DEPARTMENT OF HEALTH

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JUL 29 2019

Minnesota Medical Cannabis Program
Petition to Add an Approved Delivery Method

Section A: Petitioner's Information

Name (First, Middle, Last): [redacted]			
Home Address (including Apartment or Suite #): [redacted]			
City: [redacted]		State:	Zip Code: [redacted]
Telephone Number: [redacted]	E-mail Address: [redacted] @VIREOHEALTH.COM		

Section B: Delivery Method You Are Requesting Be Added

Please specify and provide a brief description of the proposed delivery method. Be as precise as possible in describing the delivery method you are requesting be added. *Attach additional pages as needed.*

SEE ATTACHED

DEPARTMENT OF HEALTH

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Section C: Anticipated Benefits from the Proposed Delivery Method

Describe the anticipated benefits from the proposed delivery method and why it is better than currently approved delivery methods. Identify patient populations that do not benefit from current delivery methods
Attach additional pages if needed.

SEE ATTACHED

Section D: How Current Delivery Methods Are Inadequate

Provide information regarding the extent to which the currently approved delivery methods are unable to meet the needs of patients enrolled in the medical cannabis program. *Attach additional pages if needed.*

SEE ATTACHED

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Section E (optional): Scientific Evidence of Support for the Delivery Method

It will strengthen your petition to include evidence generally accepted by the medical community and other experts that addresses the effectiveness of the proposed medical cannabis delivery method and discusses its potential risks and benefits. This includes but is not limited to full text, peer-reviewed published journals or other completed medical studies. Please attach complete copies of any article or reference, not abstracts.

☑ ***I have attached relevant articles.*** ***(check box if you have attached scientific articles or studies)***

Section F (optional): Letters in Support

Attach letters of support from persons knowledgeable about the use of the delivery method with medical cannabis.

☐ ***I have attached letters of support.*** ***(check box if you have attached letters of support)***

Section I: Acknowledgement and Signature

Please Note: Any individually identifiable health information relating to any past, present, or future health condition or health care contained in this petition is classified as a health record under Minnesota Statutes §144.291, and is not subject to public disclosure.

I certify that the information provided in this petition is true and accurate to the best of my knowledge.

[redacted]

SIGNATURE

7/25/19

DATE (mm/dd/yyyy)

DEPARTMENT OF HEALTH

Minnesota Medical Cannabis Program
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To obtain this information in a different format, call:
(651) 201-5598 in the Metro area and (844) 879-3381 in the Non-metro.

FINAL

July 24, 2019

Minnesota Medical Cannabis Program Petition to Add an Approved Delivery Method

Section A: Petitioner's Information

Name: [redacted]

Home Address: [redacted]

Telephone No: [redacted]

Email address: [redacted]@vireohealth.com

Section B: Delivery Method you are requesting Being Added

A water-soluble cannabinoid multiparticulate.

Multiparticulates are commonly used in medication formulation and include powdered mixtures, granules and pellets.

Based on recent FDA guidance, multiparticulates labelled for use on, or mixed in with orally consumable material should have a target size of 2.5mm or less. These formulations are often considered for use as a pediatric medication format solution, however older patients also benefit from their use, such as in treatment of Parkinson's disease, osteoporosis and phenylketonuria, where very specific material formats for oral consumption are required to accommodate the disease process (altered dexterity, altered ability to swallow, altered ability to digest or process certain substances etc.).

Cannabis oil is currently the basis for all delivery methods in Minnesota. Through a variety of processing techniques, it can made into a water-soluble multiparticulate, appearing as coarse grains.

Our methodology uses a proprietary heat and mixing technique to combine cannabis oil extract with isomalt and a natural emulsifier, which can then be cooled and milled into grains with a target size of approximately 0.5-1.5mm, which falls within the FDA guidance.

Because of the unique granule size and use of these natural emulsifiers, the multiparticulate can overcome the ordinary lipophilic tendencies of cannabis oil to allow for increased water solubility and enhanced oral absorption.

This would add a significant new orally-available delivery method, which has distinct advantages for certain patient populations, at a cost similar to already available oral options.

