sanofi aventis

Because health matters

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December 19, 2006

BY HAND DELIVERY

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

CITIZEN PETITION

Sanofi-aventis US LLC, a subsidiary of sanofi-aventis, and successor in interest to Aventis Pharmaceuticals, S.A. ("sanofi-aventis") submits this Citizen Petition under sections 505(b) and 505(j) of the Federal Food, Drug, and Cosmetic Act ("FDCA" or the "Act") (21 U.S.C. §§ 355 (b) and (j)) and 21 C.F.R. § 10.30, to request the Commissioner of Food and Drugs to take the actions set forth below with respect to applications for generic versions of Eloxatin® (oxaliplatin injection) ("oxaliplatin") containing added acid, or a conjugate base thereof, other than oxalic acid. Sanofi-aventis is the manufacturer and distributor of oxaliplatin, a platinum based anti-cancer agent.

I. Actions Requested

Sanofi-aventis requests that the agency 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 ("Buffered Oxaliplatin"). Sanofi-aventis requests that if the agency receives such an application 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 compound 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.

II. Brief Statement of Grounds

Oxaliplatin is an antineoplastic agent with the molecular formula $C_8H_{14}N_2O_4Pt$ and the chemical name [(1R,2R)-1,2-cyclohexanediamine-N,N'] [oxalato(2-)-O,O'] platinum. Oxaliplatin is an organoplatinum compound in which the platinum atom is complexed with 1,2-diamino cyclohexane (DACH) and with an oxalate ligand as a leaving group.[1]

[1] Eloxatin Prescribing Information, *available at* http://products.sanofi-aventis.us/eloxatin/eloxatin.html (last visited 11 December 2006).

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2006P-0523

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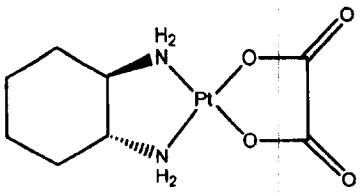

The molecular weight of oxaliplatin is 397.3.

Sanofi-aventis' 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(DACH) complexes, which are likely to have biological activity and toxicity.[2]

One example of a new Pt(DACH) complex caused in such solutions is tartaroplatin. Tartaroplatin is the result of ligand exchange of the oxalic acid in oxaliplatin with tartaric acid. The literature demonstrates that tartaroplatin may be biologically active.[3] 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 oxaliplatin and Eloxatin. The experience with tartaric acid suggests that similar results may be obtained through the addition of other acids to oxaliplatin.

As a result, if a company were to propose formulating oxaliplatin in a system containing tartrate, or the conjugate base of any other acid, it should be incumbent on that company to demonstrate that no formation of new Pt(DACH) complexes occurs under anticipated storage and use conditions. If new Pt(DACH) complexes did form upon storage or use, as would be expected, pre-clinical and/or clinical tests should be performed to determine that these by-products do not have any unexpected toxicity and retain the same tumor specificity and efficacy as oxaliplatin.

Sanofi-aventis therefore requests that FDA take appropriate precautions when reviewing applications for marketing authorization for Buffered Oxaliplatin products citing our

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[2] *See* Declarations of Professor Stephen Chaney (hereinafter "Chaney Declaration") and Professor Nicholas Farrell (hereinafter "Farrell Declaration") attached hereto as Appendix A.

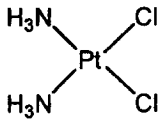
[3] See Chaney Declaration at 4, n.55 (citing Schwartz P, et al. Preparation and antitumor evaluation of water soluble derivatives of dichloro(1,2-diaminocyclohexane)platinum(II). *Cancer Treat. Rep.* 1977; 61:1519-1525); Farrell Declaration at 11 (citing Schwartz, *id.* at 1523; Speer et al. Antitumor Activity of Platinum Complexes of 1,2-Diaminocyclohexane Isomers. *J. of Clin. Hem. & Onc.* 1978; 8:44).

proprietary brand of Eloxatin as the reference drug product. FDA should require that such applications contain preclinical and/or clinical data necessary to show that new platinum compounds created by the addition of an acid to oxaliplatin do not differ significantly in terms of safety and efficacy from oxaliplatin. FDA may not approve abbreviated new drug applications (ANDAs) filed under section 505(j) of the FDCA if they include clinical trials necessary to demonstrate the safety or effectiveness of the modified generic drug. Therefore, if clinical testing is required to make this determination, the generic applicant must submit its application as an NDA under section 505(b) of the FDCA.

