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| **TRAN & TRAN**  **INTELLECTUAL PROPERTY CO., LTD**  **\*\*\*\*\***  **No.: 009/HB-CV/2022** | **SOCIALIST REPUBLIC OF VIETNAM** Independence - Freedom - Happiness Hanoi, December 29, 2022 |

## **To: INTELLECTUAL PROPERTY OFFICE OF VIETNAM (IP VIETNAM)**

## 384-386 Nguyen Trai - Hanoi

***Re: Explanation of reasons for requesting invalidation of Patent No. 1- 0014607***

Dear Department:

We, Tran & Tran Intellectual Property Co., Ltd., are an industrial property representative service organization, authorized by the **Action Center for People living with HIV,** located at Group 18, Ngoc Thuy Ward. , Long Bien district, Hanoi city to proceed with filing a request for invalidation of a Patent in Vietnam.

In this writing, we respectfully request the IP Vietnam to consider and invalidate the Patent (hereinafter referred to as “**the Patent**”) with the following details:

Patent number: **1- 0014607**

Granted date: September 29, 2015

Expiry date: 10/03/2029

PCT application No.: PCT/US2009/036635

PCT filing date: March 10, 2009

International publication number: WO2009/114512

Priority data: US Patent Application No. 61/035.662 filed on 11/03/2008

Title of invention: Azetidin and cyclobutane derivatives as Janus Kinase (JAK) inhibitors and pharmaceutical compositions thereof

Owner: **INCYTE HOLDINGS CORPORATION**

Address: 1801 Augustine Cut-Off, Wilmington, DE 19803, United

States of America

Specifically, we request to cancel the entire validity of the claims (hereinafter referred to as the “Claims”) of the Patent No. 1- 0014607 (or Patent No. 14607) of the owner **INCYTE HOLDINGS CORPORATION** (hereinafter referred to as “**INCYTE”)** is based on the following legal basis and arguments:

**1. Legal basis applied according to current regulations**

According to the provisions of Article 96.1.b of the Law on Intellectual Property No. 50/2005/QH11 as amended and supplemented according to the Law amending and supplementing a number of articles of the Law on Intellectual Property 2009 (hereinafter referred to as "Intellectual property Law"): “*A protection title shall be entirely invalidated in the following cases:..* *The subject matter of industrial property fails to satisfy the protection conditions at the time the protection title is granted".*

According to the provisions of Article 96.3 of the Intellectual Property Law: “*Organizations and individuals may request the state management agency in charge of industrial property rights to invalidate all or part of the validity of the protection title, provided that they pay fees and charges.”*.

**2. Legal basis applied at the time of granting Patent No. 00014607**

Patent No. 1-0014607 was granted on September 29, 2015 based on the international application No. PCT/US2009/036635 with the filing date of March 10, 2009 and the number of application entering the Vietnamese national phase of 1-2010-02422 is considered after the date of the introduction of the Law on Intellectual Property No. 50/2005/QH11 (effective from July 1, 2006). Therefore, according to the provisions of Article 220.3 of the Intellectual Property Law, the patent protection conditions at the time of granting the Patent applicable to the protected objects of the Patent No. 1- 0014607 shall be applied in accordance with the provisions of the Law on Intellectual Property. Law on Intellectual Property No. 50/2005/QH11 as amended in accordance with the Law amending and supplementing a number of articles of the Intellectual Property Law 2009 (hereinafter referred to as the Law on Intellectual Property 2005, revised 2009) and guidance documents. Specifically, according to the provisions mentioned in Section 1 and the following provisions in the Law on Intellectual Property No. 50/2005/QH11:

Article 58.1 of the 2005 Intellectual Property Law, as amended in 2009, states:

**«***Article 58.1. An invention shall be protected by mode of grant of invention patent when it satisfies the following conditions:*

*a) Being novel;*

*b) Involving an inventive step;*

*c) Capable of industrial application.»*

Article 60.1 of the 2005 Intellectual Property Law, as amended in 2009, states:

*«Article 60.1. An invention shall be considered novel if it has not yet been publicly disclosed through use or by means of a written description or any other form, inside or outside the country, before the filing date or the priority date, as applicable, of the invention registration application.»*

Article 61 of the 2005 Intellectual Property Law, as amended in 2009, states:

*“Article 61. Inventive step of inventions*

*An invention shall be considered involving an inventive step if, based on technical solutions already publicly disclosed through use or by means of a written description or any other form, inside or outside the country, prior to the filing date or the priority date, as applicable, of the invention registration application, it constitutes an inventive progress and cannot be easily created by a person with average knowledge in the art.”*

### 3. Field of the invention

The present invention relates to azetidin and cyclobutane derivatives, as well as their compositions and methods of use and preparation, which are JAK inhibitors useful in the treatment of JAK-associated diseases including, for example, inflammatory and autoimmune disorders, as well as cancer.

**4. Reference documents**

|  |  |
| --- | --- |
| **D1:** | US2007135461A filed on 12.12.2006, published on 14.06.2007. D1 provides heteroaryl-substituted pyrrolo[2,3-b]pyridine and heteroaryl substituted pyrrolo[2,3-b]pyrimidins that modulate the activity of Janus kinases and are useful in the treatment of diseases related to activity of Janus kinases including, for example, immune-related diseases, skin disorders, myeloid proliferative disorders, cancer, and other diseases. D1 also mentioned compounds according to claim 1 and claim 2 of **Patent No. 1-0014607** and their pharmaceutically acceptable salts. |

**5. Claims of the Vietnam Patent No. 1- 0014607 do not meet the criteria for granting patent**

In order to speed up the examination process of patent application in Vietnam, the **INCYTE** has amended the Claims of the aforementioned invention on the basis of Chinese Patent No. CN102026999 (B). With the above narrowing of the scope of protection, the invention was granted with Patent No. **1- 0014607** on September 29, 2015 with 15 claims as follows:

*"1. {1-(Ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl} acetonitrile, or pharmaceutically acceptable salt thereof.*

*2. {1-(Ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl} acetonitrile, phosphoric acid salt.*

*3. A composition comprising a compound of claim 1, and at least one pharmaceutically acceptable carrier.*

*4. A composition comprising a compound of claim 2, and at least one pharmaceutically acceptable carrier.*

*5. The composition of claim 3 or 4, which is suitable for topical administration.*

*6. The composition of claim 3 or 4, which is suitable for oral administration.*

*7. The compound of claim 1 or claim 2, for manufacture of a medicament.*

*8. The compounds of claim 7, wherein said medicament is for treating autoimmune disease.*

*9. The compound of claim 8, wherein said autoimmune disease is a skin disorder, multiple sclerosis, rheumatoid arthritis, juvenile arthritis, psoriatic arthritis, type I diabetes, lupus, inflammatory bowel disease, Crohn's disease, myasthenia gravis, immunoglobulin nephropathy, myocarditis, or autoimmune thyroid disorder.*

*10. The compound of claim 9, wherein said autoimmune disease is rheumatoid arthritis.*

*11. The compound of claim 9, wherein said autoimmune disease is a skin disorder, and is atopic dermatitis, psoriasis, skin sensitization, skin irritation, skin rash, contact dermatitis or allergic contact sensitization.*

*12. The compound of claim 7, wherein said medicament is for treating an inflammatory disease.*

*13. The compound of claim 7, wherein said medicament is for treating cancer.*

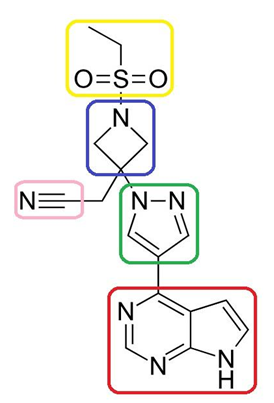
*14. The compound of claim 13, wherein said cancer is a solid tumor, prostate cancer, renal cancer, hepatic cancer, breast cancer, lung cancer, thyroid disease, Kaposi's sarcoma, Castleman’s disease, pancreatic cancer, lymphoma, leukemia, or multiple myeloma.*