Section C: Anticipated Benefits from the Proposed Delivery Method

Precision Dosing— The increased water solubility of this format creates a more predictable and reproducible response to the medication that is not as dependent or variable on the patient's intake of various lipid containing foods (as current products are). Increased precision and stability of dose effect will enable pharmacists to more quickly and accurately dose oral-format medication in patients using a multiparticulate product.

Most current oral ingestible products contain, at a minimum, an amount of active ingredients around 2.5 mg (cannabinoids). We have heard from some of our patients that they would like to have the capacity to "micro-dose" effectively. "Micro-Dosing" refers to taking a fractional dose of the active medication in order to avoid side effects and titrate more gradually as needed. This is not possible to customize with capsules, softgels or pills, since these products come in specific dose formats intended to provide clinical relief at the full dose contained in each unit.

Tinctures and solutions can theoretically be "micro-dosed", but the liquid amounts in a "micro-dose" are miniscule; too small to easily or accurately be measured out with an oral syringe or small dropper and requiring significant manual dexterity in both cases (which, unfortunately, many of our ill patients do not have).

Additionally, oily liquids cling to the sides of containers and patients are often concerned that small amounts remain on the insides of syringes or other delivery devices, which, especially when dosing very small quantities, can lead to a significant difficulty with or inability to accurately measure out the intended dose.

Multiparticulates, on other hand, can be more easily measured out, dosed and consumed. A precise amount of this granulated cannabis oil extract, packaged in a small, sealed, single micro-dose "stick-pack" could contain, for example, a total amount of 1mg/1mg of THC/CBD. This dose could be rapidly and homogeneously dissolved in 8 oz of tap water. The patient then would be able to take varying, yet precisely dosed aliquots of the liquid to achieve the desired dose.

In this example, if the patient needed a lager dose, they could combine 2 or 3 micro-dose "stick-packs" into the same amount of water before consuming the dose. Dosing algorithms recommended by the pharmacist could be highly tailored to each patient with very precise control over time without uncertainty introduced by malabsorption or residual oil left in a dosing syringe.

Quicker Availability—It is well understood that solubility and gastrointestinal permeability are fundamental to the bioavailability of a medication. Particle size reduction is a recognized strategy to improve solubility. In order to reduce cannabis oil extract "particle" size, our process employs natural emulsifiers and techniques described in pharmaceutical manufacturing of current FDA approved drugs. The resulting increase in water solubility of the lipophilic cannabis oil extract can lead to the faster absorption of the active ingredient, as is typically seen with water soluble substances.

Current oral capsules have a delayed time of onset of up to 90 minutes. Water soluble cannabinoid multiparticulate formats can reduce this onset time as a larger portion of medicine gets absorbed into the blood stream faster. At the same time, absorption of water-soluble material is less affected by other fatty foods or oils in the diet, which can alter how fast and how much lipophilic medication is absorbed (such as all current approved formats).

More rapid, predictable absorption can be helpful in providing quicker symptom relief, but can also reduce the need for adjunctive "breakthrough" symptom delivery formulations, such as vaping or tincture use, which typically have a faster onset of action.

Section D: How Current Delivery Methods are Inadequate

Some children and older adults share difficulty in swallowing typical capsules. Some patients require medication to be administered via a gastrostomy tube. These patients typically have care givers and we have received consistent feedback over time that current available formulations can cause various difficulties with these patient groups.

Current liquid formats cannot be homogeneously dissolved in water and are difficult to administer via gastrostomy tube (which commonly require a water flush after use). The lipophilic solutions can adhere to the tube itself and be difficult to flush. Pressed tablet formulations, though currently not manufactured, would need to be crushed before use in this case, resulting in some likely product loss and a non-uniform "Crushed pill" which is not as predictable in its solubility or absorption.

Patients administered medications through feeding tubes require a multistep process of measuring a dose of solution, instilling it into the tube, and then flushing with water. Dissolving the multiparticulate cannabis medication in a precisely measured amount of water would allow a single step flush procedure. This form of medication dose, alternatively, could be mixed with any of the patient's supplemental feeding liquids necessary for sustenance or hydration.

