

# Patent Issues Concerning Pharmaceutical Impurities

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## I. Review of the concept “micro-innovations”

Undoubtedly, conventional small - molecule chemical drugs have made extraordinary contributions to human health. However, after the rapid development of chemical drugs in the last century and on account of less mature targets and lower success rate, there is a view that chemical drugs have gradually entered into a plateau period, which is also called a stable period by optimists. From the perspective of patents, it seems that a larger number of applicants turn their attention to further modify and optimize the existing structures and develop new crystal forms, new dosage forms and new uses. There are also enterprises making great efforts to delve into studies on impurities in drugs that have been approved to be marketed, with an aim of making breakthroughs in enhancing drug safety and market competitiveness. In addition to conventional R&D thoughts, some industry insiders put forward a concept of “micro-innovations”.

As the name implies, “micro-innovations” are “micro”. In order to obtain a patent successfully, one needs to accurately find out a suitable entry point for the completion of an invention, and make an overall plan about the title of the invention, its inventive concepts and the technical problem solved, even the drafting manner of claims, description of experimental results, analysis of experimental data and the like. In one word, it is required to break through the conventional patent application mode. For instance, one of the “brilliant” micro-innovations is to change the impurity into a form of pharmaceutical composition, or file an application for the new “use” of first separated impurities as a new compound or composition.

Nevertheless, there seems to be a paradox in front of us, that is, from the viewpoint of the legislation of the patent law, there is no such thing as “micro”-innovation. As far as

the grant of patent rights is concerned, at least the non-obviousness and contribution made to the field must meet the requirements of inventiveness under Article 22.3 of the China’s Patent Law, and the “height” of such innovation should be evaluated in accordance with the corresponding examination criteria. It can be seen that a real “micro” innovation, if inherently insufficient, cannot pass the inventiveness examination as prescribed by the patent law.

It is undeniable that the concept “micro - innovation” has its advantages as it reminds innovative entities of some blind spots in their R&D which in turn promotes technological innovations. An interesting thing is that the “micro-innovation” subtly introduces the economic ideology of costs and profits into the construction of invention-creations. In the early days of working in the IP field, the authors once learnt about this from the application practice from our neighboring country, Japan. As viewed from another perspective, however, the applications on “micro-innovations” may cause difficulties during patent examination and invalidation procedures, increase the possibility of passing off the sham as the genuine, result in more problems in patent protection and use and generate further concerns in the field. The reasons for this are surely easy to understand: as far as some “micro - innovations” are concerned, even though they are still patented after administrative examination or judicial trial, it does not necessarily mean that they are real invention-creations in the sense of the patent law, but are merely conclusions made by judges in certain administrative or judicial proceedings since there were no alternative due to the evidence presented and the arguments between the parties concerned.

This article is intended to make an in-depth discussion over the impurity-related issue in the pharmaceutical field on the basis of a series of heatedly discussed invalidation cases concerning cinepazide maleate injection between Beijing Sihuan Pharmaceutical Co., Ltd. (Beijing Sihuan)

and Qilu Pharmaceutical Co., Ltd. (Qilu Co.).

## II. Introduction to invalidation cases concerning cinepazide maleate

Cinepazide maleate is a drug widely used for the treatment of cardiovascular and cerebrovascular diseases, the sales of which reached RMB 3.8 billion in 2015. The drug was once withdrawn from the market in a few countries such as Spain, France, and Italy at the end of 20th century due to adverse reactions harming the blood system. Beijing Sihuan submitted several patent applications for invention relating to the impurity compound “cinepazide oxynitride” around the year of 2009, and wrote cinepazide oxynitride as an examination item into the national standards for cinepazide maleate. It was later reported that the decrease in leukocyte induced by cinepazide was mainly associated with the impurity “cinepazide oxynitride”.<sup>1</sup>

The series of patent applications submitted by Beijing Sihuan claimed the benefit of the patent application for invention No. ZL200910163103.9, and three of them had been granted. Claim 1 of the invention patent No. ZL200910176994.1 (hereinafter referred to as Patent 1) seeks for protection of a cinepazide oxynitride, and the description thereof recites that a cinepazide oxynitride is the impurity resulting from the oxidation of cinepazide under illumination and can be used as a reference substance or standard substance in the pharmaceutical quality standards, and that a cinepazide oxynitride has insecticidal activity.

The claims of the invention patent No. ZL200910180174.X (hereinafter referred to as Patent 2) seek for protection of the use of cinepazide oxynitride for the preparation of a reference substance for a cinepazide drug or a preparation thereof. In addition to the insecticidal activity of cinepazide oxynitride, its description also recites that the toxicity of cinepazide oxynitride is much greater than that of cinepazide, which may give rise to a decrease in the number of mouse leukocytes and have a serious impact on the generation and differentiation of granulocytes, whereas the high-purity cinepazide and other two impurity compounds have no influence on the number of mouse peripheral blood leukocytes. And it is further recommended that for the sake of drug safety, the content of cinepazide oxynitride in cinepazide or the salt thereof shall not be higher than 0.20%.