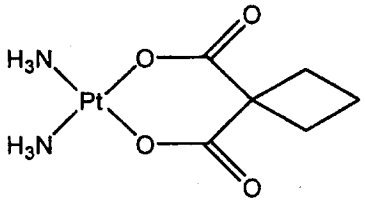
III. Complete Statement of Grounds

A. Platinum-Based Anticancer Agents

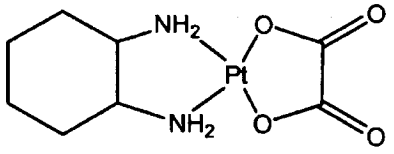
There are currently several platinum-based anticancer agents approved for use in the United States in cancer patients. Three examples include cisplatin, carboplatin and oxaliplatin:



Cisplatin

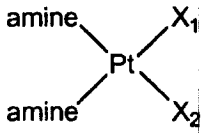


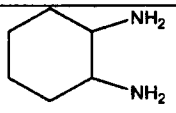
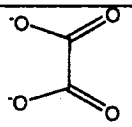
Carboplatin



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

B. Mechanism of Action of Platinum-Based Anticancer Agents

1. Chemical

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 or X_2 ligands are substituted.

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.[4] 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.[5] 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.[6]

2. Biological

Platinum complexes are thought to enter the cell by passive diffusion[7], although recent research has suggested that certain transporters[8,9] and/or endocytosis[10,11] may play a role as well. It is believed that once inside the cell, most platinum anticancer agents, including oxaliplatin, become extremely reactive aquated platinum(II) complexes, which react with cellular

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

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

[6] Hartmann JT, et al. Toxicity of Platinum Compounds. *Expert Opin. Pharmacother.* 2003; 4:899, 899.

[7] Mauldin SK, et al. Displacement of the bidentate malonate ligand from (*d,l-trans*-1, 2-diaminocyclohexane)malonatoplatinum(II) by physiologically important compounds *in vitro*. *Biochem. Pharmacol.* 1988; 37:3321-3333.

[8] Safaei R and Howell SB. Copper transporters regulate the cellular pharmacology and sensitivity to Pt drugs. *Crit. Rev. Oncol. Hematol.* 2005; *53*:13-23.

[9] Safaei R, et al. The role of copper transporters in the development of resistance to Pt drugs. *J. Inorg. Biochem.* 2004; 98:1607-1613.

[10] Liang XJ, et al. A pleiotropic defect reducing drug accumulation in cisplatin-resistant cells. *J. Inorg. Biochem.* 2004; 98:1599-1606.

[11] Liang XJ, et al. Trafficking and localization of platinum complexes in cisplatin-resistant cell lines monitored by fluorescence-labeled platinum. *J. Cell. Physiol.* 2005; 202:635-641.

membranes, protein, RNA and DNA.[12] In dividing cells, oxaliplatin binds to the DNA and is thought to kill the cell.[13] In non-dividing cells, toxicity may be caused by damage to the cell membranes, inactivation of critical enzymes, or inhibition of transcription.[14] In addition, the presence of platinum-DNA complexes (adducts) has been postulated to trigger apoptosis directly[15] or "hijack" essential transcription factors.[16,17] Once again, this biological activity is dependent in part upon the rate of chemical substitution and thus the identity of the leaving group (X).

C. Oxaliplatin - Mechanism of Reaction

The kinetics of the alkaline hydrolysis of oxaliplatin have been measured – the first step is ring-opening with a half-life of 16 minutes in which a monodentate oxalato intermediate is formed.[18] The oxalate group is then lost with a half-life of 92 minutes. At pH 7.4 the monodentate oxalato intermediate constitutes only a very small fraction of the total oxaliplatin concentration. This reaction is described below:

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[12] Pinto AL and Lippard SJ. Binding of the antitumor drug *cis*-diamminedichloroplatinum(II) (cisplatin) to DNA. *Biochim. Biophys. Acta*. 1985; 780:167-180.

