sanofi aventis

Because health matters

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Division of Dockets Management (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Citizen Petition Supplement**

**(2006P-0523)**

Sanofi-aventis U.S. LLC ("sanofi-aventis"), a member of the sanofi-aventis group, submits this Supplement (the "Supplement") to its Citizen Petition filed December 19, 2006 (2006P-0523/CP1) (the "Citizen Petition"). Sanofi-aventis is the manufacturer of Eloxatin® (oxaliplatin injection) ("oxaliplatin"). The Citizen Petition urges the agency to give special consideration to any application for a generic version of oxaliplatin solution containing an acid other than oxalic acid or a conjugate base thereof. This Supplement urges the agency to take similar precautions when considering applications for generic oxaliplatin solution containing added sugars.

## I. BACKGROUND

### A. The Citizen Petition

In its original Citizen Petition, sanofi-aventis notes that its marketed Eloxatin® solution product contains only oxaliplatin and water for injection. It does not contain an acid added, for example, to aid stability or to buffer the solution. Solutions containing oxaliplatin and the conjugate base of inorganic or carboxylic acids are likely to undergo chemical exchange reactions in which the conjugate base displaces the oxalate ligand. This reaction would lead to the formation of free oxalate and new Pt(diaminocyclohexane) complexes ("Pt(DACH) complexes"), which are likely to have biological activity and toxicity.[1]

Tartaroplatin, discussed at length in the Citizen Petition, is one example of a new Pt(DACH) complex caused in such solutions. Tartaroplatin is the result of ligand exchange of

[1] *See* Citizen Petition at 6-11 (citing Declarations of Professor Stephen G. Chaney and Professor Nicholas P. Farrell).

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the oxalic acid in oxaliplatin with tartaric acid. The literature demonstrates that tartaroplatin may be biologically active.[2] Moreover, the tumor specificity and the toxicity of tartaroplatin and similar platinum complexes formed in this manner are not predictable. Therefore, the safety and effectiveness profile of such a product cannot be assumed to be the same as Eloxatin.

The experience with tartaric acid suggests that similar results may be obtained through the addition of other acids to oxaliplatin solutions, for example, either inorganic acids (*e.g.,* phosphoric acid, carbonic acid) or organic acids (e.g., carboxylic acids, amino acids). The Citizen Petition therefore argues that if a company were to propose formulating oxaliplatin in a buffer system containing tartrate, or the conjugate base of any other acid, it should be incumbent on that company to demonstrate that no significant formation of new Pt(DACH) complexes occurs under anticipated storage and use conditions. If significant amounts of new Pt(DACH) complexes did form upon storage or use, as a result of added acids, then preclinical and/or clinical tests should be performed to determine that these by-products do not have any unexpected toxicity or efficacy difference cmpared to the innovator's oxaliplatin. The Citizen Petition therefore requests that if FDA receives an application for a generic version of oxaliplatin solution containing an acid other than oxalic acid or a conjugate base thereof and citing our proprietary Eloxatin® solution as the reference listed drug, the agency require that the applicant demonstrate through sufficient preclinical and/or clinical testing that any new compounds resulting from the addition of an acid, or a conjugate base thereof, to oxaliplatin does not compromise the safety or efficacy of the drug product.

### B. The Current Supplement

Sanofi-aventis has determined that the addition of sugars to solutions of oxaliplatin raises the same concerns as are presented by the addition of acids when storage durations and conditions consistent with that of a product for routine use are considered. During its development of Eloxatin®, sanofi-aventis (then sanofi-synthelabo) conducted experiments in which sugars were added to oxaliplatin in water in the hope of minimising oxidative degradation. The experiments were unsuccessful, however, because sanofi-aventis found that, as is the case when acids are added to oxaliplatin, adding sugars to oxaliplatin results in the formation of new Pt(DACH) complexes without stabilizing the product.[3] Like the Pt(DACH) complexes that are formed with the addition of acids to oxaliplatin, these new sugar-induced Pt(DACH) complexes are likely to be active, with unknown and unpredictable levels of toxicity.

