“Unofficial” CN Orange Book user guide for pharmaceutical patents (Dec 2021 ver.)

Abstract

The equivalence of the US Orange Book in China, the “CN Orange Book” has been operating since 29 June 2021. This “CN Orange Book” is a mountain full of treasures, for example clear indication on what claim is covering which subject matter in a particular drug patent. This “unofficial” user guide aims to provide foreigners information on how to navigate this “CN Orange Book”, which operates in Chinese. This is the only tool available to a new drug owner to delay approval of the corresponding generic drugs marketing approval process, as China does not provide new drug/biologic exclusivity.

“Unofficial” CN Orange Book user guide for pharmaceutical patents (Dec 2021 ver.)

In the US, the Orange Book is a publication from the US FDA that identifies drug products with marketing approval from the FDA and related patent and exclusivity information. Information in the Orange Book could be used in actions under the Hatch-Waxman Act, which allows a patentee to file an artificial act of infringement that allows the drug innovator to file suit before the generic drug is commercialized, such that the drug marketing approval process of the generic drug at the US FDA could be suspended.

China is required to introduce a similar system under the Phase-I Trade Agreements signed with the US in January 2020. I have been following this since then, and have several articles and posts on this topic. Recently, this “CN Orange Book” (official name: China listed drugs patent information registration platform) has become officially online on 29 June 2021, with many developments thereafter, and I have received many questions on how to use this. This motivates me to write this “unofficial” user guide, mainly for foreign users. This user guide may need updates periodically as things are changing too fast in China.

This drug patent linkage system is the only tool available to a new drug owner to delay approval of the corresponding generic drugs marketing approval process, as China does not provide new drug exclusivity (5 years for chemical, and 12 years for biologic) as in the US.

The equivalence of the US FDA in China is the China National Medical Products Administration, the NMPA.

This is the December 2021 version of this guide, as there have been many developments after my first July 2021 version that was finished on 19 July 2021, and my second October 2021 version finished on 14 October 2021.

Available to anyone, but could only search in Chinese

The “CN Orange Book” is available at https://zldj.cde.org.cn/home. Anyone can access information therein. Below is a screen shot of the first page showing different functions thereon:

For searching drug patent information already registered, the information is divided into three tabs, each respectively directed to Chinese medicine, chemical drug, and biological drugs as shown below (with the tab of chemical drugs chosen):

Searches could be done and directed to the drug name, the format of the drug, dosage, and the drug marketing number at the NMPA. Mostly the name of the drug is used. Partial search for drug patent information already registered is available, but could only be done in Chinese. For example, using only the last three words of Palbociclib in Chinese (“柏西利” in “哌柏西利”) resulted in the following search results:

Extensive information contained therein – good for FTO research

The “CN Orange Book” has the following number of entries as of different dates in the table below:

Type of drugs	30 Jun 2021 no.	19 Jul 2021 no.	3 Oct 2021 no.	5 Dec 2021 no.
Chinese medicines	30	143	243	280
Chemical drugs	278	448	532	568
Biological drugs	39	60	78	80

There was a relatively big surge in July 2021, shortly after the database was firstly introduced on 29 June 2021, while the number of registrations slowed down significantly thereafter, particularly after October 2021. This could be expected, as every drug owner would rush into the register at the beginning.

One amazing feature of the “CN Orange Book” is the inclusion of extensive information in each entry. Below is a screenshot of the entry in the “CN Orange Book” for the drug Palbociclib capsule 125mg (Note: only part of the entries of one of the three patents registered for this drug is shown below due to limit of the screen shot that could be taken):

It can be seen that in addition to the patent number, the following information in the “CN Orange Book” database entries is also available:

1) The granted patent itself is available for downloading at a link on the same page.
2) The claim number(s), and the relevant subject matter, are clearly identified.
3) The full-term expiry of the patent(s) is clearly identified.
4) Whether the patent has survived through invalidation is also specified in the note section.