[13] *See id.*

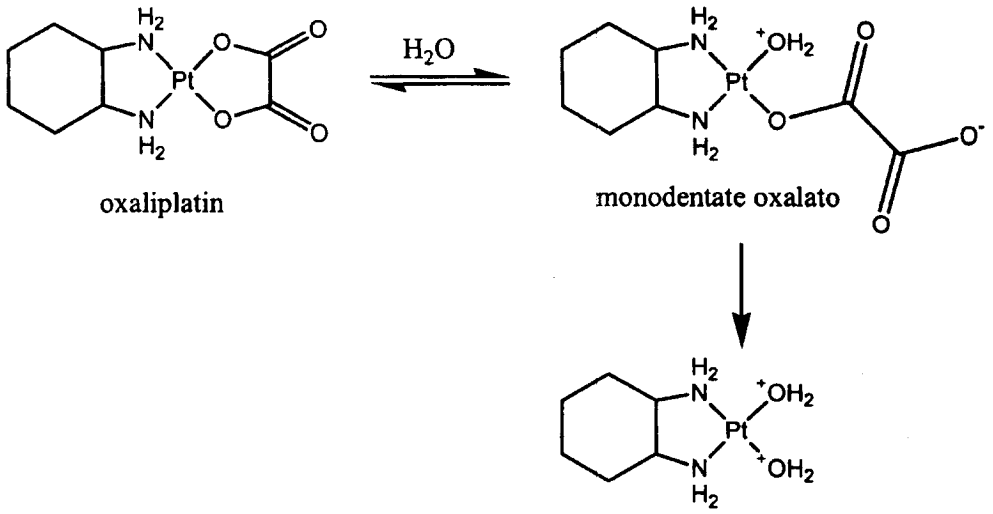
[14] Chaney SG. The chemistry and biology of platinum complexes with the 1, 2- diaminocyclohexane carrier ligand. *Int'l. J. Oncol.* 1995; 6:1291-1305.

[15] Christen RD, et al. Signaling and drug sensitivity. *Cancer Metastasis Rev.* 1994; 13:175-189.

[16] Treiber DK, et al. Cisplatin-DNA adducts are molecular decoys for the ribosomal RNA transcription factor hUBF (human upstream binding factor). *Proc. Nat'l. Acad. Sci. USA*. 1994; 91:5672-5676.

[17] Zhai X, et al. Cisplatin-DNA adducts inhibit ribosomal RNA synthesis by hijacking the transcription factor human upstream binding factor. *Biochemistry* 1998; 37:16307-16315.

[18] *See* Farrell Declaration at 5.



D. The Addition of Acid Buffers Can Form New Platinum Compounds

In an attempt to develop new biologically active platinum complexes that are water soluble, researchers have attempted to make new derivatives of the very water insoluble [$PtCl_2$(DACH)] by reacting it with mono and bidentate ligands such as dicarboxylic acids or other ligands.[19] As described in the attached declarations of Professors Stephen Chaney and Nicholas Farrell, should any of these acids or other ligands be added to a solution of oxaliplatin in water, they likely will similarly react with oxaliplatin or diaquaDACH platinum to form new platinum compounds.[20]

For example, Professor Chaney investigated byproducts of the reaction of diaquaDACHPt(II) or oxaliplatin with carboxylic acids. His data show that new, reactive platinum complexes are formed when the conjugate base of either inorganic acids (phosphoric acid, carbonic acid) or organic acids (carboxylic acids and amino acids) displace the oxalate ligand from oxaliplatin.[21]

Effective platinum anticancer agents are relatively stable in the bloodstream and are activated to aquated platinum(II) complexes once they are taken up by the cell. Studies by Professor Chaney, however, have shown that both bicarbonate and phosphate at physiological

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[19] *See* Schwartz, *infra* note 36.

[20] *See* Chaney and Farrell Declarations.