*15. The compound of any of claims 7 to 14, wherein said medicament is is suitable for oral administration.”*

Thus, the scope of protection of invention No. **1- 0014607** includes:

| **Subject matter** | **Claims** | **Note** | **Structural formula and notes** |
| --- | --- | --- | --- |
| Compound | 1 | **Baricitinib** compound *(original claim 14)* |  |
| Compound | 2 | **Baricitinib**'s phosphate salt  *(original claim 15)* |  |
| Composition | 3-6 | Pharmaceutical composition comprising compounds according to claim 1 or claim 2 |  |
| Compound | 7-15 | Compounds according to claim 1 or claim 2 use for making medicine | Dependent of claim 1 or claim 2 |

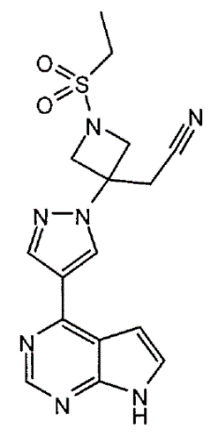
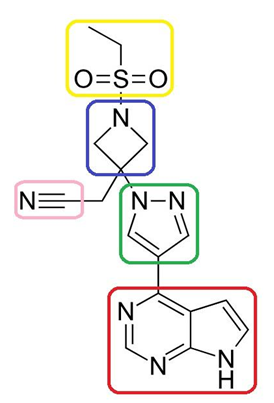
For the convenience of analysis and evaluation, the structure of Baricitinib (claim 1) and its parts are highlighted as below:



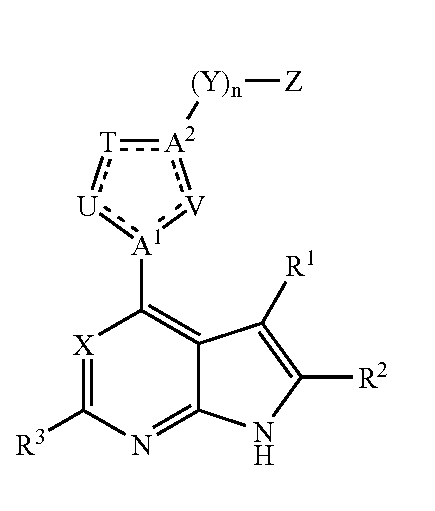
Baricitinib and its parts: a pyrrolopyrimidine ring in red, a pyrazole ring in green, an azetidine ring in blue, a sulfonamide in yellow and a nitrile in pink

1. *Claim 1 of the Patent No. 1- 0014607 lacks of novelty*

Claim 1 of the Patent refers to “*{1-(Ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl} acetonitrile, or pharmaceutically acceptable salt thereof*”.

**(or )

However, claim 1 of US2007135461A1 (D1) described heteroaryl-substituted pyrrolo[2,3-b]pyrimidin compounds as modulators of the activity of Janus kinases with Formula I compounds including pharmaceutically acceptable salt forms or prodrugs thereof:



Markush Formula I disclosed in D1 (claim 1)

wherein:

**A1**and **A2***are independently selected from* **C** *and* **N;**

**T** *,* **U** *and* **V** *are independently selected from O, S,* **N** *,* **CR 5***and NR 6;*

*wherein the 5-membered ring formed by A 1,A 2,U, T and V is aromatic;*

**X** *is* **N** *or CR4;*

**R1***,* **R2***,* **R3** *and R4 are independently selected from* **H** *, halo, C1-4 alkyl, C2-4 alkenyl, C2-4alkynyl, C1-4 haloalkyl, halosulfanyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, CN, NO2 , OR7 , SR7, C(O)R8,C(O)NR9R10,C(O)OR7OC(O)R8, OC(O)NR9R10, NR9R10,NR9C(O)R8, NRcC(O)OR7, S(O)R8,S(O)NR9R10, S(O)2 R8, NR9S(O)2R8 and S(O)2NR9R10;*