For patients with limited dexterity, tremors or muscle spasticity, an oral medication option that does not require the potentially difficult task of measuring out small amounts of oral solution would be a significant improvement.

Taste, smell and palatability of medications are major concerns, especially in the pediatric population. Per patient feedback, current alternatives to pills, like solutions, tend to taste oily and bitter due to the cannabis oil itself—even when masked by flavoring.

The isomalt particulate process improves the palatability, as it moderates the oily texture and sensation and alters the product taste to a more palatable isomalt flavor profile.

For the older population, we sometimes have concerns about esophageal retention and increased aspiration risk.

Some patients who require a thick liquid or soft food diet (due to aspiration risk) could have their medication dose easily mixed into the recommended soft foods without adding any undesirable taste sensations. A particulate can be mixed in with whatever diet is medically deemed the safest for the patient, whether it be thickened or soft, based on the swallowing difficulty.

This method of administration would also simplify medication delivery to certain elderly patients, e.g., those with dementia, for whom the act of taking a pill is often distasteful or emblematic of a loss of control.

This medication format is also an established method of administering certain pharmaceuticals to children when they cannot tolerate pills and refuse oral liquids; e.g., Depakote Sprinkles used to treat epilepsy.

Section E: Scientific Evidence in Support for the Delivery Method

Food and Drug Administration (FDA). Guidance for industry size of beads in drug products labeled for sprinkle, 2012. http:// www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM240243.pdf. Accessed 11 Jul 2014.

Khadka P, Ro J, Kim H, et al. Pharmaceutical Particle Technologies: An approach to improve drug solubility, dissolution and bioavailability. Asian J. of Pharm Sci. 2014;9:304-16.

Tissen C, Woertz K, Breitkreutz J, et al. Development of minitablets with 1 mm and 2 mm diameter. Int J Pharm. 2011;416:164–70.

Liu F, Ranmal S, Batchelor H, et al. Patient centered Pharmaceutical Design to improve acceptability of Medicines: Similarities and differences in Pediatric and Geriatric Patients. Drugs 2014:74;1871—89.

Cloyd JC, Kriel RL, Jones-Saete CM, et al. Comparison of sprinkle versus syrup formulations of valproate for bioavailability, tolerance, and preference. J Pediatr. 1992;120:634–8.

Sevilla C, Jimenez Caballero PE, Alfonso V, et al. Current treatments of Alzheimer disease: are main caregivers satisfied with the drug treatments received by their patients? Dement Geriatr Cogn Disord. 2009;28:196–205.

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Guidance for Industry

Size of Beads in Drug Products Labeled for Sprinkle

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2012
CMC
Rev. 1

Guidance for Industry

Size of Beads in Drug Products Labeled for Sprinkle

Additional copies are available from:
Office of Communications
Division of Drug Information, WO51, Room 2201
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druginfo@fda.hhs.gov
www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2012
CMC
Rev. 1

Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Guidance for Industry[1]
Size of Beads in Drug Products Labeled for Sprinkle

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides applicants preparing or submitting new drug applications (NDAs), abbreviated new drug applications (ANDAs), and biologics licensing applications (BLAs) the Center for Drug Evaluation and Research's current thinking on appropriate size ranges for beads[2] in drug products that are labeled to be administered via sprinkling (e.g., capsules or packets containing beads).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Certain drug products that contain beads within a capsule indicate in the labeling that the capsule can be broken and the internal beads can be sprinkled on soft foods and swallowed without chewing as an alternative administration technique. This is particularly common with drug products designed to have extended- or delayed-release characteristics (i.e., the beads are manufactured to release the drug product at different rates). To make certain that the intended product performance is achieved—whether from a capsule that has been broken or from a packet containing beads—it is important to have reasonable assurance that the patient will be able to swallow the beads (uncrushed) with the food with which the beads are mixed without stimulating the urge to chew. Additional assurances may be needed when the label also includes specific language concerning alternate administration via an enteral feeding tube.