Later on, a divisional application No. ZL201110006357.7, which was derived from the Patent 2,

was granted (hereinafter referred to as Patent 3), which seeks to protect a pharmaceutical composition containing cinepazide or its pharmaceutically acceptable salt, and a structural compound (namely, cinepazide oxynitride) represented by the formula III and having a content of not more than 0.5%, wherein the weight ratio of the cinepazide or its pharmaceutically acceptable salt to the compound of the formula III is not less than 500:1. The patent won the 19th China Patent Gold Award.

In the invalidation case against the Patent 1, since no evidence demonstrates that the prior art teaches compounds, which are similar to the new compound “cinepazide oxynitride”, possess the insecticidal activity, the former Patent Reexamination Board (hereinafter referred to as the “PRB”) of the State Intellectual Property Office found the patent novel and inventive, issuing the Invalidation Decision No. 32428 to maintain the validity of the patent. Nevertheless, the court reversed the decision to some extent in the first and second instances. Eventually, the second-instance judgment determined that the experimental data in relation to the insecticidal activity of the compound were doubtful, which in turn led to the invalidation of the claims concerning the insecticidal use due to insufficient disclosure; and meanwhile, the second-instance judgment also hold that the disclosure on its use as reference substance or standard substance was sufficient and based on such use the compound cinepazide oxynitride was inventive.

In the invalidation case concerning the Patent 3, the PRB decided in the Invalidation Decision No. 29876 that the prior art did not teach how to solve the problem of relieving the side effects of leukocyte and granulocyte reduction, and maintained the validity of the patent. The case was also reversed after the trial by the first-instance court. The first-instance judgment determined that the toxicity experiments recited in the description were doubtful, so that the disclosure in the description was insufficient and the patentee’s argument that the pharmaceutical composition achieves an unanticipated technical effect on the basis of the toxicity experiments was untenable.

The invalidation case concerning the Patent 2 is still undergoing examination at the Reexamination and Invalidation Examination Section of the Patent Office of the China National Intellectual Property Administration (CNIPA).

The above-mentioned series of invalidation cases has aroused heated discussions. The main concerns go to the following two aspects: on the one hand, any compound can

be used as a reference substance or a standard substance for measuring its own content, and the grant of patent for impurity compounds may induce a great number of patent applications for impurity compounds of existing drugs in the future, which may impose restrictions on improving the safety and quality of drugs already approved to be marketed; and on the other hand, purity depends on the content of impurities, a compound characterized by a new impurity of a defined content is not essentially different from a compound with a defined purity, and it is very likely that the scope of protection of such claims may cover approved drugs, which may disrupt the normal order of R&D and market operation in the pharmaceutical industry and have a negative effect on common health.

### III. Patentability of subject matters of inventions relating to pharmaceutical impurities

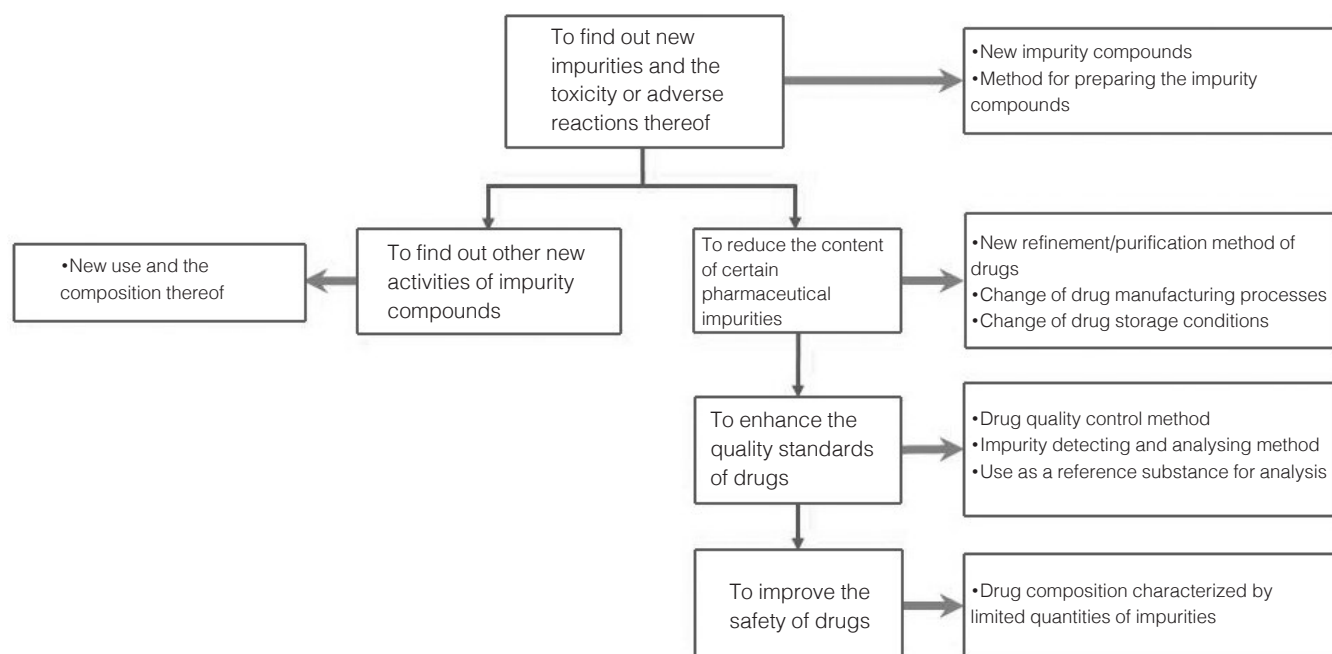
#### 1. Outline of inventions relating to pharmaceutical impurity compounds