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[2] *See id.* at 2, n. 3 (citing supporting literature).

[3] *See* Sanofi Synthelabo Recherche Internal Report: Stability of Oxaliplatin Solution in the presence of dissolved sugars (August 2004)(hereinafter the "Report") attached hereto as Appendix A. *But see* Dabur Pharma. Ltd. U.S. Patent Application No. US 2007/0054957 A1 (filed Sep. 5, 2006)(reporting use of small amounts of added sugar to stabilize an oxaliplatin solution product without addressing whether new Pt(DACH) complexes were formed).

As a result, sanofi-aventis believes that the arguments it made in the original Citizen Petition with respect to oxaliplatin products with added acids are equally applicable to oxaliplatin products to which sugars have been added. If a company were to propose formulating an oxaliplatin solution in a system containing added sugars, it should be incumbent on that company to demonstrate that new Pt(DACH) complexes do not form under anticipated storage and use conditions. If new Pt(DACH) complexes did form upon storage or use, as would be expected, preclinical and/or clinical tests must be performed to determine that these by-products do not have any unexpected toxicity and retain the same tumor specificity and efficacy as oxaliplatin. If clinical data are required to make this determination, then an ANDA is not appropriate, and the application must be submitted as an NDA under section 505(b) of the Act.

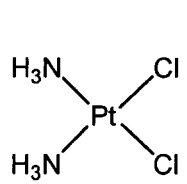
## II. SUPPLEMENTAL ACTIONS REQUESTED

Sanofi-aventis requests that if the agency receives an application for a generic version of oxaliplatin solution containing added sugars and citing our proprietary Eloxatin® solution as the reference drug, the agency require that the applicant demonstrate through sufficient preclinical and/or clinical testing that any new compounds resulting from the addition of such sugar to oxaliplatin does not compromise the safety or efficacy of the drug product.

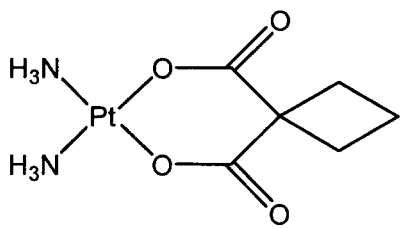
## III. DISCUSSION

### A. Platinum-Based Anticancer Agents.

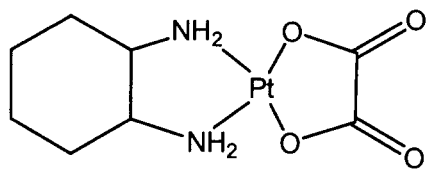
As discussed in the original Citizen Petition, there are currently a number of platinum-based anticancer agents approved for use in the United States in cancer patients. Three examples include cisplatin, carboplatin and oxaliplatin:




Cisplatin

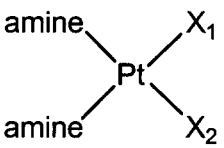


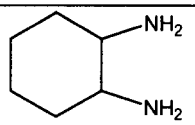
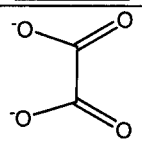

Carboplatin




Oxaliplatin

The general chemical structure of these agents is illustrated below where X is a leaving group/ligand:




| | Amine | Platinum | Leaving Group/Ligand (X1, X2) |
|---|---|---|---|
| **Oxaliplatin** |  diaminocyclohexane (DACH) | Pt |  Oxalate |

In the approved platinum-based drugs and other platinum agents reported in the literature, the amine-based nitrogen-platinum bond is considered inert and remains bound to platinum during chemical reactions. The leaving group(s) are substituted through chemical reactions with biological molecules. Thus, this class of platinum-based agents is commonly considered *bifunctional* because both $X_1$ and $X_2$ ligands are substituted.[4]

Platinum-based drugs are activated before eliciting biological effects via substitution of the leaving group to form a reactive aquated platinum(II) species in solution.[5] Consequently, the biological activity (both desirable and toxic) is dependent in part upon the rate of substitution and thus the identity of the leaving group (X). For example, the pharmacokinetic differences between cisplatin and carboplatin are due mainly to their comparative chemical stability due to their different leaving groups.[6] Also, the negligible nephrotoxicity of oxaliplatin and carboplatin in comparison to cisplatin is thought to be related to the slow rates of substitution of the leaving groups to form an aqua reactive species in solution.[7]

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[4] *See* Citizen Petition at 4.