[21] *See* Chaney Declaration at 2.

concentrations were relatively effective at displacing malonate and oxalate ligands to form new platinum compounds Pt(DACH)(phosphato) and Pt(DACH)(bicarbonato). Because both the Pt(DACH)(phosphato) and Pt(DACH)(bicarbonato) complexes readily dissociated to form aquated Pt(DACH) complexes, these reactions likely activated the platinum (II) complexes.[22,23,24,25] The presence of bicarbonate and/or phosphate species, or any other products in the formulation, is therefore likely to affect toxic side effects and cellular uptake processes and hence cytotoxic potency.[26] Glutathione, amino acids, citrate, lactate and creatine at physiological concentrations were also capable of displacing the malate and oxalate ligands, with glutathione and the sulfur-containing amino acids being the most reactive.[27] On the basis of his data, Professor Chaney postulated that the displacement of the malonate and oxalate ligands from malonatoplatin and oxaliplatin, respectively, by glutathione and amino acids most likely inactivated the platinum complexes.[28,29]

The biotransformation studies are shown in the following model.[30,31,32]

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[22] Mauldin SK, et al. High-performance liquid chromatographic separation of platinum complexes containing the cis-1,2-diaminocyclohexane carrier ligand. *Anal. Biochem.* 1986; 157:129-143.

[23] Luo FR, et al. High-performance liquid chromatographic separation of the biotransformation products of oxaliplatin. *J. of Chromatography B* 1999; 724:345-356.

[24] Mauldin, *supra* note 7.

[25] Furthermore, the rate of these reactions was sufficient to explain the intracellular activation of malonatoplatin and oxaliplatin under physiological conditions.

[26] Centerwall CR, et al. Cisplatin carbonato complexes. Implications for uptake, antitumor properties, and toxicity. *J. Amer. Chem. Soc.* 2005; 127:12768-12769.

[27] *See* Mauldin, *supra* notes 7 and 22; Luo, *supra* note 23.

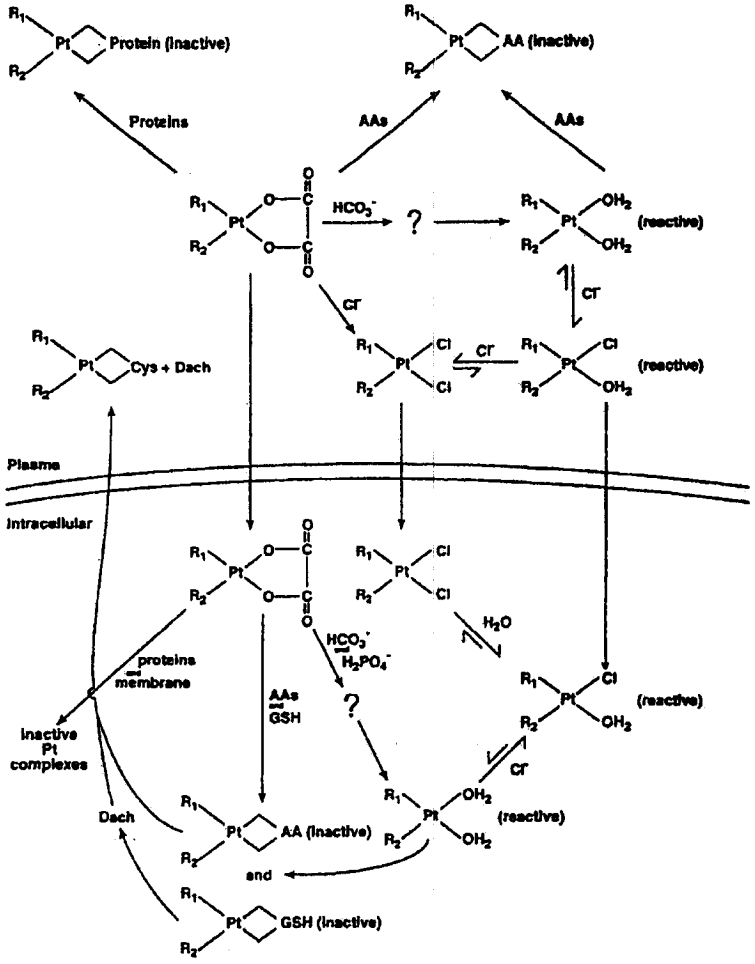
[28] *See* Chaney Declaration at 2; Luo, *supra* note 23; Mauldin, *supra* note 7.

[29] Mauldin SK, et al. Intracellular biotransformation of platinum compounds with the 1, 2-diaminocyclohexane carrier ligand in the L1210 cell line. *Cancer Res.* 1988; 48:5136-5144.

[30] *See* Luo, *supra* notes 23; Mauldin, *supra* note 29.

