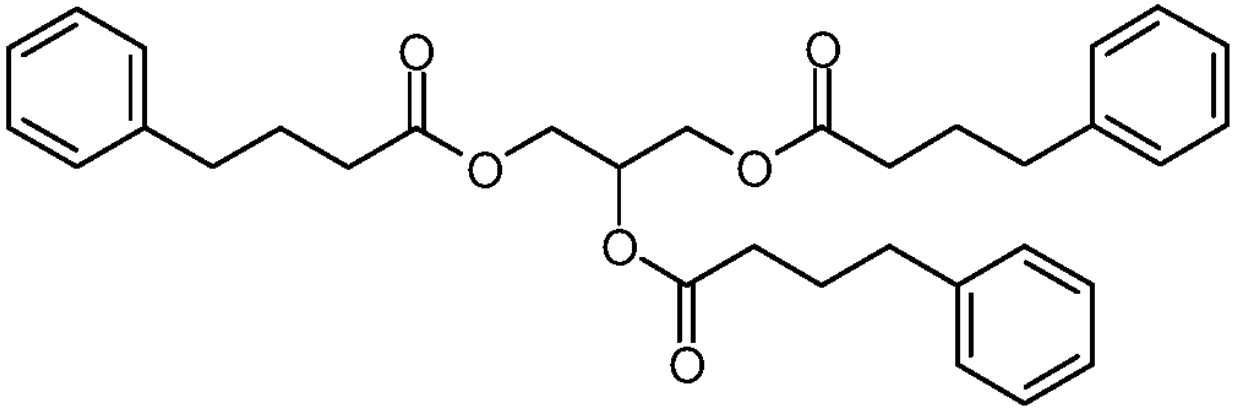
Report for Proposals- 5000 ML of Glycerol Phenylbutyrate

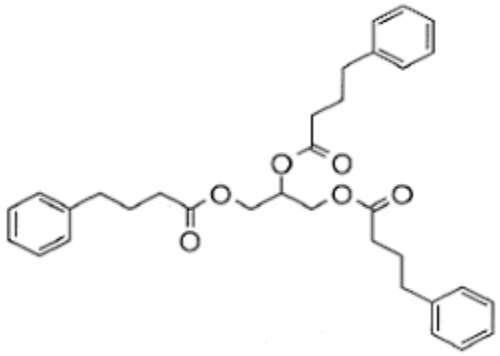
**Molecule-**

- Glycerol Phenylbutyrate is composed of 33 carbon atoms, 38 hydrogen atoms, and 6 oxygen atoms. This gives the chemical formula of $C_{33}H_{38}O_{6.}$

- Image of molecule:



- Image of the Ravicti Molecule intended for oral consumption:



**Quantity Needed-**

- The requested supply: 5000 ML (milliliters)

**Date Drug Is Needed-**

- In three months' time, meaning October 26, 2021.

**Drug Grade-**

- The request grade: GLP (Good Laboratory Practice)

**Manufacturing Process-**

- Glycerol Phenylbutyrate, also known as Ravicti, is prepared throughout the following process:

  Initially, glycerol (III) is reacted with 4-phenylbutanoyl chloride (II) in a d- C5 chlorinated hydrocarbon solvent. It should be noted that this reaction is in the presence of an organic base. The reaction process is carried out within a temperature range of -10 degrees Celcius to 20 degrees Celsius. The quantity of 4-phenylbutanoyl chloride (II) will be 3 to 4 the molar equivalent of glycerol (III). The aforementioned organic base will either be imidazole or related to 1-alkyl imidazole such as 1-methylimidazole. After being selected, this organic base will be kept at 4 to 5 molar equivalents of glycerol (III). The chlorinated hydrocarbon is chosen from one of the following- ethylene dichloride, chloroform, a carbon based tetrachloride, and dichloromethane. Finally, after the reaction between 4-phenylbutanoyl chloride (II) and the chlorinated hydrocarbon solvent, the glycerol phenylbutyrate can be extracted through column chromatography.