[1] This guidance has been prepared by the Office of Pharmaceutical Science in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] For the purposes of this guidance, the term *beads* will be used to describe the component particles in drug products labeled for sprinkle (i.e., beads, granules, pellets, sprinkles, particles, mini-tablets).

III. DISCUSSION

The recommendations in this guidance are based on literature on chewing and swallowing particle size and on Agency experience with NDAs and ANDAs submitted for these dosage forms. This guidance provides the following information related to drug products labeled for sprinkle: (1) appropriate maximum size for the beads, (2) special considerations for sprinkle drug products that include language in labeling concerning alternate administration via an enteral feeding tube, and (3) bioavailability or bioequivalence recommendations.

A. Maximum Bead Size for Drug Products Labeled for Sprinkle

To determine an appropriate maximum bead size, the Agency took two actions. First, the Agency reviewed studies of human mastication, which demonstrated that food is chewed to a median particle size range from 0.82 to 3.04 mm before swallowing.[3,4] Second, we examined currently approved drug products labeled for sprinkle that contain beads up to 2.4 mm and found no recognized safety risks or loss of efficacy associated with the bead size.

Based on this information, the Agency recommends a target bead size up to 2.5 mm with no more than 10 percent variation over this size, to a maximum size of 2.8 mm. The recommended bead size allowances consider the variability and differing manufacturing processes of beads (e.g., pellet versus mini-tablet manufacturing). If the proposed bead size is greater than that recommended in this guidance, the applicant should provide justification for the proposed bead size, including studies demonstrating that the bead can be swallowed without chewing using sprinkle administration in the intended population.

The Agency recognizes the specific importance of a maximum size limit for modified-release products, where unintentional chewing of beads may lead to pharmacokinetic differences, but also believes that maintaining a consistent maximum bead size for all drug products labeled for sprinkle is appropriate. Inadvertently chewing beads labeled for sprinkle may lead to noncompliance with taking medication because of taste, safety issues, and decreased drug product efficacy. The target and maximum bead size recommendations thus apply to all drug products that contain particles that are labeled for sprinkle administration, whether the product has immediate-, delayed-, or extended-release characteristics. Target and maximum bead size, including bead size distribution, can be determined through analytical sieving in accordance with USP <786>[5] or other appropriately validated methods.

The bead size distribution can be provided in the 3.2.P.3.3 (Description of Manufacturing Process and Process Controls) section or 3.2.P.5.1 (Specification) section, and the maximum bead size can be provided in the 3.2.P.1 (Description and Composition of the Drug Product) section or 3.2.P.3.4 (Control of Critical Steps and Intermediates) section of a common technical document (CTD) formatted application.

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[3] Jalabert-Malbos, M.L., Mishellany-Dutour, A., Woda, A., and Peyron, M.A., 2007, "Particle size distribution in the food bolus after mastication of natural foods," *Food Quality and Preference,* 18, 803-812.

[4] Peyron, M.A., Mishellany, A., and Woda, A., 2004, "Particle size distribution of food boluses after mastication of six natural foods," *Journal of Dental Research,* 83(7), 578-582.

[5] See USP <786> *Particle Size Distribution Estimation by Analytical Sieving.*

This recommendation applies only to NDAs, ANDAs, and BLAs for products that are not yet approved. Sponsors of currently approved NDAs, ANDAs, or BLAs for products that contain beads that do not meet the recommended limits in this guidance need not modify their product specifications, unless there is reason to believe that an individual product poses a particular risk to public health because of its bead size.

An ANDA that references a currently approved reference listed drug (RLD) that exceeds the recommended limits in this guidance may propose a target and maximum bead size equal to or less than that used in the currently approved RLD. If the proposed target and/or maximum bead size is greater than that used in the currently approved RLD, the applicant should provide justification for the proposed bead size, as described above. If the ANDA applicant has data regarding the RLD bead size variation, then those data should be provided to support the size(s) of the beads in the ANDA product. This information can be provided in the 3.2.P.2 (Pharmaceutical Development) section or 3.2.P.5.6 (Justification of Specification) section of a CTD formatted application.