On the other hand, there exists entries without the above extensive information of 1)-4), as shown below as of 19 July 2021:


专利信息登记详情

专利信息

相关专利号： ZL03821144.0　　专利名称： 包含盐酸伐地那非三水合物的药物

专利权人： 拜耳知识产权有限责任公司　　专利被许可人：

专利授权日期： 2010-12-15

授权证明文件： 文件1：伐地那非片-ZL03821144.0-专利证书.pdf
文件2：伐地那非片-ZL03821144.0-法律状态.pdf
文件3：伐地那非片-ZL03821144.0-说明书权利要求书摘要_.pdf

上市许可持有人与专利权人的关系： 普通实施许可合同的被许可人

药品与相关专利权利要求的对应关系：

序号	权利要求项编号	专利类型	专利保护期届满日	状态	备注
1					

上市许可持有人联系信息

境内联系人： 刘红强　　境内联系电话： 010-65893290

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The same entry above has its information updated as of 3 October 2021, indicating claims 5 to 8 of the relevant patent CN ZL03821144.0 are directed to the drug composition containing the active pharmaceutical ingredient API vardenafil hydrochloride trihydrate:

It should be noted that the relevant regulations, the NMPA Measures (see below), put the onus on the patentee/drug marketing approval holder DMAH to ensure the accuracy of the information registered on the platform, which requires the claim(s) covering what aspect of the drug to be identified (Article 4 of the NMPA Measures). Failure to do so could be legally liable (Article 15 of the NMPA Measures), while it is unclear what exactly are the punishments.

Most of the entries in the “CN Orange Book” contain extensive information like the one of Palbociclib capsule 125mg above (if not, updated could be expected). Such information could be very useful for a freedom-to-operate (FTO) exercise. The immediate availabilities of the grant patent publication and the full-term expiry are already very useful. The specific identifications of the claim(s) and relevant subject matter are even more so.

By contrast, the equivalent FDA records only contain the US patent numbers and the full-term expiry date, but nothing further. Below is the screenshot of Palbociclib capsule 125mg in the US FDA Orange Book records:

Patent and Exclusivity for: N207103

Product 003
PALBOCICLIB (IBRANCE) CAPSULE 125MG

Patent Data

Product No	Patent No	Patent Expiration	Drug Substance	Drug Product	Patent Use Code	Delist Requested	Submission Date
003	6936612	01/16/2023	DS	DP			02/26/2015
003	7208489	01/16/2023	DS	DP		Y	02/26/2015
003	7456168	01/16/2023			U-1998 U-2515		02/26/2015
003	10723730	02/08/2034	DS	DP			08/27/2020
003	RE47739	03/05/2027	DS	DP			12/19/2019

Exclusivity Data

Product No	Exclusivity Code	Exclusivity Expiration
Your search did not return any results		

Restrictions on the type of patents that could be registered

The “CN Orange Book” restricts that only the following types of patents could be registered for the respective drugs (Articles 5 and 12 of the NMPA Measures):

- Chemical drugs – chemical compound of the active ingredient; composition comprising the active ingredient; medical use
- Biological drug – sequence structure of the active ingredient; medical use
- Chinese medicine – composition; extracts from Chinese medicine; medical use

As biologics are also included in the Chinese platform, such is in fact a combination of the US Orange (for chemicals) and Purple (for biologics) Books.

While not specified in the articles of the NMPA measures, the accompanying explanations of the NMPA measures specify that patents covering intermediates, metabolites, crystal form, method of manufacturing and testing methods are **not** considered as relevant patents under the patent linkage system, i.e. these patents should not be registered on the “CN Orange Book”. Therefore, the above types of patents would not be seen in the “CN Orange Book”.

Having said so, one way to get around the restriction on crystal form is to record a patent having a composition claim, or medical use claims (in the form of Swiss-type claim, as

method of treatment is not patentable in China) containing the crystal form of the API. An example will be shown below in the first contentious drug patent linkage declaration.

Only Chinese company could register, and make entries on the platform

While everyone could access the platform to view information therein, in order to register entries on the platform (either for a drug, or making a declaration against a drug), one must register as a user on the platform. However, only a Chinese company could do so, as it is required to input the so-called "unified social credit codes" (compulsory) during registration, which are available to all Chinese companies. Further, the registration requires a CN mobile number to complete (for receiving a confirmatory text message). See the screenshot below:

Declaration from a generic drug applicant against an innovative drug

For details on how such a declaration works, please refer to my articles below:

https://www.linkedin.com/pulse/cn-patent-inkage-measures-trial-finalized-issued-nmpa-toby-mak (This article talks about the finalized NMPA measures, which is based on the draft measures below)

https://www.linkedin.com/pulse/cn-drug-patent-registration-system-orange-book-opened-toby-mak (This article talks about the draft NMPA measures)

As a summary, when a generic drug applicant applies for drug marketing approval at the NMPA, the generic drug applicant is required to make a declaration of any one of the following four types:

1. That there is no patent information registered related to the drug.

2. That the patent(s) has already expired, or been declared invalid.

3. The date on which the patent(s) will expire, and that generic applicant promises that the generic drug will not go on the market until the expiry of the patent(s).

