.3	Aminoalkyl Methacrylate Copolymer E monograph in the official monographs for pharmaceutical excipients
Annex 10.1	The United States Pharmacopeial Convention August 1, 2017 p. 7511
Annex 11.1	COMMISSION REGULATION (EU) No 231/2012 of 9 March 2012
Annex 11.3	Official Journal of the European Union 29.8.2013, L 230/1
Annex 11.5	Safety of the proposed amendment of the specifications for basic methacrylate copolymer (E 1205) as a food additive, EFSA Journal (2016); 14(5):4490; doi: 10.2903/j.efsa.2016.4490
Annex 11.6	Official Journal of the European Union, COMMISSION REGULATION (EU) 2017/324 of 24 February 2017