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State Enterprise Ukrainian Intellectual Property Institute (Ukrpatent)

1 Hlazunova Str., city of Kyiv-42, 01601

Department for Examination of Applications for Inventions, Utility Models and Integrated Circuit Topographies

Division of Pharmaceutics

Expert K.O. Kotyk

Acting under the Power of Attorney from the *All-Ukrainian Network of People Living with HIV/AIDS*, we additionally file herewith the materials to the Preliminary Report of SubstentiveExamination of December 03, 2015 evidencing that the invention “METHODS OF OBTAINING DIASTEREOMETRICALLY PURE PHOSPHORAMIDE PRO-DRUGS” according to Application No. a 2013 01999 of July 19, 2011 fails to meet the patentability criteria for "novelty" and "an inventive step" as defined by Article 7 of the Law of Ukraine "On Protection of Rights to Inventions and Utility Models" (hereinafter, the Law) as well as fails to meet the requirement for unity of invention as defined by Part 4 of Article 12 of the Law.

1. Bibliographic data of the Application No. a 2013 01999 of July 19, 2011

Application No. a 2013 01999 of July 19, 2011 for the invention "METHODS OF OBTAINING DIASTEREOMETRICALLY PURE PHOSPHORAMIDE PRO-DRUGS" was filed in Ukraine as a national phase of International Application PCT/US2011/044581 published under WO2012012465. International Application PCT/US2011/044581 covers the methods of obtaining the compound such as sofosbuvir. Sofosbuvir is a hepatitis C virus (HCV) NS5B polymerase inhibitor developed by the company Gilead Pharmasset LLC (US) and is used for the treatment of chronic hepatitis C (CHC) as a component of the combination antiviral therapy in adult subjects in combination with other medicines. Preparations containing sofosbuvir are also known as Sovaldi, Hepcinat, Resof, Hepcvir, SoviHep, Harvoni. Please note that Application PCT/US2011/044581 relates to secondary (derivative) patent applications relating to certain forms of the use or obtaining of the already known compounds, facts of which have already been disclosed.

2. Regulations

According to Article 7 of the Law (the citations are italicized hereinbelow):

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"3. An invention (utility model) shall be considered to be new provided if it does not form part of the state of the art.

4. The state of the art comprises all the facts made available to the public throughout the world before the date of filing of the application with the Office or, if the priority has been claimed, before the date of its priority.

…

7. An invention shall be considered as involving an inventive step provided if it is not obvious to a person skilled in the art, i.e. an invention does not proceed obviously from the state of the art."

According to Section 6.5.3.1 of the Rules of Examination of an Application for Invention and Application for Utility Model (hereinafter, the Rules of Examination):

«An invention has an inventive step if, having regard to the state of the art, it is not obvious to a person skilled in the art. When assessing the inventive step, the claimed invention is compared not only with separate documents or their parts, but with combination of documents or their parts (so called composite prototype), when the possibility of combining the documents or their parts is obvious for a person skilled in the art.

When an inventive step is checked, it is established whether the influence of the combination of the features of the claimed invention on obtaining the technical result indicated by the applicant is known from the state of the art. If this fact is not established, the invention is considered to meet the criterion of inventive step. (Sec. 6.5.3.2 of the Rules).

The fact that influence of combination of features of the claimed invention on the technical result is known may be proved by combining two or more information sources or their parts, different excerpts from one and the same source or from any different information sources. Involvement of arguments based on knowledge well-known in a specific art without indication to any specific information sources is permissible. (Sec. 6.5.3.6 of the Rules).

If the claimed invention meets the criterion of an inventive step with regard to the independent claim(s), the respective dependent claims are not further checked (Sec. 6.5.3.8 of the Rules)".

According to Part 4 of Article 12 of the Law:

"The application for an invention shall relate to one invention only or to a group of inventions, so linked as to form a single inventive concept (requirement of unity of invention)".

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According to Section 2.6 of the Rules of Preparing and Filing an Application for Invention and Application for Utility Model (hereinafter, the Rules of Preparing):

"2.6.1. Unity of invention exists in a group of invention where there is a technical relation among the claimed inventions involving one or more of the same or corresponding special technical features defining the contribution, which each of the inventions, considered as a whole, makes over the prior art.