**R 5***are* **H** *, halo, C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, C1-4 haloalkyl, halosulfanyl, CN, NO2, OR7,SR7,C(O)R8,C(O)NR9R10, C(O)OR7,OC(O)R8,OC(O)NR9R10, NR9R10, NR9C(O)R8, NR9C(O)OR7 ,S(O)R8, S(O)NR9R10, S(O)2R8, NR9S(O)2R8 or S(O)2NR9R10;*

Therefore, **the core structure** of Baricitinib of claim 1 of **the Patent** was covered when:

* **A1** is **C** and **A2** is **N;**
* **T** is **N;**
* **U** and **V** is **CR5** and **R5** is **H;**
* **X** is **N;**
* **R1** , **R2** , **R3** is **H.**

And that is the Compounds disclosed in Formula IV in D1 (claim 45):

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| Formula I disclosed in D1  (claim 1) | Formula IV disclosed D1 (claim 45) | Baricitinib of claim 1 of **the Patent** |

Regarding the other part of the molecules **(Y)n -Z component** in **D1**, according to claim 1 of the D1:

***Y*** *is C 1-8 alkylene, C 2-8 alkene, C 2-8 alkylylene, (CR1R1)p -(C3-10 cycloalkylene)-(CR11R12)q, (CR11R12)p-(arylen)-(CR11R12)q, (CR11R12)p-(C1-10 heterocycloalkylene)-(CR11R12)q, (CR11R12)p, -(heteroarylen)-(CR11R12)q, (CR11R12)pO(CR11R12)q, (CR11R12)pS(CR11R12)q, (CR11R12)pC(O)(CR11R12)q, (CR11R12)p C(O)NRc (CR 11R12)q,(CR11R12)pC(O)O(CR11R12)q, (CR11R12)pOC(O)(CR11R12)q , (CR11R12)pOC(O)NRc(CR11R12)q, (CR11R12)p NRc(CR11R12)q, (CR11R12)p NRcC(O)NRd(CR11R12)q , (CR11R12)pS(O)(CR11R12)q , (CR11R12)pS(O)NRc(CR11R12)q, (CR11R12)pS(O)2(CR11R12)q , or (CR11R12)pS(O)2 NRc (CR11R12)q , where C1-8 alkylene, C2-8 alkene, C2-8 alkylylene, cycloalkylene, arylen, heterocycloalkylene, or heteroarylen, optionally substituted with 1, 2, or 3 independent substituents chosen from -D1 -D2 -D3 -D4;*

***Z*** *is H, halo, C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, C1-4 haloalkyl, halosulfanyl, C1-4 hydroxyalkyl, C1-4 cyanoalkyl, ═CR i, =NR i , Cy, CN, NO 2, OR a, SR a, C(O)R b, C(O)NRcR d , C(O)OR a, OC(O)R b, OC(O)NRcRd, NRcRd, NRcC(O)Rb, NRcC(O)NRcRd , NRcC(O)ORa,C(═NRi)NRcRd , NRcC(═NRi)NRcRd, S(O)Rb, S(O)NRcRd, S(O)2Rb , NRc S(O)2Rb,C(═NOH)Rb, C(═NO(C 1-6 alkyl)Rb,and S(O)2NRcRd,which say C1-8 alkyl, C2-8 alkenyl, or C2-8 alkynyl, optionally substituted by 1, 2, 3, 4, 5 or 6 substituents independently chosen from the halo, C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, C1-4 haloalkyl, halosulfanyl, C1-4 hydroxyalkyl, C1-4 cyanoalkyl,* ***Cy 1*** *, CN, NO 2, OR a , SR a , C(O)R b , C(O)NRcRd , C(O)ORa , OC(O)R b , OC(O)NRcRd , NRcRd , NRcC(O)Rb , NRcC(O)NRcRd , NRcC(O)ORa , C(═NRi)NRcRd, NRcC(═NRi)NRcRd , S(O)Rb , S(O)NRcRd , S(O)2Rb , NRcS(O)2Rb , C(═NOH)Rb ,C(═NO(C1-6 alkyl))Rb,and S(O)2NRcRd;*