4. That the patent(s) is not infringed, or should be declared invalid.

As of 5 December 2021, 745 declarations have been announced on the CN platform, showing a significant increase from 410 declarations on 3 October 2021. The vast majority of the declarations are types 1 to 3 declarations. The first type 3 declaration was announced on 9 July 2021, with the screen shot below:

The key is the type of the declaration filed, in the screen shot above being type 3. It should also be noted that this page subdivides declaration type 4 into the following two subtypes:

- 4.1 - The patent(s) should be declared invalid.

- 4.2 – The generic drug does not fall within the scope of the patent(s).

The type of the declaration determines whether the drug patentee/DMAH could take action against the subject generic drug marketing approval application. It appears only action could be taken against declaration type 4.2 (the generic drug does not fall within the scope of the patent(s)). While Article 7 of the NMPA measures could be literally read as allowing complaints to be filed at a court or the China National Intellectual Property Administration (the CNIPA) for all 4 types of declarations, when combining with the relevant measures of the Supreme People's Court and the CNIPA, it appears that there is a typographical error in Article 7 of the NMPA measures, and complaint could only be filed for declaration type 4.2.

Therefore, if a generic drug applicant filed a type 4.1 declaration, and even if the generic drug applicant did not file a subsequent invalidation petition, the drug marketing approval process would still proceed as normal by the NMPA as if drug patent linkage protection does not exist.

On the other hand, if the generic drug applicant did file a subsequent invalidation petition and could successfully invalidate the patent, a 12-months exclusivity period would be offered to the first successful challenger, i.e., drug marketing approval would not be granted to another generic drug applicant during this 12-months period.

Type 4.1 declaration has already been announced, with an example shown below:


专利声明详情

化学仿制药/中药同名同方药/生物类似药信息

药品名称: 替格瑞洛片　　药品类型: 化学药品

剂型: 片剂　　规格: 90mg

申请人: 山西德元堂药业有限公司　　通讯地址: 山西省晋中市山西示范区晋中开发区汇通产业园区开发区机械园

联系人: 段陈平　　联系电话: 0354-3072288-805

电子邮箱: dcp207@126.com

被仿制药等相关信息

药品名称: 替格瑞洛片　　批准文号/注册证号: 大包装注册证号：H20171080/小包装注册证号：H20171079

持有人名称: AstraZeneca AB

序号	登记的专利号	登记的权利要求项编号	专利声明类型	备注
1	无	无	4.1类	无

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In the above, the drug at issue is ticagrelor 90mg tablet, with AstraZeneca being the DMAH, and the generic drug applicant being Shanxi Deyuantang Pharmaceutical Co.,Ltd. (Deyuantang). As mentioned above, in this situation, there is nothing AstraZeneca could do to delay the drug marketing approval process of the generic ticagrelor 90mg tablet from Deyuantang at the NMPA.

The first type 4.2 declaration

This was announced on 23 July 2021 directed to the drug dapagliflozin (达格列净) 5 and 10 mg, with AstraZeneca as the DMAH in China. The relevant screen shot for the 5mg drug is shown below, while that of the 10 mg drug has similar contents.