[5] McKeage MJ. Comparative Adverse Effect Profiles of Platinum Drugs. *Drug Safety* 1995; 13:228, 230.

[6] *Id.* at 237-38.

[7] Hartmann JT, et al. Toxicity of Platinum Compounds. *Expert Opin. Pharmacother.* 2003; 4:889, 889.

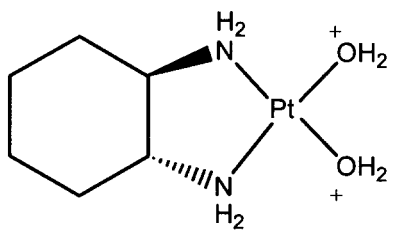
## B. The Addition of Sugars to Oxaliplatin Can Form New Platinum Compounds

In 2004, Sanofi-Synthelabo Recherche developed its internal Report containing the results of its experiments in which various sugars were added to oxaliplatin.[8] In that study, the authors added lactose, maltose, glucose, and sucrose at a concentration of 5% w/v to various 5 mg/ml solutions of oxaliplatin in water. Sanofi-aventis' approved solution formulation of oxaliplatin concentrate for solution for infusion is a plain aqueous solution of 5 mg/ml of water, with no added sugar.[9]

The data in the Report demonstrate the effect of adding sugars to an oxaliplatin solution. The data also allow for the comparison with a plain aqueous control solution stored under the same conditions. The levels of known Pt(DACH) and new Pt(DACH) species were monitored. The known diaquoPt(DACH) complexes appear in three forms:

1. DiaquoPt(DACH) (*i.e.* the complex shown as Figure 1)
2. SR200028 (*i.e.* the diaquoPt(DACH) dimer complex shown as Figure 2)
3. SR200034 (*i.e.* the platinum (IV) complex shown as Figure 3).

New Pt(DACH) species were detected and monitored using the same chromatographic conditions used for the above, known, species.




DiaquoPt(DACH) complex

Figure 1

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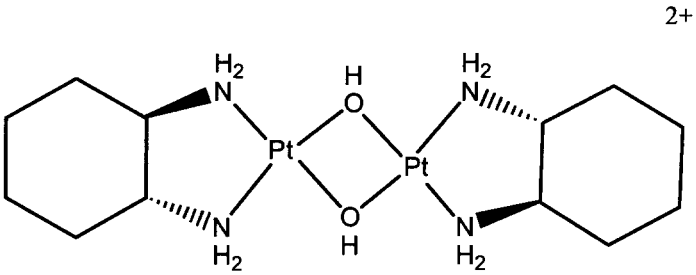
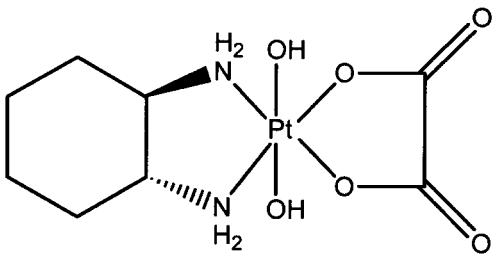
[8] *See* Report, attached hereto as Appendix A.

[9] *See* Eloxatin prerscribing information, available at http://products.sanofi-aventis.us/eloxatin/eloxatin.html (last visited March 27, 2007). Prior to use, the solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection ( USP) and after this dilution step the solution must be used within 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)]




SR 200028
Diaquo DACH dimer species

Figure 2




SR 200034
Platinum (IV) complex

Figure 3

The Report shows that the addition of sugar to a plain aqueous solution of oxaliplatin causes increases in three types of Pt(DACH) complexes upon testing after three months in ambient conditions (25° C, 60% humidity) in comparison to the control (plain aqueous solution).[10] These data are presented in Table 1 below. It should be noted that although SR200034 is a known species it is not detected in Oxaliplatin Concentrate for Solution and, in this context, represents a new impurity. Similarly, the unspecified impurities shown to increase in those solutions containing sugars are not found at significant levels in Oxaliplatin Concentrate for Solution for Infusion.