Pharmaceutical impurities are usually divided into organic impurities, inorganic impurities, and residual solvents. Organic impurities can be introduced in the produc-

tion or storage of pharmaceutical products, including reaction starters, by-products, intermediates, reagents, ligands and catalysts, geometric and stereoisomers, and degradation products. Since such impurities are generally similar or related to active ingredients in terms of chemical structure, they are often referred to as related substances. In addition, impurities can also be divided into toxic impurities and signal impurities according to toxicity. Toxic impurities affect the safety of drugs, and the content thereof needs to be under strict control. Although the signal impurities are non-toxic, the content thereof can reflect the purity of drugs and the problems occurred in the manufacturing processes or procedure<sup>2</sup>.

The purpose of conducting research on impurities in drugs is to find out toxic impurities, analyse the cause thereof, and design processes and methods for removing the same so as to ensure the content of toxic impurities in the drug is within a safe and controllable range. Researches on impurities generally focus on the following two aspects: one is to delve into the cause of adverse reactions or toxic side effects of drugs and further determine the chemical structure of toxic impurities; and the other is to directly separate and identify the components of pharmaceutical impurities, study the toxicity of each impurity after knowing its structure, and then find out which impurity compound causes

#### Outline of inventions relating to pharmaceutical impurity compounds



the adverse reactions or toxic side effects.

After discovering a new impurity compound in a drug, an inventor usually can draft applications for his invention of the following types: one is to claim an impurity compound product; second is to claim a pharmaceutical compound or composition having limited quantities of impurities, which is similar to a purity-defined product with a low impurity content; third is to claim a refinement/purification method, a synthesizing process or a storage method designed to reduce the new impurity's content; and fourth is to claim a drug quality control method or a method for detecting and analysing the new impurity. The series of cases relating to cinezapide as mentioned above pertains to the first and second types respectively, namely, they relate to product claims in the form of impurity compounds and pharmaceutical compositions.

## **2. Inventive step of inventions relating to pharmaceutical impurity compounds**

As regards inventions relating to pharmaceutical impurities, the most important legal provision that affects the grant and validity of a patent is the inventive step provision. The inventive step of inventions relating to impurities will be systematically reviewed and discussed under the following three circumstances.

Under the first circumstances, only a certain new impurity in a drug is found and the chemical structure thereof is determined. In most cases an impurity compound has no activity and sometimes even is the root of adverse drug reactions, this explains why people usually study impurities not for producing impurities and using the same in some industry to create values, but for reducing the content of impurities in the target product to improve the drug quality. Except for serving as their own reference substance or standard substance in the impurity detection and analysis, impurities of this kind generally have no practical value. Hence, drug impurity studies usually focus on the drug quality. Moreover, it is self-evident to professionals in the relevant industry that, as a general rule, reducing the content of impurities in the drug will improve the drug quality. Even if the structure of impurity compounds is still unknown, those skilled in the art can determine the specific structure thereof by separating and identifying the potential impurities in the drug for the sake of drug quality control, and further readily conceive of using those separated impurity compounds as their own reference substances and standard substances in the detecting method. As a result, in a

patent application in this sense, impurity compounds themselves or compositions delimited by impurities, as well as the use thereof, are not patentable due to lack of inventive step, unless the discovery of such impurities brings unexpected technical effect.

Under the second circumstances, if an impurity compound of a novel structure is found to be particularly significant to the drug quality improvement, for example, the impurity is found to be the main substance causing some adverse reactions or toxic side effects of drugs, it is possible to take pertinent measures to control the content thereof within such an extent that severely adverse reactions or toxic side effects can be prevented and the safety of drugs be improved. This provides an opportunity for patent applications relating to the impurity compound to meet the inventive step requirements.

Two types of applications can be filed conventionally at this stage. One is a process invention characterized by reduction of the content of new impurities. After discovering a certain impurity compound and the effect thereof on the drug quality, those skilled in the art will usually try to reduce the content of the impurity in the drug as much as possible so as to prevent its toxic side effects. If a new refinement or purification method or a new synthesizing process is invented accordingly, such an invention is the technical contribution made by the inventors. The grant of patent for such inventions on the premise of satisfying other conditions is in line with the principle that the scope of protection shall be compliant with the technical contributions. The other type is an invention relating to a method for detecting and analysing a new impurity. Since it has been found that the new impurity compound has an impact on the drug quality, it is essential to design a specialized detecting and analysing method so as to control the drug quality more effectively. An invention relating to a method for detecting and analysing a new impurity is also eligible for patent protection.