*wherein when Z is H, n is 1;*

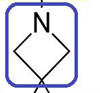
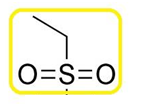
*or the -(Y)n -Z moiety is taken together with i) A 2 to which the compound is attached, ii) R5 or R6 of either T or V, and iii) C or N atom to which the R5 or R 6 of either T or V is attached to form a 4- to 20-membered aryl, cycloalkyl, heteroaryl or heterocycloalkyl ring fused to the 5-membered ring formed by A1, A2, U, T andV,wherein said 4- to 20-membered aryl, cycloalkyl, heteroaryl, or heterocycloalkyl ring is optionally substituted by 1, 2, 3, 4, or 5 substituents independently selected from -(W)m-Q;*

*(...)*

***Cy1*** *and Cy2 are independently selected from aryl, heteroaryl, cycloalkyl and* ***heterocycloalkyl****,* ***each optionally substituted by*** *1,* ***2*** *, 3, 4 or 5 substituents independently selected from halo, C1-4 alkyl, C2-4 alkenyl, C2-4 alkynyl, C1-4 haloalkyl, halosulfanyl, C1-4 hydroxyalkyl,* ***C1-4 cyanoalkyl*** *, CN, NO2, ORa″ , SRa″ , C(O)Rb″ , C(O) NRc″Rd″,C(O)ORa″,OC(O)Rb″, OC(O)NRc″Rd″ , NRc″Rd″, NRc″C(O)Rb″, NRc″C(O)ORa″ , NRc″S(O))Rb″, NRc″S(O)2Rb″, S(O)Rb″, S(O)NRc″Rd″,* ***S(O)2Rb″****, and* ***S(O)2 NRc″Rd″;***

**Rb″**are independently selected from H, **C1-6 alkyl**,C1-6 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl and heterocycloalkylalkyl, wherein said C1-6 alkyl, C1-6 haloalkyl, C2-6 alkenyl, C2-6 alkynyl, aryl, cycloalkyl, heteroaryl, heterocycloalkyl, arylalkyl, heteroarylalkyl, cycloalkylalkyl or heterocycloalkylalkyl is optionally substituted with 1, 2 or 3 substitutions independently selected from OH, CN, amino, halo, C1-6 alkyl, C1-6 haloalkyl, C1-6 haloalkyl, halosulfanyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl and heterocycloalkyl;

**n** is **0** or 1;

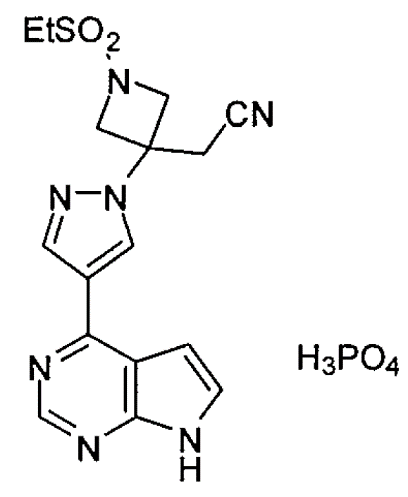
Thus, when **n** is **0** and **Z** is **Cy1**, and **Cy1**is **heterocycloalkyl** ( ) optionally substituted by two substituents selected from: cyanoalkyl ( ) and substituent ***S(O)2Rb″****, where* ***R b”****is chosen from* **C 1-6 alkyl** ( ), then the compound will be Baricitinib of the claim 1 or claim 2 of **the Patent:**

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|  | => |  |
| Compound of claim 45 of D1 |  | Compound of claim 1 of **the Patent** |

Therefore, it can be concluded that D1 has disclosed Baricitinib of claim 1 of **the Patent.** Therefore, claim 1 of the Patent lacks of novelty.