2.6.2. Ascertainment whether a group of inventions is so linked as to form a single inventive concept shall be made irrespective of whether these inventions are claimed in separate claims or as an alternative within one claim.

2.6.3. The requirement of unity of invention is satisfied when:

the application relates to one invention, namely one product, process (method), including new use of a previously known product or process;

the application relates to one invention characterized by the development or improvement of its certain embodiments, which development or improvement do not involve substitution or elimination of certain features included in an independent claim;

the application relates to a group of inventions so linked as to form a single inventive concept.

The requirement of unity of invention is satisfied by a group of inventions, where the application in particular relates to:

inventions, one of which is adapted for obtaining (manufacturing) of the other, for example, an apparatus or substance and a process for obtaining (manufacturing) of the said apparatus or substance as a whole or of its part;

inventions, one of which is adapted for carrying out of the other, for example, a process and an apparatus for carrying out the said process as a whole, or of one of its steps;

inventions, one of which is adapted for use of the other (in the other), for example, a process or an apparatus and its part; a process and substance for the use in the said process; new use of a known apparatus or substance and a process for their new use; new use of an apparatus or a substance and an apparatus or a composition comprising them, etc.;

inventions, which are the subject matters of the same type, having one and the same intended purpose, and, which provide obtaining of one and the same technical effect (variants)".

4. Cited documents

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The following documents are cited in the opposition:

- Publication of International Application WO 2008/121634 A2 of **October 09, 2008**, referred to Section 4 of the Preliminary Report of Substantive Examination (document D1),

- ALI H M ET AL: "Quantitative structure-activity relationships (QSAR) of two series of O-aryl or N-aryl O-ethyl phosphoramidate and phosphorodiamidate fungicides incorporating amino acid ethyl esters", BULLETIN OF ENVIRONMENTAL CONTAMINATION AND TOXICOLOGY, SPRINGER-VERLAG, NE, vol. 65, no. 4, 1 October 2000 (**2000-10-01**), pages 415-420, XP019698851, ISSN: 1432-0800 (document D2).

5. The invention according to independent claims 1 and 23 fails to meet the requirement for unity of invention

The invention according to claim 1 is the method of obtaining a compound of Formula Ia or Ib or a pharmaceutical salt or acid thereof, that is the method of obtaining the compound with antiviral activity, in particular pro-drugs of inhibitors of RNA-dependent RNA polymerase of hepatitis C. The invention according to claim 23 is the method of obtaining a compound of Formula IIIa or IIIb or a salt of a compound ester thereof, which is used for obtaining a compound of Formula Ia or Ib according to claim 1 and has no antiviral activity. This means that the invention according to claim 1 and claim 23 have different purposes, are aimed at solving various objects and do so in different ways, so they are not related by the single inventive concept. The only common feature for these compounds is an application of phosphate derivatives, which are known from D2, however the methods according to claim 1 and claim 23 have no other common technical features. Moreover, it is clear that the compounds according to claim 1 and claim 23 have different technical result. Accordingly, methods for obtaining these compounds are not characterized by a set of similar or relevant essential features, which determine the contribution to the prior art by each of the inventions according to claim 1 and claim 23. Therefore the inventions according to claim 1 and claim 23 do not meet the requirement for unity for a group of inventions as defined by Section 2.6.1 of the Rules of Preparing and Part 4 of Article 12 of the Law.

5. The invention according to claims 1-22 does not meet the patentability criteria for “novelty” and “an inventive step”

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As stated in the Preliminary Report of Substantive Examination, the invention does not have an inventive step according to claims 1-22, in particular in view of D1. For example, D1 discloses synthesis of pro-drugs based on phosphate nucleosides and illustrates obtaining of such compound using phosophorochloridate derivatives. Even taking into consideration the fact that in the examples of D1 the halogen is used as a substituent, D1 also includes a list of alternative substituents (see page 668, lines 15-26), which include, in particular, pentafluorphenoxide and p-NO_2-phenoxyde referred to in claim 1 of the invention. Thus, D1 (page 668) fully discloses the use of synthesis of pro-drugs phosphate nucleosides using alternative substituents , which is the same of claims 1-22, i.e. the invention according to claims 1-22 is not new. Use of the said substituents for fusion reactions described in D1 is obvious for a person skilled in the art. This further confirms that the invention according to claims 1-22 is obvious from D1 and, as such, does not meet the patentability criterion for "an inventive step".