[10] *See id.* at 8-10.

**Table 1**[11]

**Stability Studies at 3 months in ambient conditions (25°C, 60% humidity)**

| 5 mg/ml Oxaliplatin in Water | Diaquo Unspecified Impurities | SR200034 | SR200034 Unspecified Impurities |
|---|---|---|---|
| **Plain aqueous solution** | None ≥ 0.05 % | ND < 0.02 % | None ≥ 0.02 % |
| **Lactose** | 0.11 % | 0.13 % | None ≥ 0.05 % |
| **Glucose** | 0.06 % | 0.10 % | None ≥ 0.02 % |
| **Maltose** | 0.06 % | 0.07 % | None ≥ 0.02 % |
| **Sucrose** | 0.05 % | D < 0.05 % | None ≥ 0.02 % |

(ND = non-detectable; D = detectable)

The addition of these sugars also causes significant increases in the formation of these complexes upon testing after three months in standard accelerated conditions (40° C, 75% humidity) in comparison to the control (plain aqueous solution), as shown in Table 2 below:

**Table 2**[12]

**Stability Studies at 3 months accelerated conditions (40°C, 75% humidity)**

| 5 mg/ml Oxaliplatin in Water | Diaquo Unspecified Impurities | SR 200034 | SR 200034 Unspecified Impurities |
|---|---|---|---|
| **Plain aqueous solution** | 0.11 % | ND < 0.02 % | None ≥ 0.02 % |
| **Lactose** | 1.04 % | 0.43 % | 0.35 % |
| **Glucose** | 1.43 % | 0.62 % | 0.94 % |
| **Maltose** | 1.18 % | 0.42 % | 0.21 % |
| **Sucrose** | 1.10 % | 0.42 % | 0.20 % |

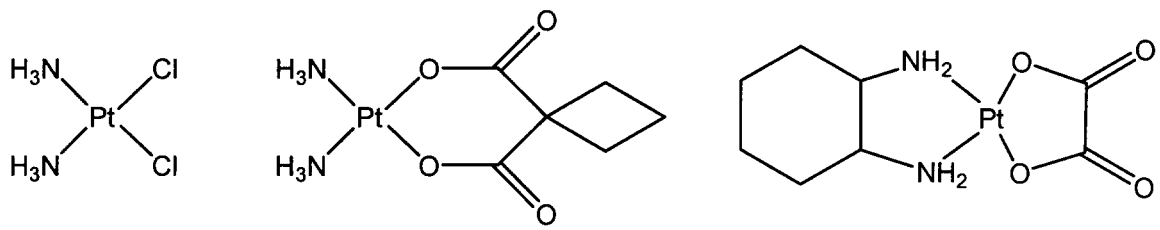
[11] *See id.*

[12] *See id.*

Based on these results, and their knowledge of the chemistry of platinum species, Professors Stephen G. Chaney and Nicholas P. Farrell opine in their attached supplemental declarations that a reaction is occurring between the added sugar and the oxaliplatin or diaquoPt(DACH) complex in aqueous solution over time.[13] Solutions stored at room temperature for any commercially relevant period of time (*i.e.*, six months or more) likely would generate these complexes above 0.2%.[14] Indeed, because temperature affects only the rate of reaction, one would expect to see the same, high levels of these complexes at room temperature storage as were generated under the accelerated conditions used in this test, after only a longer period of time.[15] The trend from time zero to three months under ambient conditions demonstrates the early formation of those complexes.[16]

### C. New Pt(DACH) Complexes Are Likely to be Active

New Pt(DACH) complexes formed by the addition of sugars to oxaliplatin are likely to be active. In the approved platinum-based drugs shown in Figure 4 below:




Cisplatin Carboplatin Oxaliplatin

Figure 4

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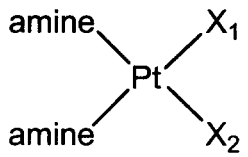
[13] *See* Supplemental Declarations of Professor Stephen G. Chaney (hereinafter "Supplement Chaney Declaration") and Professor Nicholas P. Farrell (hereinafter "Supplemental Farrell Declaration") attached hereto as Appendix B.