Under the third circumstances, if a new impurity compound is found incidentally to have other uses irrelevant to the drug quality, then the impurity compound has an independent application value just like other compound inventions. Therefore, the assessment of the inventive step of such inventions is in principle identical with that of conventional compound inventions. If the new uses of the impurity compound are not obvious for those skilled in the art over the prior art, it is expected that patents on the compound and the uses thereof will be granted.

As a matter of fact, the necessity of granting patents for impurity-related applications has been proved by conspicuous values of impurity compounds. For instance, thalidomide was once widely used as a sedative-hypnotic drug for easing pregnancy symptoms in the 1950s, which led to the birth of more than eight thousands infants with phocomelia (also known as thalidomide disaster) in Europe and Canada. It was later discovered that (R)-thalidomide has a central sedative effect, (S)-thalidomide causes severe anomalies during embryonic growth, any isomer can be converted to a corresponding enantiomer in vivo and reach a balance, and it is impossible to eliminate the toxic side effects caused by (S)-isomer through chiral separation, all of which forced the drug out of the market globally. Researches revealed that (S)-isomer is suitable to be inserted into the part of DNA that is rich in guanine-cytosine to affect the genes in the promoter region that control the formation of limbs, ears and eyes, wherein the obliteration of newly formed blood vessels is the main cause of teratogenicity of thalidomide. However, further studies showed that thalidomide may have the effect of inhibiting tumor angiogenesis, and thalidomide is also proved to be clinically useful in treating many cancers such as multiple myeloma and has been approved to be marketed again under the condition that pregnancy shall be avoided during medication administration, as well as before and after treatment. Although (S)-isomer of thalidomide was originally noticed due to its toxic side effects, it has been found to have a good anti-cancer effect after in-depth studies on the mechanism of its toxic side effects and therefore can be successfully applied in new therapeutic fields<sup>3</sup>.

The particularity of impurity compounds, however, is an important factor that can't be ignored in pursuit of a proper mode to deal with impurities and is mainly embodied in the inseparable close connection between the impurity and the drug. An impurity compound patented for its new use may produce an impact on the ordinary exploitation of normal drug patents, as well as the manufacturing, assessment and quality control of the drugs, because of the impurity's well-known impact on the drug quality control, no matter whether the impurity compound will be used in a new technical field on account of its new use. This leads to the concerns in the field about the grant of patent for impurity compounds, and such concerns have grown recently due to the cinepazide invalidation cases. Therefore, in consideration of the purpose of establishing the patent system and the

principle of fairness, we shall hold a prudent attitude towards the assessment of the inventive step of patent applications relating to impurity compounds to prevent such applications that are actually not patent-eligible from being granted.

To be specific, first of all, the grant of patent for a new compound having an unanticipated new use fits the purpose of the patent system. However, some patent applications of impurity compounds disguised with "new" uses are submitted for the sake of huge economic benefits gained from the drug and take advantage of some limitation in the patentability assessment process. Particularly, the patent prosecution is primarily based on written documents, and it may be really hard to distinguish authentic inventions from such "grudging" inventions in some circumstances. How can we make breakthroughs without changing the current examination mode? At present, efforts can be made from the following three aspects to avoid some mistakes.

The first aspect is how to determine the technical effects. In cases where patents are based on new uses or new effects, the factual findings related to whether such new uses or new effects do exist become the essential step, and to ascertain the "new" facts surely relies on the support of experimental evidence. The examination in the patent grant phase is based on written documents, and, despite a huge number of applications to be examined, should be conducted with a strict timetable. As for the authenticity of the effects asserted by the applicants and of experimental evidence submitted for proving said effects, there lacks verifying means such as test, less professional support can be further obtained from professionals or expert witnesses in the field, and more importantly, it is impossible to find out problems through an adversarial party. Therefore, all the judgments are usually made on the basis of examiners' understanding of the prior art and general technical knowledge in the relevant field. The authenticity of experimental evidence and effects will not be questioned only when the experimental evidence does not meet the formality requirements or the effects and the processing of obtaining the effects have obvious defects such as violation of common sense or mutual contradiction. Things are almost the same according to the authors' understanding on the examination situations in the same field at other major patent offices in the world. As a matter of fact, it is not hard to make the experimental evidence formally eligible and qualified. If examiners are unable to make more accurate and in-

depth judgments in terms of the design and implementation of experiments, as well as the collection and analytical processing of experimental data, it may result in that patents are wrongly granted for unqualified applications. Although the above-mentioned problems may be less severe in the invalidation proceeding, they still exist due to the limitation in the party's capability to produce evidence. In addition, although technical appraisal facilitates the factual findings, there still exist some problems during the appraisal procedure that severely affect the function of the technical appraisal.