Thus, the claimed invention according to claims 1-22 does not meet the criterion of "novelty" according to Part 3 of Article 7 of the Law and does not meet the criterion of "an inventive step" according to Part 7 of Article 7 of the Law.

With regard to the possible corresponding patents granted in other countries for the similar invention, please note that this may be due to different approaches applied in the substantive examination of secondary (derivative) patents.

Furthermore, on behalf of the principal, we would like to provide below additional information which is not related to the invention, but rather intended to explain the motivation of the objection filed by a legal entity, which is a charitable non-for-profit organization and, as such, may neither manufacture nor distribute medicinal products and, hence, cannot compete with the applicant in Ukraine.

Hepatitis C virus (HCV) is a major global problem for public health. The virus is transmitted by direct contact with blood of an infected person. People with injuries from needles, healthcare professionals working with blood/blood products, recipients of transfusions/blood products, organ transplant recipients and injection drug users are among the risk groups for HCV infection. According to the World Health Organization, 170+ million people are chronic carriers of hepatitis B virus which can cause cancer and/or cirrhosis. Ukraine has about 1.2 million people who are chronically infected with HCV[1].

[1] Уніфікований клінічний протокол: вірусний гепатит С, затверджений наказом МОЗ № 233, від 02 березня 2014, стор. 7 [Unified Clinical Protocol: Viral Hepatitis C approved by MoH Order No. 233 dd. March 02, 2014, p. 7, *in Ukrainian*]
http://www.dec.gov.ua/mtd/dodatki/2014_233VirysGepatitC/2014_233_YKPMD.doc

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Today, about 66 thousand patients with HCV[2] require therapy, while the National Targeted Programme for Prevention, Diagnosis and Treatment of Viral Hepatitis for the Period until 2016 provide treatment to about 1,300 patients only due to high treatment costs.

In addition, there are about 231,409 people living with HIV (PLHIV) in Ukraine[3]. Given global co-infection rate is 15%, which means that about 34,000 people living with HIV are also infected with HCV. HIV affects the progression of HCV, which leads to higher rates of HCV progression in a chronic form, accelerates progression of HCV infection and contributes to high mortality. In the era of antiretroviral therapy, patients co-infected with HIV/HCV are at higher risk of morbidity and mortality compared to patients with HIV infection only and those with chronic hepatitis C alone.

HIV-infected patients still demonstrate a five times greater mortality rate compared to non-HIV-infected people, and chronic hepatitis C is associated with a 50% increase in mortality rate among patients diagnosed with AIDS.[4]

Taking into consideration the crisis related to HCV and HIV/AIDS in Ukraine's public health, it is important that people living with HCV and HIV can get access to the latest and most effective treatment methods without "evergreen" patents, which stand on their way. "Evergreen" patents allow a company to obtain "artificial" exclusive rights. This allows setting extremely high prices for medicines making them absolutely unaffordable for Ukrainian patients. For example, Gilead set the price for a treatment course with Sovaldi as high as EUR 41,000.00 and USD 84,000 in France and in USA, respectively.

We kindly ask the expert to review the submitted materials and the information about lack of patentability criteria for claimed invention and to take them into account under examination.

Enclosure:

- Power of Attorney issued by *All-Ukrainian Network of People Living with HIV/AIDS*, 1 page 1 copy

Sincerely,

Patent Attorney

[2] http://hvstop.org/news.php?id_news=168

[3] Український центр контролю за соціально небезпечними хворобами, Інститут епідеміології та інфекційних хвороб імені Л. В. Громашевського, Інформаційний бюлетень № 40, Київ, 2013, стор. 14. http://ucdc.gov.ua/uk/statystyka/informatsijni-byuleteni/vil-infektsiya [Ukrainian Center for Control over Socially Dangerous Diseases, L.V. Gromashevsky Institute for Epidemiology and Infectious Diseases, Information Bulletin No. 40, Kyiv, 2013, p. 14 *in Ukrainian*]

[4] Branch AD, Van Natta ML, Vachin ML, et al. Mortality in HCV-infected patients with a diagnosis of AIDS in the era of combination anti-retroviral therapy. Clin Infect Dis 2012;55:137-144

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