Supplemental Declaration of Nicholas P. Farrell, Ph.D.

I, Nicholas P. Farrell, Ph.D., hereby make the following declarations in support of that Supplemental Position Paper submitted by Sanofi-Aventis S.A.:

I. Background and Qualifications

I am a professor of inorganic chemistry and chairman of the Department of Chemistry at Virginia Commonwealth University. I am a graduate of University College Dublin. Afterwards, I obtained my Ph.D. from Sussex University and completed postdoctoral fellowships at The University of British Columbia. My research interests are in medicinal uses of inorganic compounds, especially platinum-based anticancer agents. In my laboratory research the fundamental molecular concepts of chemistry and DNA structures are integrated with pharmacological and cell biology parameters (mechanisms of cellular resistance, gene expression) in rational design of new medically useful agents. The first genuinely structurally novel platinum drug to enter clinical trials in thirty years has arisen from my laboratory research. With this advance, the paradigm of cisplatin-based anticancer agents has been altered.

I have written or co-edited three books in the area of platinum anticancer agents and medicinal inorganic chemistry. I have authored over 200 refereed (peer-reviewed) papers and review chapters. I have received over sixty patents worldwide for my inventions. I was Chair of the first Gordon Research Conference on Metals in Medicine and, in October 2003, chaired the Ninth International Symposium on Platinum Compounds in Cancer Chemotherapy. I was recently honored as Distinguished Research Scholar of Virginia Commonwealth University for 2003-2004.

I am the same Nicholas P. Farrell who authored a declaration in support of the original Position Paper submitted by sanofi-aventis S.A.
II. Oxaliplatin Formulations Containing Sugars

I have been provided with an internal report from Sanofi-Synthelabo Recherche dated August 2004. That Report details a study in which 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 for direct injection is a plain aqueous solution of 5 mg/ml of water, with no added sugar.

The data in the Report show that the addition of these sugars to oxaliplatin increases the formation of certain Pt(DACH) compounds - namely diaquoPt(DACH) complexes and platinum (IV) complexes. The diaquoPt(DACH) complexes appear in three forms: Diaquo complexes (i.e. diaquoPt(DACH) complex shown as Figure 1), SR200028 (i.e. the diaquoPt(DACH) dimer complex shown as Figure 2), and Diaquo unspecified complexes (i.e. unidentified diaquoPt(DACH) (not figured):

![Diaquo Species](image1)

**Figure 1**

![SR 200028 Diaquo DACH dimer species](image2)

**Figure 2**

- 2 -
Similarly, the platinum (IV) complexes appear in two forms: SR200034 (i.e. the platinum (IV) complex shown as Figure 3) and SR200034 unspecified complexes (i.e. unidentified platinum (IV) complexes) (not figured):

![Platinum IV species](image)

SR 200034
Platinum IV species
Figure 3

That Report shows that the addition of sugar to oxaliplatin in a plain aqueous solution increases formation of three of these 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).¹ These data are presented in Table 1 below.

Table 1²

| Stability Studies at 3 months in ambient conditions (25°C, 60% humidity) |
|---|---|---|---|
| 5 mg/ml Oxaliplatin in Water | Diaquo Unspecified Impurities | SR200034 Unspecified Impurities |
| Plain aqueous Solution | None ≥ 0.05% | ND < 0.02% | None ≥ 0.02% |
| Lactose | 0.11% | 0.13% | None ≥ 0.05% |

² See id.
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**

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

<table>
<thead>
<tr>
<th></th>
<th>Glucose</th>
<th>Maltose</th>
<th>Sucrose</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg/ml</td>
<td>0.06%</td>
<td>0.06%</td>
<td>0.05%</td>
</tr>
<tr>
<td>Oxaliplatin in Water</td>
<td>0.10%</td>
<td>0.07%</td>
<td>D &lt; 0.05%</td>
</tr>
<tr>
<td></td>
<td>None ≥ 0.02%</td>
<td>None ≥ 0.02%</td>
<td>None ≥ 0.02%</td>
</tr>
</tbody>
</table>

(ND = non-detectable; D = detectable)

Based on these results and my knowledge of the chemistry of platinum species, it is evident that a reaction is occurring between the added sugar and the oxaliplatin or DACH in aqueous solution over time. I would expect that solutions stored at room temperature for any commercially relevant period of time (i.e. six months or more) would generate

/3 See id./
impurities above 0.2%. Indeed, because temperature affects only the rate of reaction, I would expect to see the same high levels of impurities at room temperature storage as were generated under the accelerated conditions used in some of the experiments reported in the Report, after only a slightly longer period of time.

I would expect the platinum complexes formed in sugar-containing formulations, including unspecified complexes possessing a platinum-DACH moiety, to have activity in humans. In vivo tests of compounds similar to the above-mentioned named platinum (IV) complexes have shown these compounds to be active.² Likewise, it is well known that diaquoDACH platinum (IV) compounds are active in vivo.⁵ Indeed, one such compound, tetrachloro-(d,l-trans)-1,2-diaminocyclohexaneplatinum(IV), was tested in humans and was found to be active, but too neurotoxic, as compared to cisplatin and carboplatin, for continued development.⁶ I would expect that SR 200034 and any related impurities containing a platinum IV species to be active and potentially toxic. In the 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

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² See; 1982 Khokhar et al., Synthesis and Antitumor Activity of 1,2-Diaminocyclohexane Platinum (IV) Complexes, 54. J. Inorg. Biochem. 39, 51 (showing the activity of the dichloro platinum IV species).


aqua reactive species in solution. 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). The extent and type of activity (e.g., toxic or anti-cancerogenic) cannot be predicted without the appropriate studies given the uncertainty of biological interactions with identified and unidentified platinum containing species.

The concentration of the sugars in solutions that have been studied are similar to what is obtained after reconstitution of sanofi-aventis' Eloxatin® lyophilized powder formulation (containing lactose). According to the labeling of that product, regulatory authorities, including the FDA, do not permit storage of reconstituted lyophilized solution more than 24 hours under refrigeration [2-8°C (36-46°F)]. After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].

Dated: 03/07/01

Nicholas P. Farrell

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