Factual findings serve as the basis for the application of law. Decisions regarding the cinepazide cases had been reversed several times in the judicial proceeding, which showed that administrative departments and courts at different levels have different understandings of the same data, and also proved that the examination of experimental evidence plays a significant role in this type of cases. It should be noted that in determining the technical effect, the first-instance and second-instance courts also considered the experimental evidence later submitted by the parties concerned in the litigation proceedings. Although the courts, when examining the validity of administrative decisions, can accept new evidence that was not submitted during the making of administrative decisions, since this may weaken the effectiveness of the administrative patent affirmation procedure to some extent, the acceptance of new evidence has been viewed differently by the administrative departments responsible for patent grant and affirmation procedures in various countries. Due to space restrictions, this article is not going to discuss such issues as whether the new evidence later accepted by the court exceeds the scope of administrative litigation and whether the court reasonably assigns the burden of proof to the parties.

The second aspect is how to evaluate the technical effect. An examiner is responsible for examining applications in a relatively broad range of technical fields, so that it is possible that he does not have sufficient knowledge or keep up with technological updates timely in certain fields, and therefore the examination on the relationship between experimental data, technical effects and uses may be superficial. For instance, the technical effects as asserted by the applicant are usually considered as true according to the experimental data recorded in the application documents, with no consideration of the irrationality of the experimental design and the indefinite connections between

some immature mechanisms and indications. Consequently, it may give rise to misunderstandings of the technical information embodied in the experimental data. A typical case is that some experimental data, though being authentic, seemingly support the existence of certain use, but the use cannot be put into practice at all.

The third aspect is to determine whether the prior art provides any teaching for the technical effect. Impurity compounds exist in the prior art as unwanted components in drugs and are therefore "cold-shouldered". The participants in the industry are only concerned about how to remove or avoid the creation of impurity compounds so as to enhance the purity of drugs, rather than studying the advantageous uses of impurities. Thus, it is very rare to see researches about the characteristics of impurity compounds in the prior art, or even if there is such kind of information, it is too covert to be retrieved easily. Once the new use of an impurity is confirmed, it is not easy to find strong evidence in support of technical teachings during the assessment of the inventive step. In reality, however, we do not rule out the likelihood that the new use of the impurity can be anticipated on the basis of its structural similarity with the existing compounds in the prior art or inherent correlation between different functions and uses. But it is for sure that the invalidation request will rely more on expertise of the participants.

### **3. Novelty issue of inventions relating to pharmaceutical impurity compounds**

From the perspective of the stability of patents, in invalidation proceedings, patents which are declared invalid for lack of novelty are less than those for lack of inventive step. But there are comparatively more disputes over the examination criteria regarding novelty. The main reason may be that the examination of patents on impurities under the novelty clause involves more of the particularity of impurities, and different judges have different understandings of the essence of such claims due to their different acquaintances with inventions relating to impurity compounds. Moreover, it is usually not easy to obtain strong evidence to invalidate a patent for lack of novelty.

As regards the product claim characterized by limited quantities of impurities, since the criterion for examination on novelty is whether technical solutions are "essentially" the same, how to understand the essence of such kind of products becomes crucial to the result. Because the afore-said product can be regarded as a variant of a product claim defined by purity, the judgment on novelty thereof



shall be made in a way identical to the judgment of the latter. Thus, reference can be made to the existing mature approach to judge the novelty of the product characterized by limited quantities of impurities.

To be specific, for the reasons as stated above, the claim of such kind of product characterized by limited quantities of impurities, regardless of being drafted in the form of a composition or a compound, is in essence the known drug itself. For the known drug disclosed in the prior art, it shall be understood that where the purity of the drug is not recited or the drug is not of high purity, it mainly attributes to the non-necessity of the high purity and economic concerns. For instance, when the prior art only focuses on whether a target compound can be obtained with a certain preparing method, the documents usually will not deliberately mention the type and content of the impurities in the target compound. A claim that defines a known pharmaceutical product by limited quantities of impurities is generally considered as lacking in novelty, unless it can be proved that in the prior art the defined product cannot be obtained. Otherwise, if the detection and analysis of the type and content of impurities objectively existing in the known product are merely made for the purpose of facilitating the applicant's re-characterization of the drug in another way to meet the novelty requirements under the patent law, such a guidance to the future inventions is doomed to failure.

An important thing is that the above opinion regarding compounds and compositions with impurities shall be accepted in the judgment on novelty because the recognition of those skilled in the art on the impurity issues on all occasions during the patent examination shall be consistent. For instance, in regard to a prior art compound, if the structure of a compound prepared in an embodiment in the prior art is identical to the one claimed in a patent application, our conclusion will be that the latter does not possess novelty. Although those skilled in the art know that the prior art compound contains impurities, it cannot stop us from considering that the structure of the compound in the patent application has been disclosed. Similarly, as regards patent applications with the subject matter of compounds, we can prove the sufficient disclosure of the technical solution of the claim, as well as the support of the scope of protection, with specific compounds recited in the embodiment, even though those skilled in the art know that the compound synthesized by the method disclosed in the embodiment is, in some sense, a "mixture" containing impurities. In the techni-

cal effect comparison step during the assessment of inventive step, we usually recognize the technical effects of the compound showed in filed data regarding its activity, unless counter-evidence proves otherwise, without considering the impurities in the tested compound. Furthermore, in the infringement judgment, the people's court regards the unavoidable impurities in normal quantities in the accused infringing product as an exception<sup>4</sup> at the time of determining the scope of protection of the close-ended composition claim.

