I refer to my letter of 14 October 2024, and the Warning letter referred to therein.

It is apparent to the company that, conceptually, the FDA misconstrues the product which the Company sells to needy people who are seeking assistance in treatment of one of the world's worst health issues – that of heart disease.

The Company's product is not one which is innovative or new, such that it deserves the description which you have given the product, as a "new drug".

It would be of assistance to embark first of all upon a brief discussion about the product 2-Hydroxypropyl- beta - Cyclodextrin. (hereafter described as 'CD').

A brief history and overview

CDs were discovered in the late 19th century, and were first reported by Villiers as carbohydrates which precipitate slowly in the form of radiant crystals.[1]

In the early part of their discovery period, and into the second half of the 20th century, CDs were found to protect sensitive organic guest molecules from violation and from oxidisation and their stabilising action on apolar guests made them attractive for a variety of applications.

With the new millennium came developments in CD biomedical research demonstrating that CDs may in fact be used to treat some human ailments.

Regulatory Status of CDs

Native CDs are regarded in Japan as natural products, and for this reason they are used without many restrictions both in medicines and in foods. In western countries, the ingestion of native cyclodextrins is regulated by the JECFA (Joint WHO/FAO Expert Committee on Food Additives) with the pharmaceutical applications falling under the European Medicines Agency (EMA) in Europe and under the Food and Drug Administration in the United States of America.

Native CDs can be ingested without significant absorption, being thus 'Generally Regarded As Safe' by the FDA[2] . They are commonly referred to as molecules with 'GRAS status'. α-CD

[1] Villiers M.A. Sur la fermentation de la fecule par l'action du ferment butyrique. *C.R. Acad Sci* [1891]:112:69-71
[2] *Agency Response letters Gras notices GRN No 155/2004; GRN No 74/2001; GRN No 46/2000.*

and γ-CD can be taken without restrictions [3]while the oral intake of β-CD should be limited to a maximum of 5 mg per kilogram of weight each day.[4]

Regarding parenteral use, native cyclodextrins suffer from much stronger re-strictions. Indeed, the EMA recommends against the administration of α-CD and β-CD directly into the bloodstream due to renal toxicity.[5]

In addition, native CDs are known to cause hemolysis in vitro, at concentrations of 6, 3, and 16 mM for α-, β-, and γ-CDs, respectively, due to extraction of phos-pholipids and cholesterol from the erythrocyte membrane.[6]

Native CDs can be functionalized to afford a large variety and number of derivatives, surpassing 1500 different molecules according to a report of 2012.[7] Of these, only a few are approved for human use in the fields of pharmaceutics.

The U.S. Food and Drug Administration (FDA) lists 2-hydroxypropyl-β-cyclodextrin (HPβCD) and 2-hydroxypropyl-γ-CD (HPγCD) as approved inert materials (excipients), with HPβCD being suited for oral and intravenous administration while HPγCD can only be used in topical products and in a maximal concentration of 1.5% (*w*/*v*) (FDA, 2016).

Within *O*-methylated CDs, the approval status varies from one molecule to the next. For instance, heptakis-2,3,6-tris-*O*- methyl β-CD (TRIMEB) is deemed unsafe for human use due to its hemolytic action and renal toxicity.

Its sister cyclodextrin, heptakis-2,6-di-*O*-methyl-β-CD (DIMEB), also features some toxicity, mostly targeting the liver: Doses of 300 mg/kg in mice caused elevated levels of glutamate-pyruvate transami-nase (GPT) and glutamate-oxaloacetate transaminase (GOT) [22], two biomarkers of hepatic injury.

Despite this, DIMEB is approved by the FDA for commercial use in a few injectable vaccines,[8] probably due to the fact that it is present in low amounts in such products. Cyclodextrins that have undergone *O*-methylation in random positions have different safety profiles, according to the different degrees of substitution.

RAMEB (from randomly methylated beta-cyclodextrin), with an average of 1.8 methoxyl groups per glucose unit, has some hydrolytical action on erythrocytes, as well as renal toxicity that is higher than that of the parent βCD.

CRYSMEB does not cause hemolysis and it is already approved for dermal ap-

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[3] Kroes R. Verger P. Larsen J.C Safety evaluation of certain food additives *WHO Food Addit. Ser* 2006;54:3-15*; Abbott P.J.* JEFCA 55th meeting *WHO Food Addit. Ser.* 2000; 44; 969

[4] Pollit F.D Safety evaluation of sertain food additives *WHO Food Addit Ser* 1996;35:257-268.

[5] European Medicines Agency. *Background review for Cyclodextrins Used as Excipients.* EMA ; London 2014

[6] Ohtani *et al;* Differential effects of cyclodextrins on human erythrocytes. *Eur, J. Biochem* 1989; 186: 17-22.

[7] Nitalikar *et al;* The Cyclodextrins : A Review *J. Curr. Pharm. Res* 2012;10: 1-6

[8] Vaccine Exipients Summary. Excipients Included in U.S. Vaccines

plications and as an ingredient in cosmetics. Another biocompatible CD is sulfobutyl ether β-CD (SBEβCD), developed to be non-nephrotoxic and present in several FDA-approved marketed medications for both oral and intravenous administration.[9]

Conclusions

Though lengthy, the above dissertation indicates that there has been a proliferation of products with CDs as their foundation which have been considered and approved by the FDA such that the emergence of Remchol in the last four years is such that its base of pure CDs with a water combination would not be of any concern to the FDA whatsoever.

The Company's Cavidex product is therefore commonly found in the world domain since around July 2020, and has been used by thousands of people globally.

To now suggest that Remchol requires approval as a "new drug" is simply perverse.

The "Warning Notice"

It is therefore obvious that the company's products do not constitute 'unapproved new drugs' within the definitions contained in the Federal Food, Drug and Cosmetic Act of the United States.

It is of interest to understand that the Australian comparator (The Therapeutic Goods Administration) has also been aware of the existence of the Company's products for over four years now, and has not seen fit to impose any conditions upon the Company to date, notwithstanding correspondence passing between the Company and the authority.

What is more, no other country in the world has even enquired as to the Company's right or entitlement to sell its products in those jurisdictions.

The assumption contained at the foot of page one of the Warning Notice that the company's products are "drugs under section 201(g)(1) of the FD&C Act because of the reason contained therein, is simply a "bridge too far".

At page 4 (immediately before the heading "Conclusion") it is stated that :

> *"Your … products are not generally recognised as GRASE for their above referenced uses".*

Having regard to the FDAs multitude of examinations of similar, and possibly identical products over the last fifty years, the assumption raised in the paragraph under reply is, with respect, a nonsense[10].

[9] Captisol (accessed on 17 September 2019)
[10] See footnote 2 above and the source reference.

The Company therefore disagrees with the conclusion which has been reached by the delegate who authored the Warning Notice.

What next?

Obviously, neither the FDA nor the Company wishes to become embroiled in costly and needless litigation when common sense should prevail.

The Company therefore invites the FDA to withdraw the present regime of warnings and notices on the understanding that both parties enter into meaningful and proper dialogue to resolve the impasse which has arisen.

We invite you to desist from undertaking further action to disrupt the company's reasonable sales activity in the United States for a per determined period whilst both parties come to a point whereby your obligations as regulator are seen to be satisfied, and our ability to trade in your jurisdiction is resumed without harm to the Company.

To this end, the Company is willing to commence meetings with the FDA immediately via audio visual means (eg Skype, Zoom or the like) to start getting things back on track.

In suggesting this course, the Company of course reserves all rights it has in respect of its position to remain firmly of the view that the process undertaken by the FDA to date is incorrect.

Let's start again.

We await your response