[31] Luo FR, et al. Biotransformations of oxaliplatin in rat blood *in vitro*. *J. Biochem. Molec. Toxicol.* 1999; 13:159-169.

[32] Chaney SG, et al. Carrier ligand effects in platinum resistant cell lines. *In* S. B. Howell (ed.), Platinum and other metal coordination compounds in cancer chemotherapy, pp. 269-283. New York: Plenum Press, 1991.



Biological Activity of Species formed by Displacement Reaction

These new platinum compounds formed by the addition of an acid to an aqueous oxaliplatin solution may be active and may differ from oxaliplatin significantly in terms of safety and efficacy. As discussed above, the biological activity of oxaliplatin is dependent upon the rate of substitution and, thus, the identity, of the leaving group. Thus the substitution of a new leaving group for the oxalate ligand normally found in oxaliplatin could create a new active substance.[33]

[33] *See* Chaney and Farrell Declarations.

As a result, formulations of oxaliplatin with other diacid or monoacid compounds would likely form active species.[34] Many, but not all, of the Pt(DACH)(carboxylato) complexes that can be formed by displacement in this manner have anti-tumor biological activity. For example, Pt(DACH) complexes containing citrate, isocitrate, ascorbate, tartrate and 4-carboxyphalate as the leaving ligand all displayed comparable cytotoxicity to malonatoplatin and oxaliplatin in the mouse L1210 tumor model, while Pt(DACH) complexes containing pyruvate or aspartate as the leaving ligand did not display any anti-tumor biological activity.[35,36,37,38,39,40] Moreover, the type and severity of toxicity caused by these complexes may well be different from oxaliplatin. For example, in phase I/II clinical trials the Pt(DACH)(4-carboxyphalato) and Pt(DACH)(isocitrato) complexes both showed greater myelosuppression and less neurotoxicity than oxaliplatin.[41,42] The results of these preclinical and clinical tests demonstrate that the biological activity of Pt(DACH) complexes cannot be predicted based solely on determinations of structural similarity.

The chemistry and biology of platinum agents is complex, and one cannot precisely predict how a Buffered Oxaliplatin product will behave in humans. Thus the extent and type of activity (e.g., toxic or anti-cancerogenic) of a Buffered Oxaliplatin cannot be predicted without appropriate studies. Any generic manufacturer wishing to introduce a Buffered Oxaliplatin product must conduct studies to determine the effects of the active

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[34] *See* Schwartz *infra* note 36 and Speer *infra* note 37, which provide *in vitro* activity and toxicity data for numerous mono and diacid DACH Pt derivatives. Such formulations include those discussed in the recent patent literature: *See* U.S. 2003/0109514 A1 and 6,476,068 describing oxaliplatin solutions containing lactic acid; and U.S. 2003/0109515 A1 describing oxaliplatin solutions containing malonic acid.

[35] Macquet JP, et al. Pharmacological and preclinical toxicology studies of 1,2-diaminocyclohexane(isocitrato)platinum(II). *Cancer Res.* 1984; *44*:3736-3743.

[36] Schwartz P, et al. Preparation and antitumor evaluation of water soluble derivatives of dichloro(1,2-diaminocyclohexane)platinum(II). *Cancer Treat. Rep.* 1977; 61:1519-1525.

[37] Speer RJ, et al. Preclinical testing of some cisplatin cogeners as potential antitumor agents. *J. Clin. Hemat. Oncol.* 1980; *10*:9-13.

[38] Burchenal JH, et al. Rationale for development of platinum analogs. *Cancer Treat. Rep.* 1979; 63:1493-1498.

[39] Hacker MP, et al. Ascorbato(1,2-diaminocyclohexane):platinum(II) complexes, a new series of water-soluble antitumor drugs. *Cancer Res.* 1985; 45:4748-4753.

[40] Hrubisko M, et al. Antitumor activity and cross-resistance studies with Pt-ascorbato complexes. *Neoplasma* 1989; 36:651-657.

[41] Chun H, et al. Phase II trial of 1,2-diamincyclohexane-(4-carboxyphthalato) platinum(II) in patients with refractory germ cell tumors. *Cancer Treat. Rep.* 1985; 69:459-460.