B. Enteral Feeding Tube Administration

A small number of sprinkle drug products include language in the labeling that specifically provides for alternative administration via enteral feeding tubes to accommodate patients who cannot safely swallow or are unable to tolerate oral intake. Successful delivery of sprinkle drug products through an enteral feeding tube requires that all of the beads (uncrushed) be able to safely pass through the feeding tube and not cause tube occlusions.

Drug products that include this alternate administration method should demonstrate that the entire contents can be adequately administered. For example, in vitro in-use tests of the sprinkle drug product with feeding tubes indicated in the labeling can be used to support the product use with labeled routes of administration. Such a study or studies, as applicable, are recommended for NDAs and ANDAs, as bead size may vary or coating may differ between these products, resulting in varying ability to pass through a feeding tube. If there are questions about the design or analysis of such studies, the sponsors and/or applicants should contact the appropriate review division within the Office of New Drugs or the Office of Generic Drugs. There is no recommendation for these studies if the labeling does not specify enteral feeding tube administration. These studies can be provided in the 3.2.P.2 (Pharmaceutical Development) section or 3.2.P.5.6 (Justification of Specification) section of a CTD formatted application.

C. Bioavailability/Bioequivalence Recommendations

The acceptability of bead size and bead size differences from a bioavailability (BA) or bioequivalence (BE) perspective is directly evaluated in BA/BE studies.

In NDAs, in the case of capsules containing beads, for the labeling to indicate that the beads in the drug product can be sprinkled on soft foods, additional in vivo relative BA studies may be needed. This can be accomplished by administering beads that have been sprinkled on one of the soft foods (e.g., applesauce) that are listed in the labeling (test treatment) and comparing the sprinkled product's BA results to those of the product administered in the intact form (reference

treatment). Both products should be administered under fasting conditions.[6] In addition, the administration of beads when mixed with soft foods should be evaluated for the ability to take the product without chewing the beads. If there are questions about the design or analysis of such BA studies, the sponsors and/or applicants should contact the appropriate review division within the Office of New Drugs.

In ANDAs, when the labeling for the RLD for a modified-release drug product indicates that the product may be sprinkled on soft foods, a sprinkle study comparing the test and RLD products should be performed. Both treatments should be sprinkled on one of the soft foods that are listed in the labeling (e.g., applesauce). The BE data should be analyzed using average BE, and the 90-percent confidence interval criteria should be used to evaluate BE. Specific BE requirements for individual drug products can be found in the guidance for industry on *Bioequivalence Recommendations for Specific Drug Products*.[7]

In ANDAs, for immediate-release (IR) drug products labeled for sprinkle, it is generally not necessary to conduct a sprinkle BE study, as the expectation would be that the sprinkles would behave similarly for the test and RLD IR products.

If there are questions about the design or analysis of specific BE studies, the sponsors and/or applicants should contact the appropriate review division within the Office of Generic Drugs. The Agency may request additional BE studies under special circumstances if deemed appropriate.

[6] Information on BA studies of sprinkled drug products also can be found in the guidance for industry, *Food-Effect Bioavailability and Fed Bioequivalence Studies*, December 2002. CDER updates guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[7] See www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm.

Attached References

Cloyd, J.C., et al. "Comparison of sprinkle versus syrup formulations of valproate for bioavailability, tolerance, and preference," The Journal of Pediatrics (April 1992) 120: 634-638.

Khadka, P. et al., "Pharmaceutical particle technologies: An approach to improve drug solubility, dissolution and bioavailability," Asian Journal of Pharmaceutical Sciences (2014) 9: 304-316.

Liu, F. et al., "Patient-Centered Pharmaceutical Design to Improve Acceptability of Medicines: Similarities and Differences in Paediatric and Geriatric Populations," Drugs (2014) 74: 1871-1889.

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Sevilla, C. et al., "Current Treatments of Alzheimer Disease; Are Main Caregivers Staisfied with the drug Treatments Received by Their Patients?" Dementia and Geriatric Cognitive Disorders (2009) 28: 196-205.

Tissen, C. et al., "Development of mini-tablets with 1mm and 2mm diameter," International Journal of Pharmaceutics (2011) 416: 164-170.