专利声明详情

药品名称：达格列净片　　药品类型：化学药品

剂型：片剂　　规格：5mg

申请人：江苏豪森药业集团有限公司　　通讯地址：连云港经济技术开发区东晋路9号

联系人：王瑞军 李琴　　联系电话：13951499819 0518-83099366

电子邮箱：13951499819@163.com liq1@hspharm.com

被仿制药等相关信息

药品名称：达格列净片　　批准文号/注册证号：H20170117、H20170118

持有人名称：AstraZeneca AB

序号	登记的专利号	登记的权利要求项编号	专利声明类型	备注
1	ZL 200910158686.6	1，2，3，14，15，16	3类	
2	ZL 200880016902.7	8	4.2类	组合物的API与该专利不同
3	ZL 201210201489.X	1，2，3，7，8，9	4.2类	组合物的API与该专利不同
4	ZL 200780024135.X	9	4.2类	API与该专利不同

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It is interesting to note that the generic drug applicant Jiangsu Hansoh Pharmaceutical Group Co., Ltd. (江苏豪森药业集团有限公司, Hansoh) filed a type 3 declaration against CN200910158686.6 directed to the chemical compound of the API dapagliflozin itself, i.e. Hansoh undertakes that they would only put their drug onto the market after CN200910158686.6 has expired on 15 May 2023 (CN200910158686.6 is a divisional from CN03811353.8).

On the other hand, Hansoh filed type 4.2 declarations against the following 3 CN patents, i.e. Hansoh declared that their generic drug does not fall within the scope of the following 3 CN patents that are directed to specific formulations and medical uses:

1) CN200880016902.7 (full term expiry 21 March 2028) - specific formulation comprising the API in the form of dapagliflozin propylene glycol hydrate, microcrystalline cellulose, lactose, crospovidone, silicon dioxide, magnesium stearate, with each components presents in respective specific amounts (claim 8).
2) CN200780024135.X (full term expiry 21 June 2027) - Medical use (Swiss-type claim) of dapagliflozin propylene glycol hydrate with specific crystalline structure (note: as mentioned above patents directed to crystalline structure of a drug per se should not be registered in the CN Orange Book) in treating diabetes, insulin resistance, hyperglycemia, hyperinsulinemia, elevated blood levels of fatty acids or glycerol,

hyperlipidemia, dyslipidemia, obesity, hypertriglyceridemia, or diabetic complications (claim 9).

3) CN201210201489.X (full term expiry 21 March 2028) - specific formulation comprising the API in the form of dapagliflozin propylene glycol hydrate with a specific dosage regime (claim 1), with further components including bulking agent, binder, disintegrant, and so on (claims 2 and 3), and the medical uses of such specific formulation (Swiss-type claims) for treating diabetes.

For 2), it should be noted that the patent is in fact directed to the crystal form of the API in the form of dapagliflozin propylene glycol hydrate, and therefore the CN Orange Book registration is directed to the medical use in Swiss-type claim containing such specific crystal form. Therefore, for China, it is important to include at least one composition or medical use Swiss-type claim for drug crystal form patent.

According to the above, Hansoh chose to challenge the patents directed to specific formulations comprising the API dapagliflozin propylene glycol hydrate, and the medical use of the crystalline API. Comparing with the chemical compound patent CN200910158686.6 (which Hansoh chose to deal with using a type 3 declaration), there is higher chance to get around these formulation and medical use patents, for example by not using dapagliflozin propylene glycol hydrate, but uses dapagliflozin itself (whether this would be caught by equivalence is another question). In fact, Hanosh declared that the API in their generic drug is different from that in these 3 CN patents, i.e. dapagliflozin propylene glycol hydrate.

AstraZeneca had until 6 September 2021 (45 days from 23 July 2021) to file a complaint against Hansoh's type 4.2 declaration against the 3 CN patents above at the Beijing IP Court, or at the CNIPA. Failure to do so would result in that the drug marketing approval application would be processed as normal by the China National Medical Products Administration as usual, i.e. without any delay.

If AstraZeneca filed the complaint and was accepted (by the Beijing IP Court, or the CNIPA), and a decision was made within 9 months from the date of acceptance of the complaint:

- if the decision was in favor of AstraZeneca, the drug marketing approval would be delayed to shortly before the expiry of the above three patents, i.e. maximum delay up to 2028.
- if the decision was not in favor of AstraZeneca or not within 9 months, the drug marketing approval would be processed as normal with no delay.

However, as Hanosh undertakes a type 3 declaration against CN200910158686.6, the earliest date that Hanosh could put their generic drug on the market in China is 15 May 2023.