[14] *See* Supplemental Farrell Declaration, at 4-5. These levels would exceed the maximum thresholds for degradation products in new drug products, as set forth by ICH's Guidance on Impurities in New Drug Products. *See* ICH Topic Q 3 B (R2): Impurities in New Drug Products (June 2006).

[15] *See id.*

[16] According to ICH Guidelines, "If long-term studies are conducted at 25° C ± 2° C/60% RH ± 5% RH" and 'significant change' occurs at any time during six months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. Testing at the intermediate storage condition should include all tests unless otherwise justified. "Significant change" for a drug substance is defined as failure to meet its specification. *See* FDA Guidance for Industry: Q1A(R2) Stability Testing of New Drug Substances and Products (Nov. 2003).

the general chemical structure of these drugs is illustrated below where X is a leaving group/ligand and amine is the amine derivative:




In these approved platinum-based drugs and other platinum agents reported in the literature, the amine derivative is considered inert (*i.e.* it has a slow rate of substitution) and remains bound to platinum throughout chemical reactions with biomolecules. The platinum-based drugs are activated before eliciting biological effects via substitution of the leaving group to form an aqua reactive species in solution.[17] The biological activity (both desirable and toxic) is dependent in part upon the rate of substitution and thus the identity of the leaving group (X). For example, the pharmacokinetic differences between cisplatin and carboplatin are mainly due to their comparative chemical stability due to their different leaving groups.[18] Also, the negligible nephrotoxicity of oxaliplatin and carboplatin in comparison to cisplatin is thought to be related to their slow rates of substitution of the leaving groups to form an aqua reactive species in solution.[19] Based on those results and the above scientific principles, Professors Chaney and Farrell opine that they would expect the platinum complexes formed in sugar-containing formulations, including unspecified complexes possessing a Pt(DACH) moiety, to have activity in humans.[20]

It is well known that platinum (IV) complexes similar to SR200034 have been shown to be active.[21] In particular, diaquoDACH platinum (IV) compounds are active *in vivo*.[22]

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[17] McKeage, *supra* note 5, at 230.

[18] *Id.* at 237-38.

[19] Hartmann, *supra* note 7, at 889.

[20] *See* Supplemental Chaney Declaration, at 2; Supplemental Farrell Declaration, at 5-6.

[21] *See* Luo FR, et al. Comparative neurotoxicity of oxaliplatin, ormaplatin, and their biotransformation products utilizing a rat dorsal root ganglia *in vitro* explant culture model. *Cancer Chemother. Pharmacol.* 1999; 44:29-38; Siddik ZH, et al. Role of p53 in the ability of 1,2-diaminocyclohexane-diacetato-dichloro-Pt(IV) to circumvent cisplatin resistance. *J. Inorg. Biochem.* 1999; 77:65-70; Holmes et al. Comparative neurotoxicity of oxaliplatin, cisplatin, and ormaplatin in a Wistar rat model. *Toxicol. Sci.* 1998; 46:342-351; Luo FR, et al. Cytotoxicity, cellular uptake, and cellular biotransformations of oxaliplatin in human colon carcinoma cells. *Oncol. Res.* 1998; 10:595-603; Yamashita T, et al. Cytotoxicity of platinum(IV) and platinum(II) complexes containing *1R, 2R*-cyclohexanediamine as a ligand. *Biol. Pharm. Bull.* 1993; 16:1014-1018; Khokhar AR, et al. Synthesis and antitumor activity of 1,2-diaminocyclohexane platinum (IV) complexes. *J. Inorg. Biochem.* 1994; 54:39, 51 (showing the activity of the dichloro platinum IV species).