As regards claims relating to impurity compounds, unlike some interpretations<sup>5</sup> of the invalidation decisions made by the PRB, the authors contend, after the cinepazide cases, that the judgment on the novelty of impurity compounds should be different from the judgment on the novelty of new structural compounds first discovered in natural extracts. Since the structure of a specific compound contained in a natural mixture is usually unpredictable, it is generally believed that the first-discovered compound with a new structure possesses novelty; whereas impurity compounds are at a higher risk of being questioned about their novelty.

For instance, although the prior art does not disclose the structure of the impurity compounds contained in the drug, if the method for preparing the drug disclosed in the prior art is the same as that disclosed in the patent application, it can be presumed that the impurity compounds generated by the preparing processes are identical to each other. Some senior examiners once proposed that under the above circumstances, the prior art can be understood as a product defined by a method, so that it is natural and logic to "presume" a product claim characterized by structural features to be "lacking in novelty". Moreover, during that examination, if the drug claimed in the patent application and the one disclosed in the prior art are identical or substantially identical in terms of the effect, and the effect is in close association with the purity of the drug, as well as the type and content of a particular impurity, it may further prove the examiner's viewpoint and support the rationality of such presumption. When presumed as being lacking in novelty, the burden of proof will be transferred to the applicant unless the applicant has sufficient evidence or reasons to overturn such presumption; or otherwise, relevant claims are ineligible for patent protection.

However, if the prior art does not disclose the method that result in impurities and the causes thereof so that those

skilled in the art can hardly predict the presence of a certain impurity, we can further analyse, during the assessment of inventive step, for example, the steps of the preparation process and corresponding reaction conditions, possible degradable routes, etc. to predict potential impurities and chemical structures thereof, and may conclude that the compound or the composition containing impurities are obvious, on the basis of relevant contents recited in other prior art documents and with common technical knowledge of those skilled in the art.

Novelty has once been regarded as one of the key issues in the cinepazide invalidation cases. There is also a view that cinepazide drug always contains cinepazide oxynitride as impurity, so the impurity does exist in said drug even before the grant of patent for cinepazide oxynitride<sup>6, 7</sup>. Then, are the claims on cinepazide oxynitride obvious over the previously marketed cinapzide drug containing the impurity of cinepazide oxynitride due to “disclosure through use” and thus not novel?

However, regardless of patent examination or judicial trial, what is pursued is the legal truth. Although discussed in the context of the invalidation cases, we can analyse examining rules beyond the scope of invalidation requests in a specific case, as well as the evidence, reasoning, response at trials and the arguments and counter arguments of the parties, it is still impossible to analyse a certain case without considering its details. Of course, as the case enters into the litigation phase, the understanding of the facts of the case may change along with the variation of evidence and the investigation of the case. But it seems that the above viewpoint can hardly be sufficiently supported in view of the evidence at the current stage. Furthermore, if the cinepazide oxynitride impurity can be proved as not novel from the perspective of “disclosure of publications”, the preconditions for presuming the lack of novelty of the compound must be satisfied as stated above. In one word, in the absence of necessary evidence, the authors can only interpret their understanding of the rules under various possible situations but not provide a conclusion to a particular case.

#### IV. Response to the concerns in the IP and pharmaceutical field

Inventions relating to pharmaceutical impurities usually involve the quality standards of drugs, and will have an im-

pact on the relevant drug market after the grant of patent. The following discussions are from the aspects of the availability of drugs to the public, the significance of drug quality improvement to the public health, the development of the pharmaceutical industry and the safeguard of a good innovative environment, as well as the correspondence between the scope of protection of patents and their contributions.

##### 1. How to prevent abuse of rights and safeguard the public interests

In regard to the cinepazide case, the main concern is, when granted, how claims covering the impurity compounds, the product defined by impurities in limited quantities, or the process for controlling the content of impurities will affect the production and sales of the drug. To be specific, the method for testing the cinepazide with oxynitride as a reference substance has been written into the national drug standards of cinepazide. Does it mean that any cinepazide manufacturing company should get permission from the patentee or otherwise will face the risk of patent infringement?

A patented drug that has been successfully put into the market often involves a plurality of patents, including such core patents as compound and composition patents that are generally considered as decisive. It shall be understood that due to the huge investment and lengthy time spent on drug research, the “absolute protection” provided by a product patent matches with the contributions made by a new drug to the public health. After obtaining a core patent, a pharmaceutical company tends to further maintain the monopolistic status of its patented drug by applying for peripheral patents relating to new crystal forms, dosage forms, preparation methods and second medical use. But with the rise of impurity-related patents, another sharp issue comes into being, i.e., since the patents of those mature drugs have expired and the original core technologies thereof have been known and available to the public, it is possible that the holder of an impurity-related patent can force other companies out of the market by means of its impurity-related patent. At least, it can be said that some concerns in the field are not groundless.