Current drug patent linkage complaint situation in China in Dec 2021

For the first type 4.2 declaration discussed above, I have tried to check whether AstraZeneca had filed the complaint at the Beijing IP Court the CNIPA by 6 September 2021, but no luck. In light of the relative ease of getting around the above three subject patents, and Hansoh undertakes that they would only put their drug onto the market after 15 May 2023, AstraZeneca may choose not to file the compliant against the type 4.2 declarations.

On the other hand, according to the announcements from the CNIPA and the Beijing IP Court at the respective links below, 12 drug patent linkage complaints (out of 23 filed) have been accepted by the CNIPA as of October 2021, while 1 has been accepted by the Beijing IP Court as of November 2021 (not clear how many were filed at the Beijing IP Court and were rejected).

- https://www.cnipa.gov.cn/art/2021/10/29/art_53_171065.html
- https://mp.weixin.qq.com/s/0PNtsF0XBuwxULgYqnV-Uw

The CNIPA did not provide any details on the complaints they accepted, but the Beijing IP Court did. Specifically, the drug at issue of the complaint accepted by the Beijing IP Court is Eldecalcitol of the Japanese company Chugai Pharmaceutical Co., Ltd. (under the brand Edirol) for treating osteoporosis. The generic supplier is Wenzhou Haihe Pharmaceutical Industry. The patent at issue is CN ZL2005800098777.6.

Apparently the CNIPA has accepted more cases than the BJ IP Court. After checking with the CNIPA, the reason appears to be that the CNIPA does **NOT** require notarization and legalization of formality documents including the Power of Attorney and the business registration certificates to accept the complaints. Specifically, the CNIPA only requires Power of Attorney with a simple signature, while only notarization is required for the business registration certificates, to accept the complaint.

By contrast, the BJ IP Court requires notarization **AND** legalization of the above formality documents in order to accept the complaint. Practically, it is very difficult, if at all possible, to fulfil these requirements within 45 days, especially during the current pandemic.

Such discrepancies on handling of formality documents are reflected on the differences in the numbers of cases accepted (CNIPA 12, BJ IP Court 1).

If the CNIPA continues with this practice, such could make CNIPA a more preferable forum for filing drug patent linkage complaints than the Beijing IP Court. This is because a drug patent linkage complaint must be filed within 45 days from the date of announcement of the relevant 4.2 declaration, otherwise there would be no delay on the drug marketing approval process at the NMPA, i.e. as drug patent linkage protection does not exist. Therefore, the CNIPA is the only choice after the complaint is rejected by the BJ IP Court.

Assuming that the CNIPA made the announcement shortly after they accepted the first drug patent linkage complaint, if a decision was made on the first case by July 2022 and found the generic drug to fall within the scope of the patent, then the NMPA should stop the drug marketing approval process until 20 days before the patent expired. Otherwise, the drug marketing approval process would proceed as usual.

Comparison between the US and CN drug patent linkage system

Thanks to the suggestion from Carol Nielsen of Nielsen IP, and review and comments by Corey Salsberg of Novartis, the appendix of this guide has a table showing the differences between the US and China drug patent linkage system.

Conclusion

While the "CN Orange Book" is based on the US Orange Book (as required under the US-CN Phase-I Trade Agreements 2020), the Chinese system has the following characteristics:

a) The patent information in the Chinese system is much more extensive than that of the US.
b) There is no drug data exclusivity information in the Chinese system.
c) Action could only be taken against type 4.2 declaration (the generic drug does not fall within the scope of the patent(s)) in China.

Regarding c), this may be the substantive difference of the CN system from the US system. In essence, in China, there is nothing the DMAH could do to delay the drug marketing approval process at the NMPA if the generic drug applicant simply alleges that the patent at issue should be declared invalid, and does not even challenge the validity of the patent afterwards.

There have been many changes on the "CN Orange Book" since its establishment on 29 June 2021. For example, in the very beginning, the platform did not have different tabs for entries of chemical drug, biological drug, and Chinese medicine. Now individual tabs are available, making searching and counting much easier. Finally, all five types (types 1-3, 4.1, and 4.2) declarations have been announced.

If you are an innovative drug owner, I am not surprised that you have already registered your drug patent information on the "CN Orange Book" to deter generic drug marketing approval application.

For others, including myself heavily involved in drug freedom-to-operate work, the "CN Orange Book" is a mountain full of treasures. Once the Chinese drug name is known (hint: have a look at the drug innovator's Chinese website), the grant patent publication, claim(s) and subject matter(s) relevant (with clear indication on what claim is covering which subject matter), full term expiry, and invalidation information (if available) are all available in one place.