1. *Claim 2 of the Patent No. 1- 0014607 lacks of novelty*

Claim 2 refers to the phosphate salt of Baricitinib:



As shown above, Baricitinib is mentioned by D1. And so, the pharmaceutically acceptable salt of Baricitinib was also disclosed in D1, because on page 19, D1 states that:

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|  | 0242. The present invention also includes pharmaceutically acceptable salts of the compounds described herein. As used herein, "pharmaceutically acceptable salts” refers to derivatives of the disclosed compound wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acids salts of basic residues such as amines; alkalis or organic salts of acidic residues such as carboxylic acids; and the like. **The pharmaceutically acceptable salts of the present invention include the conventional non-toxic common salts** of the parent compound formed, for example, from non-toxic **inorganic** or organic **acids.** The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amounts of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two: generally, nonaqueous medium like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile (MeCN) is preferred. Lists of suitable salts are found in Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, p. 1418 and Journal of Pharmaceutical Sciences, 66, 2 (1977)…” |

Therefore, claim 2 of the Patent also lacks of novelty.

*c. Claim 3-6 of the Patent No. 1- 0014607 lack of inventive step*

Composition claims 3-6 of the Patent No. 1-0014607defines “*A composition comprising a known compound of claim 1 or claim 2, and at least one pharmaceutically acceptable carrier”*. However, the description of the Patent No. 1-0014607has a paragraph related to “Pharmaceutical Formulations and Dosage Forms” (page 52) which states that pharmaceutical formulation is “known in the pharmaceutical industry”:

“*Pharmaceutical Formulations and Dosage Forms*

When employed as pharmaceuticals, the compounds **of the invention can be administered in the form of pharmaceutical compositions**. These compositions can be prepared in a manner well known in the pharmaceutical art, and can be administered by a variety of routes, depending upon whether local or systemic treatment is desired and upon the area to be treated. **Administration may be topical (including transdermal, epidermal, ophthalmic and to mucous membranes including intranasal, vaginal and rectal delivery)**, pulmonary (e.g., by inhalation or insufflation of powders or aerosols, including by nebulizer; intratracheal or intranasal), oral or parenteral. Parenteral administration includes intravenous, intraarterial, subcutaneous, intraperitoneal intramuscular or injection or infusion; or intracranial, e.g., intrathecal or intraventricular, administration. Parenteral administration can be in the form of a single bolus dose, or may be, for example, by a continuous perfusion pump. **Pharmaceutical compositions and formulations for topical administration may include transdermal patches, ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders.** Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful. ”(See page 52, the Patent No. 1-0014607).

According to the UNDP “Guidelines for the examination of patent applications relating to pharmaceuticals” (2016):

“The preparation of **pharmaceutical compositions** (formulations) **requires the use of techniques and compounds commonly known to a person skilled in that field**. Patent applications on compositions will normally **confront an objection of lack of inventive step**. Generic claims over compositions associated with new active ingredients, prodrugs, etc. with unspecified carriers or excipients will also be objectionable.” (page 36)

Thus, the pharmaceutical compositionclaims 3-6 of the Patent No. 1-0014607with the description “*composition comprising a known compound of claim 1 or claim 2, and at least one pharmaceutically acceptable carrier”* lack of inventive step.

*d. Claims 7-15 of the Patent No. 1-0014607 lack of inventive step*

Claims 7-15 refer to the object of “*Compounds according to claim 1 or claim 2 for manufacture of a medicament”*, i.e. they are dependent claims of claims 1 and 2 of Patent No. 1- 0014607, and contain only features on the functions and uses of the protected subject-matter without any other basic technical features. Since claims 1 and 2 lack of novelty, the dependent claims 7-15 also lack of novelty.

**6. Request**

Based on the legal basis and the above arguments and evidence, as well as to ensure the patient's rights to have easy access to drugs, avoid abuse of power, creating a strategy to prolong the protection period of specific pharmaceutical substances, we respectfully request the IP Vietnam carry out the necessary procedures to cancel the entire validity of the Patent No. 1- 0014607 of **INCYTE**.

Sincere thanks to the IP Vietnam.

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| ***Recipients:***   * *As above;* * *Archives.*   ***Attached documents:***   * *Copy of cited document D1* | **Tran & Tran Intellectual Property Co., Ltd**  Director    **TRAN QUANG PHUONG** |