Indeed, one such compound, tetrachloro-(*d,l-trans*)-DACHplatinum(IV), was tested in humans and was found to be active, but too neurotoxic, as compared to cisplatin and carboplatin, for continued development.[23] Likewise, the SR200034 unspecified impurities (*i.e.* the unidentified platinum (IV) impurities) are also likely to be active. Based on these scientific principles and their knowledge of platinum chemistry, Professors Chaney and Farrell have opined that they would expect that SR 200034 and any related impurities containing a platinum (IV) species to be active and potentially toxic.[24]

It is well established that diaquoPt(II)(DACH) complexes are active and potentially toxic. Moreover, the type and severity of toxicity caused by these complexes may well be different from oxaliplatin. For example, it has been shown that Pt(II)(DACH)($H_2O$)(Cl) and Pt(II)(DACH)($H_2O$)$_2$ are more cytotoxic than oxaliplatin in HT-29 cells[25] and are more neurotoxic than oxaliplatin in a rat dorsal root ganglia neurite outgrowth assay.[26] Therefore, based on these scientific principles and their knowledge of platinum chemistry, Professors Chaney and Farrell have opined that they would expect that diaquo platinum complexes and any related impurities would be active and potentially toxic.[27]

### D. One Cannot Predict the Biological Effect of Compounds Resulting from the Addition of a Sugar to Oxaliplatin

The chemistry and biology of platinum agents is complex, and one cannot precisely predict how an oxaliplatin product with added sugars will behave in humans. As sanofi-aventis pointed out in the original Citizen Petition, the efficacy and toxicity of such contaminants cannot easily be predicted on the basis of its similarity to oxaliplatin. Again, Pt(II)(dach)($H_2O$)(Cl) and Pt(II)(dach)($H_2O$)$_2$ are more cytotoxic than oxaliplatin in HT-29

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[22] *See* Gibbons GR, et al. Rapid reduction of tetrachloro(*d,l-trans*)1,2- diaminocyclohexaneplatinum(IV) (tetraplatin) in RPMI 1640 tissue culture medium. *Cancer Res.* 1989; 49:1402-1407; Chaney SG, et al. *In vitro* biotransformations of tetrachloro(*d,l-trans*)-1,2- diaminocyclohexaneplatinum(IV) (tetraplatin) in rat plasma. *Cancer Res.* 1990; 50:4539-4545; Chaney SG, et al. An unexpected biotransformation pathway for tetrachloro-(*d,l-trans*)-1,2-diaminocyclohexaneplatinum(IV) (tetraplatin) in the L1210 cell line. *Cancer Res.* 1991; 51:969-973.

[23] *See* Sakata M., et al. Possible correlation between ormaplatin biotransformations and neurotoxicity. *Oncol.Res.* 1995; 7:67-71; Shord SS, et al. Oxaliplatin biotransformation and pharmacokinetics: a pilot study to determine the possible relationship to neurotoxicity. *Anticancer Res.* 2002; 22:2301-2309; Holmes J, et al. Comparative neurotoxicity of oxaliplatin, cisplatin, and ormaplatin in a Wistar rat model. *Toxicolog. Sci.* 1998; 46:342-351.

[24] *See* Supplemental Chaney Declaration at 2; Supplemental Farrell Declaration at 4-5.

[25] Luo FR, et al. Cytotoxicity, cellular uptake, and cellular biotransformations of oxaliplatin in human colon carcinoma cells. *Oncol. Res.* 1998; 10:595-603.

[26] Luo FR, et al. Comparative neurotoxicity of oxaliplatin, ormaplatin, and their biotransformation products utilizing a rat dorsal root ganglia *in vitro* explant culture model. *Cancer Chemother. Pharmacol.* 1999; 44:29-38.