[42] Gouyette A, et al. Preliminary phase I clinical study and pharmacokinetics of (1,2-diaminocyclohexane)(isocitrato)platinum (II) or PHIC. *Anticancer Res.* 1986; 6:1127-1132.

compounds formed as byproducts of the reaction of the diaquaDACHPt(II) species, or oxaliplatin and the Buffered Oxaliplatin products.[43]

F. Tartaroplatin

An example of the problem presented by Buffered Oxaliplatin is the addition of tartaric acid. In Patent Application No. WO2005/020980 A1, Mayne Pharmaceuticals describes formulations of oxaliplatin containing various amounts of tartaric acid:

> "In yet another aspect the present invention provides a method for preparing a pharmaceutical formulation, the method comprising the steps of:
>
> (i) dissolving oxaliplatin in water to form a solution;
>
> (ii) dissolving in the solution an additive selected from the group consisting of a tartaric acid, a salt of tartaric acid, a pharmaceutically acceptable derivative of a pharmaceutically acceptable tartaric acid and mixtures thereof;
>
> (iii) optionally, adjusting the pH of the solution with a pharmaceutically acceptable base.
>
> pH adjustment may be carried out with any pharmaceutically acceptable base. Preferably the pharmaceutically acceptable base is a sodium hydroxide (NaOH) solution."[44]

The patent provides specific examples of this procedure, e.g., Example 4.

> "Example 4
>
> The following formulation was prepared for the purpose of regulatory testing:
>
> Oxaliplatin 5mg
>
> Tartaric acid 0.03 mg
>
> NaOH (adjust to pH of approximately 5)
>
> WFI qs 1mL

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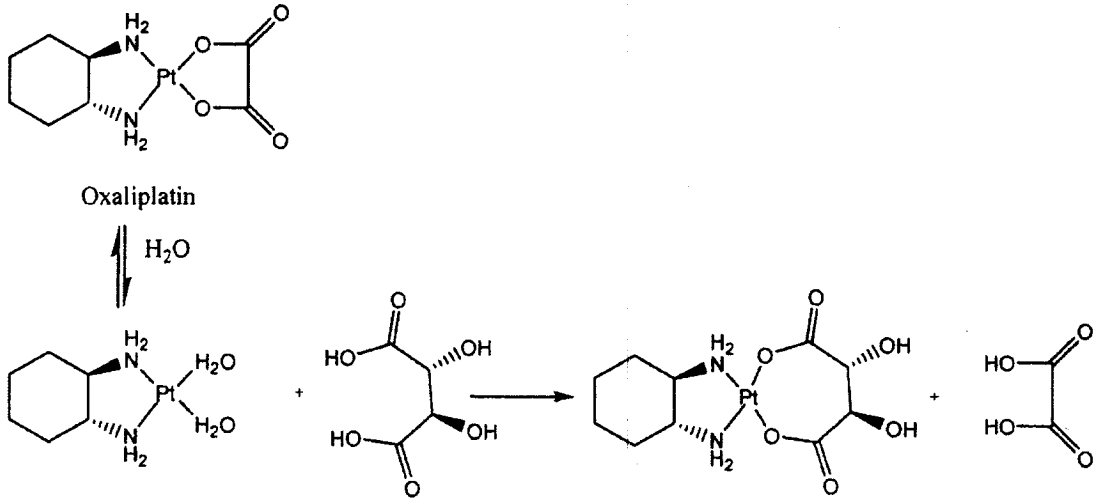
[43] *See id.*

[44] Mayne Pharma. Pty. LTD, et al. U.S. Patent Application No. WO/2005/020980 A1 (filed Oct. 03, 2005).

The pH is adjusted to pH 5 with a range of from 4.7 to 5.5 using NaOH. The concentration of tartaric acid is about 0.2 mM."[45]

Based on the above patent application and his knowledge of the chemistry of platinum species in aqueous solutions, Professor Farrell states that he would expect that the tartaric acid would react with diaquaDACH platinum (present as an unreacted material from the process to make oxaliplatin or the disassociation of oxaliplatin in solution) to form tartaroplatin according to the following reaction scheme:[46]



Professor Farrell also reviewed experiments conducted by sanofi-aventis researchers, who formulated solutions of oxaliplatin according to the Mayne patent applications. Those experiments clearly show that tartaroplatin is formed in that solution relative to the amount of added tartaric acid.[47]

G. It is Extremely Difficult to Predict the Biological Effect of the Addition of an Acid to Oxaliplatin

When evaluating the potential efficacy and toxicity of a compound such as tartaroplatin ((*trans-RR*)diaminocyclohexanetartaroplatinum(II)), it is important to understand that the efficacy and toxicity of such contaminants cannot easily be predicted on the basis of its

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[45] *See id.*

[46] *See* Farrell Declaration at 8.