An important reason for the great influence of a seemingly small impurity-related patent is that because of the specialty of patents relating to pharmaceutical impurities, those patents can obtain power over generic drug manufacturers by virtue of the compulsory force of the national drug



standards. If a patent is granted for a type of impurities due to its contribution to the drug quality as a reference substance or standard substance, the patent itself does not inhibit other manufacturers from taking other measures to enhance the drug quality. But things would be much different if the relevant content is written into the national compulsory standards.

Drug standards pertain to national compulsory standards. Patents relating to impurity compounds, regardless of whether they are called so, function as “standard-essential patents” during the compulsory implementation of the drug standards. After the implementation of the national standards, if drugs are not tested under the standards, then those drugs that have already been approved to be marketed will not be allowed to be produced and sold due to inconformity with the national safety standards; and if they are tested according to the standards and found compliant with the requirements, then the later patented technical solutions will be implemented. Under the circumstances, if license cannot be obtained from the patentee, patent infringement will inevitably occur. If other manufacturers withdraw from the market for the above reason, it can affect the public’s right to free choice of drugs and the availability of the drug, and have a negative impact on the public health. For other manufacturers who produce such drugs, they enter into the market after the original core patented technology has been known and available to the public, and may doubt whether it is fair as their interests are unpredictably affected by the later granted patent. When a patent improving the drug quality is incorporated in the amended drug standard, if such a patent covers the only solution to solve the drug quality problems, and if the threshold for license is set too high, other manufacturers may not be able to obtain authorization with reasonable price to detect the content of the impurity compound in the relevant drug by using the impurity compound as a reference substance or standard substance. This will in turn cause monopoly and hinder the existing drugs from a higher quality, which is disadvantageous to the public health. On the other hand, if a patent only provides one of the methods for solving the drug quality problems, but is incorporated into the standard through amendment, it is unfair to other manufacturers. For the above reasons, although the standard-essential patents and FRAND principle were originally put forward in the field of communications, there are still disputes over whether they are applicable in the pharmaceutical field and whether

patents involved in drug standards should be licensed under FRAND terms so as to prevent abuse of rights. It is because of the worry of abuse of rights that the licensing of impurity-related patents is put forward. It was reported that Qilu Co., which intends to produce cinepazide maleate drugs similar to Beijing Sihuan’s “cinepazide maleate injection”, has asked the latter to license its patents and got rejected. Later, Beijing Sihuan sued Qilu Co. in Inner Mongolia and Shandong provinces respectively for infringement of its patent on cinepazide maleate drugs<sup>8</sup>.

Therefore, if a new quality standard (such as a new examination item) involving a patent is written into the pharmacopoeia by means of amending the drug standards, the amendment may have a negative effect on the public interest and the patent may “kidnap” other manufacturers, which produce and market the same type of drugs. What needs to be discussed in depth is whether it is necessary to set a more prudent examination and approval procedure for the amendment of drug standards, or just like the patent invalidation proceeding, to set an *inter partes* procedure that allows the public or interested parties to file an opposition against the amendment. Correspondingly, another issue that is worthy of discussion is whether the manufacturers in the pharmaceutical industry should be more vigilant about the rationality and scientificity of the amendment of standards so as to respond more timely.

Obviously, there is another concern in the pharmaceutical industry that, since a drug inevitably contains impurities, if the grant of impurity-related patent indeed has an impact on the pharmaceutical industry, some manufacturers may be induced to turn their attention to “secondary development” of impurities in the existing drugs and apply for patents. This may set up new barriers for manufacturers which produce the same kind of products, drag more manufacturers into a quagmire of litigation, and become the breeding ground for patent trolls. If this is the case, it will further have a negative impact on the innovation environment in the pharmaceutical field, increase the internal consumption of China’s pharmaceutical industry and eventually harm the public interest.

As for the development of the China’s pharmaceutical industry, the recently heatedly-discussed patent linkage system, the patent-term compensation system and the drug experimental data protection system are all aimed to promote the coordinated development between innovative drugs and generic drugs and focus on the social welfare,

which is also the objective of the diversified adjustment of the drug patent protection and administrative protection and the drug market access system. Patent is just a piece of the puzzle. It can thus be seen that to prevent the above-mentioned series of problems from inhibiting the innovative development of the pharmaceutical industry obviously goes beyond the scope of patentability of impurities. The problems cannot be thoroughly solved if attention is only paid to how to invalidate those patents involved in the drug standards.

## 2. How to guarantee that the technical contributions made by inventors are under proper protection

Although inventions relating to impurities may give rise to some complicated legal issues, the inventors' contributions shall be protected by patents no matter if impurity compounds are turned from wastes into treasures with its new uses, or some declined drugs are revived due to their safety improvement. Nevertheless, since it is found that improper protection may force other manufacturers out of market or harm the public interest, it is necessary to carefully consider whether the cost of protection is compatible with the contributions made by the impurity-related patents over the prior art, and whether the protection boosts or impedes the overall development of the pharmaceutical industry. As a result, the core of the patent issues should lie in how to determine whether the protection conferred is reasonable and appropriate.