[27] *See* Supplemental Chaney Declaration at 2; Supplemental Farrell Declaration at 5-6.

cells[28] and are more neurotoxic than oxaliplatin in a rat dorsal root ganglia neurite outgrowth assay.[29] This unpredictability is caused by the fact that the biological activity (both desirable and toxic) is dependent in part upon the rate of substitution and thus the identity of the leaving group (X). As Professors Chaney and Farrell state in their attached supplemental declarations, the rate of disassociation of compounds containing added sugars may not be the same as that of oxalic acid.[30] As a result, both Professors Chaney and Farrell opine that the type and severity of toxicity of Pt(DACH) complexes caused by added sugar may well be different from oxaliplatin.[31]

Although some properties of platinum complexes (*e.g.*, cellular uptake, cross-resistance and mutagenicity) can be explained on the basis of their hydrophobicity, aqueous stability, and carrier ligand (*e.g. cis*-diamine vs. 1,2-diaminocyclohexane), other important characteristics are very difficult to predict on the basis of structural similarities.[32] Efficacy, tumor range, and the extent and type of toxicity (*e.g.*, toxic or anti-cancerogenic) are determined by a combination of pharmacokinetics, pharmacodynamics, biotransformations and other complicating factors that are not totally understood. These various factors limit the use of modeling or extrapolation between platinum agents and can only be answered by direct experimentation. In the case of the Pt(DACH) platinum complexes, it is quite clear that their characteristics are not solely dependent on the diaminocyclohexane carrier ligand. For example, of the Pt(DACH) complexes evaluated to date, only oxaliplatin has been shown to display clear efficacy in the treatment of metastatic colon cancer[33] and only oxaliplatin and ormaplatin have been reported to display neurotoxicity as the dose-limiting toxicity.[34]

Thus the extent and type of activity (*e.g.*, toxic or anti-cancerogenic) of an oxaliplatin product containing added sugars cannot be predicted without appropriate studies. Any generic manufacturer wishing to introduce such a product therefore must conduct the necessary preclinical and/or clinical studies to determine the effects of the active compounds formed as byproducts of the reaction of oxaliplatin and the added sugars. Failure to require such studies or, at the very least, to fully-characterize and qualify any impurities resulting from the addition of sugars to oxaliplatin, could place patients at unnecessary risk.

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[28] *See* Supplemental Chaney Declaration at 2 (citing Luo FR, et al. Cytotoxicity, cellular uptake, and cellular biotransformations of oxaliplatin in human colon carcinoma cells. *Oncol. Res.* 1998; 10: 595-603).

[29] *See id.* (citing Luo, *supra* note 25).

[30] *See* Luo, *supra* note 25.

[31] *See* Supplemental Chaney Declaration at 2; Supplemental Farrell Declaration at 6.

[32] *See* Luo, *supra* note 25. *See also* Supplemental Chaney Declaration at 2.

[33] *See* Citizen Petition at 12.

[34] *See id.*

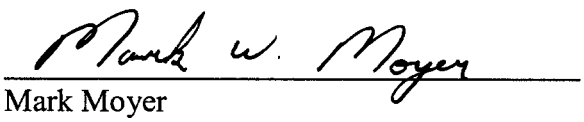
## IV. CONCLUSION

Sanofi-aventis expects that when oxaliplatin is combined with sugars, new Pt(DACH) complexes will be produced that are likely to have biological activity and toxicity. Because Eloxatin® does not contain any added sugars, the safety and efficacy of the complexes described above have not been tested.

The presence of complexes about which little is known makes it extremely difficult to characterize an oxaliplatin product containing added sugars as a generic version of Eloxatin.® Therefore, applicants for generic oxaliplatin with added sugars must provide the preclinical and/or clinical data necessary to demonstrate that the new complexes formed by use of the sugar do not alter the safety or efficacy of oxaliplatin. If clinical data are required to make this determination, then an ANDA is not appropriate, and the application must be submitted as an NDA under section 505(b) of the Act.

## CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Supplement includes all information and views on which the Supplement relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.



Mark Moyer
Vice President, U.S. Deputy Head,
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