[47] *See id. See also* sanofi-aventis Analytical Study Report: Analytical Assessment of Oxaliplatin Solutions Containing Tartaric Acid (attached hereto as Appendix B).

similarity to oxaliplatin. The rate of disassociation of tartaric acid is likely not the same as that of oxalic acid.

Tartaroplatin has been shown in the literature to be biologically active.[48,49] Based on those results, Professor Farrell predicts that the tartaroplatin formed in Mayne patent formulation (see pages 10 and 11) will have activity in humans.[50] While 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*-diammine vs. 1,2-diaminocyclohexane), other important characteristics are not predictable on the basis of structural similarities.[51] 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 or platinum systems to which an acid has been added 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[52,53] and only oxaliplatin and ormaplatin have been reported to display neurotoxicity as the dose-limiting toxicity.[54,55]

H. FDA Must Ensure Comparative Safety and Efficacy

In light of the above, sanofi-aventis urges FDA to take appropriate action to ensure the safety and efficacy of any proposed generic oxaliplatin product that contains an acid, or a conjugate base thereof, other than oxalic acid, and cites Eloxatin as the reference listed drug. FDA must require that any application for such a product contain data from preclinical and/or

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[48] *See* Schwartz, supra note 36, at 1523 (compound 265486 (tartaroplatin) has antileukemic activity in mice at doses of 12.5, 25 and 50 mg/kg and an LD50 of 60 mg/kg.).

[49] Speer RJ, et al. Antitumor Activity of Platinum Complexes of 1, 2-Diaminocyclohexane Isomers. *J. Clin. Hem. and Onc.* 1978; 8(2):44 (providing antitumor activity of + and – tartrato DACH Pt.).

[50] *See* Farrell Declaration at 11.

[51] *See id.*

[52] Wiseman LR, et al. Oxaliplatin - A review of its use in the management of metastatic colorectal cancer. *Drugs & Aging.* 1999; 14(6):459-475.

[53] Mani S, et al. Oxaliplatin: a review of evolving concepts. *Cancer Invest.* 2002; 20(2):246-263.

[54] *See supra* notes 42, 43, and 51.

[55] O'Rourke TJ, et al. Phase I clinical trial of ormaplatin (tetraplatin, NSC 363812). *Anti-Cancer Drugs* 1994; 5:520-526.

clinical testing sufficient to show that the addition of the acid buffer does not significantly alter the safety or efficacy profile of the resulting product.

If clinical testing is required to establish that the added acid has not altered the proposed generic's safety and efficacy profile, then the application may not be filed as an ANDA. Section 505(j) of the FDCA prohibits FDA approval of an ANDA if additional clinical trials are necessary to demonstrate the safety or effectiveness of the modified generic drug.[56] In this case, the applicant would have to submit its application as an NDA pursuant to section 505(b) of the Act.

IV. Conclusion

Sanofi-aventis expects that when oxaliplatin is combined with the conjugate base of an acid, new Pt(DACH) complexes will be produced that are likely to have biological activity and toxicity. Because Eloxatin does not contain an acid other than oxalic acid, the safety and efficacy of such complexes have not been tested.

The presence of complexes about which little is known makes it extremely difficult to characterize a Buffered Oxaliplatin product as a generic version of Eloxatin. Therefore, applicants for generic oxaliplatin using a Buffered Oxaliplatin must provide the necessary preclinical and/or clinical data to demonstrate that the new complexes formed by use of the added acid are not new active substances and do not alter the safety or efficacy of oxaliplatin. If clinical data is 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.

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[56] *See* 21 U.S.C. § 505(j)(2)(C)(i).

V. Required Material

A. Environmental Impact

The actions requested herein are subject to categorical exclusion under 21 C.F.R. §§ 25.30 & 25.31(a).

B. Economic Impact

An economic impact statement will be submitted at the request of the Commissioner.

C. Certification

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

Mark W. Moyer

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