**Literature References For Manufacturing Process:**

Committee for Medicinal Products for Human Use. *Committee for Medicinal Products for Human Use (CHMP) Assessment Report*. , 2015.

Pandurang JAHDAV, Sanket, et al. "Process for the Preparation of Glycerol Phenylbutyrate." *Google Patents*, 7 May 2015, patents.google.com/patent/WO2015063659A1/en. Accessed 26 July 2021.

**Analytical Testing Required:**

- Glycerol phenylbutyrate was initially approved in 2013 for the treatment of urea cycle disorders of those two years of age and older. Since then, its approval has been expanded to include those younger than two months of age. To gain this level of approval, the drug has been through a number of clinical tests and trials.
- Study 1: When glycerol phenylbutyrate, also known as Ravicti, was in testing to determine how safe it was amongst infants less than two months older, a clinical trial with 16 infants was put together. Ten of the patients transferred to Ravicti from sodium phenylbutyrate, three were transitioned from either sodium benzoate or sodium phenylacetate, and three were not treated as a control. The results showed that patients on Ravicti had more stable levels of ammonia compared to their levels prior to the clinical study. Additionally, those taking Ravicti proved to have lower levels of ammonia than those who did not take the drug.

- Study 2: Twenty-six pediatric patients, aged 2 months to 17 years, with urea cycle disorders were treated with glycerol phenylbutyrate and sodium phenylbutyrate. These two crossover studies revealed that over the course of 24 hours, mean ammonia exposure was significantly lower on glycerol phenylbutyrate than on sodium phenylbutyrate. The mean Ravicti exposure was merely 15%, while the sodium phenylbutyrate mean exposure rate was 35%. An additional 23 patients were administered glycerol phenylbutyrate over a 12 month period, which showed an 18.4% decrease in hyperammonemic attacks, which are characterized by raised levels of ammonia.

**Literature References for Published Studies:**

Berry, Susan A., et al. "Glycerol Phenylbutyrate Treatment in Children with Urea Cycle Disorders: Pooled Analysis of Short and Long-Term Ammonia Control and Outcomes." *Molecular Genetics and Metabolism*, vol. 112, no. 1, 1 May 2014, pp. 17–24, www.ncbi.nlm.nih.gov/pmc/articles/PMC4382922/, 10.1016/j.ymgme.2014.02.007. Accessed 26 July 2021.

Ernst, Diana. "Ravicti Approved for Children under 2 Months with Urea Cycle Disorders." *MPR*, 28 Dec. 2018, www.empr.com/home/news/ravicti-approved-for-children-under-2-months-with-urea-cycle-disorders/. Accessed 26 July 2021.

**Packaging/Maintenance Requirements:**

- Glycerol phenylbutyrate must be kept between 68 and 77 degrees Fahrenheit, which is 20-25 degrees Celsius.
- Regarding packaging, the most efficient way to maintain and store Ravicti is to keep it in a temperature controlled room or setting where the temperature can be set within this range. While being transported (truck or plane), the drug should be kept in a container with temperature controls so that this can be maintained. It is also recommended that the physical/individual containers that the drug doses are being held in be kept in an environment that does not pose a threat to the integrity of the containers (to prevent them from breaking).

**Budget Constraints:**

- Unfortunately, Ravicti does cost $793,632 for a year of treatment. Recently, Mrs. Amber Freed, founder of SLC6A1 Connect, has engaged in negotiations with the company that owns Ravicti, Horizon Therapeutics. These negotiations may lead to price alterations moving forwards.

**Additional Sources:**

- Below is a link to a report filed with the Canadian Agency for Drugs and Technologies in Health. The Common Drug Review published on Ravicti includes patient testimonies that speak to the effectiveness of Ravicti, even when compared to other ammonia treatment drugs.

- https://www.cadth.ca/sites/default/files/cdr/relatedinfo/SR0497_Ravicti_PI_Submissions.pdf

**Proposal Date:**

- This proposal was completed on July 26th, 2021 by Jacob Tiller.