As the first batch of drug patent linkage complaints have been accepted by the CNIPA and the Beijing IP Court at least in October 2021, there will be more revelations on how the system would work. Let us wait and see, notwithstanding that the first batch of decision should be handed down in the middle of 2022 for drug patent linkage protection to be effective.

Author: Toby MAK, Tee & Howe Intellectual Property Attorneys

Appendix - Differences between the US and China drug patent linkage systems

Chemical drug

Aspect	US	CN
New drug exclusivity	5 years	None
Types of declarations	4 types of declarations 1. That there is no patent information registered related to the drug. 2. That the patent(s) has already expired, or been declared invalid. 3. The date on which the patent(s) will expire, and that generic applicant promises that the generic drug will not go on the market until the expiry of the patent(s). 4. That the patent(s) is not infringed, or should be declared invalid.	4 types of declarations as the US, but type 4 declaration is further subdivided into the following types 4.1 and 4.2 declarations: • 4.1. the patent should be declared invalid • 4.2. the generic drug does not fall within the scope of the patent
Notification to DMAH	Generic drug applicant to notify the drug marketing approval holder (DMAH) of the type 4 declaration within 20 days after receiving FDA's acknowledgment that the Abbreviated New Drug Application (ANDA) has been received and is ready for substantive review.	DMAH to find out announcement of notice of type 4 declaration from the CN drug patent linkage platform.
Filing of drug patent linkage complaint	DMAH to file suit at a court within 45 days after receipt of notice from the generic drug applicant.	DMAH to file complaint at the Beijing IP Court or the CNIPA with 45 days after announcement of notice of type 4 declaration, but **ONLY** for type 4.2 declaration. That is, there is no delay of the drug marketing approval process if a type 4.1 declaration is filed.
Stay of generic drug marketing approval	After filing of the suit, the DMAH has an automatic 30-month stay of regulatory approval of the ANDA (which	After acceptance of the complaint, and **if and only if** a decision was made within 9 months from the date of

process after filing the drug patent linkage complaint	begins on “the later date of receipt” of the notice letter (sent by the generic drug applicant) by the DMAH.	acceptance of the complaint that the generic drug falls within the scope of the patent, the NMPA would initiate the drug marketing approval process 20 days before the patent(s) expired. Otherwise, the marketing approval process would proceed as normal, i.e., as if drug patent linkage protection does **not** exist.
Types of patents that could be registered	• The drug substance (active ingredient), **including different crystal forms** • The drug product (formulation and composition) • Medical use	• The drug substance (active ingredient), **excluding different crystal forms** [Note: However, composition patent including the different crystal forms could be registered] • The drug product (formulation and composition) • Medical use
Information contained in the drug patent database	Only US patent numbers and the full-term expiry date are listed.	Extensive information is listed in the drug patent database as below: 1) The granted patent itself is available for downloading at a link on the same page. 2) The claim number(s), and the relevant subject matter, are clearly identified. 3) The full-term expiry of the patent(s) is clearly identified. 4) Whether the patent has survived through invalidation is also specified in the note section.
Incentive to generic drug applicant	180 days marketing exclusivity to the first applicant to file the ANDA.	12-months exclusivity period to the first successful challenger who files a type 4.1 declaration and subsequently invalidates the patent successfully.

Biological drug

Aspect	US	CN
Biologic exclusivity	12 years of total market protection, including 4 years before a biosimilar application may be submitted to the FDA, and another additional 8 additional the application may be approved.	None.
Stay of generic drug marketing approval process	None	None.
Types of patents that could be registered	Any patents identified by the reference product sponsor to a biosimilar applicant during the "patent dance", in which the reference product sponsor and the biosimilar applicant exchange information of patents that may be infringed, and may include multiple waves of litigation.	• Sequence structure of the active ingredient • Medical use
Incentive to generic biologic applicant	12 to 42 months for "interchangeable biosimilars" (with more information and data available showing the impact of switching such that the intervention of the health care professional is not required, with the first approved by the FDA on 28 July 2021), depending on whether infringement suit is filed, and if filed, the duration of the infringement suit	None.