It was once suggested in the pharmaceutical industry that "in the patent grant and affirmation stage, it is necessary to clarify the scope of protection of an 'impurity'-related patent; and in the right enforcement stage, the technical solution of such a patent should be strictly interpreted to determine the scope of protection thereof."<sup>9</sup>

The authors are, however, of the view that it is currently non-feasible to clarify the scope of protection of an "impurity"-related patent in the patent grant and affirmation stage. The principle that the scope of protection of a patent is defined by claims, stipulated in Article 59 of the China's Patent Law, is universally applicable, and an exception can hardly be made just for the subject matter of impurities. Different from the "judging" procedure in such countries as Japan where the judging department of the patent office determines the scope of protection of a patent, courts in China determine the scope of protection in infringement procedures. Comparatively speaking, it is more advisable that the scope of protection of an "impurity"-related patent should

be strictly interpreted by courts.

As far as the scope of protection is concerned, the product patent relating to impurity compounds may be the most sensitive. In this regard, the authors contend that although chemical substance patents provide "absolute protection" as the scope of protection thereof can be extended to all the fields, account shall still be taken of the difference between impurity compounds and common chemical substances, since the presence of impurity compounds is harmful to drugs. Obviously, impurity compounds are inevitably contained in drugs, rather than intentionally used in drugs. There should be a discrepancy between them. It is worthy of discussion whether the impurity compound inevitably contained in the drug infringes the patent relating to the impurity compound. What's more, as stated above, a substance patent is granted for an impurity compound usually because of its contribution to a new use, rather than the field of the original drug containing the impurity. If the scope of protection extends to cover the original drug, the contribution made by the impurity compound is not compatible with the scope of protection.

Still take the cinepazide cases as an example. The Patent 1 on the impurity compound "cinepazide oxynitride" was granted for its new use with insecticidal activity. If the protection conferred is confined to insecticide use, it obviously will arouse no concerns. But if the protection covers the use for improving the cinepazide quality or the cinepazide drug itself, the scope of Patent 1 is essentially the same as that of Patent 2 or Patent 3. In such circumstances, Patent 1 is unnecessary and its grant seems meaningless.

In addition, due to the specialty of the medical field, there has been a consensus that certain support in the patent policy can be provided. When determining the scope of protection of claims relating to impurity compounds in a drug, we may also study from the practices in other countries. For instance, in Europe medical uses can limit the scope of protection of compound patents in determining the establishment of infringement so as to prevent the granted impurity compounds from affecting the production and business of the original drug by virtue of its new use. This practice not only complies with the purpose of the patent law for protecting invention-creations and encouraging innovations, but also balances the interests of the public and those of patent holders. However, the method may be effective in the case where the new use of the impurity compound is a medical use, but things would be different if the

new use is not.

## V. Conclusion

Although “impurities” in drugs are a kind of special substance, impurity-related inventions are not totally rejected by the patent system. Professionals in the IP field are required to grasp the essence of such type of “inventions” through various forms of impurity-related claims, focus on their true value, and avoid the rigid and mechanical or even wrongful application of the general principles. In-depth researches on the basis of our national conditions and administrative and judicial practices are still required, so as to find out how to provide scientific protection for such claims appropriately. ■

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<sup>1</sup> Tian Yan, Lu Jingkun, Dong Zhiqiang *et al.* (2011). Experimental study on adverse reactions of blood system caused by cinpezide. *Journal of Toxicology*, Vol. 25, No. 4, 273-275.

<sup>2</sup> Pharmacopoeia of the People’s Republic of China (2015), Vol. 4: Guidelines for Drug Impurity Analysis (pp.377-378).

<sup>3</sup> Bai Donglu and Shen Jingkan (editors in chief) (2014). New Drug R&D Case Study—How Innovative Drugs Go from the Laboratory to the Market (Chapter 3, pp. 40-53). Chemical Industry Press.

<sup>4</sup> Interpretation (II) of the Supreme People’s Court on Several Issues Concerning the Application of Law in the Trial of Dispute over Patent Infringement [No. Fashi 1/2016], wherein Article 7 reads “where any alleged infringing technical solution is supplemented with other technical features on the basis of including all technical features of the claims for any enclosed composition, the people’s court shall determine the alleged infringing technical solution does not fall within the scope of protection of the patent right, except when the added technical features do not fall within the scope of the conventional quantity of inevitable impurities.”

<sup>5</sup> Wang Quan. How to obtain patent protection for impurity compound in drug. Zhichanli. (25 September, 2018).

<sup>6</sup> Chen Zhefeng and Chen Shenjun. Analysis of patentability of “impurities” in drug. Zhichanli. (20 September, 2018).

<sup>7</sup> Meng Bayi. Can drugs be protected through impurity patents? (I and II). Tongxieyi. (9-10 April, 2018).

<sup>8</sup> Chris Tang. New strategy in litigation—Based on *Qilu Co. v. Beijing Sihuan*. Yilvzhuanli. (28 February, 2017).

<sup>9</sup> Zhao Hao. Drug impurity patents—Starting from cinpezide maleate. Zhichanli. (2 January, 2018).