Guidelines and strategy of the International Conference of Harmonization (ICH) and its member states to overcome existing impurity control problems for antibiotics in China

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[ABSTRACT] In the present report, we review the technical guidelines and principles on impurity research and control for antibiotics established by various agencies, including the International Conference of Harmonization (ICH), the US Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the China Food and Drug Administration (CFDA). Progresses with the US Pharmacopoeia (USP), the European Pharmacopoeia (EP) and the Chinese Pharmacopoeia (ChP) to control impurities in antibiotics are also presented. Next, our discussion is focused on analyzing the CFDA’s requirements on impurity research and control for antibiotics, and the implementation of ICH, FDA and other technical guidelines for generic drugs impurity control in China. Existing problems are further reviewed, in order to improve the overall process for the control of antibiotic purity

[KEY WORDS] China; Impurity control; Antibiotics; Bridging; Guidelines

[CLC Number] Q5

Introduction

Characterization and control of drug impurity is crucial to ensuring drug product quality. Unlike small molecule drugs produced through chemical synthesis, antibiotic products feature with complex structures, numerous homologues and isomers, multiple pathways involved in impurity introduction, and unfavorable chemical stability [1-9]. Moreover, many impurities suffer from instability, resulting in difficulties in preparation of reference standards for their detection and analysis.

These factors present a great challenge to the characterization of impurities, leading to relative a weak impurity control in antibiotic products for years. For example, prior to 2010, impurity testing was not commonly adopted for antibiotic products in US Pharmacopoeia (USP), nor had strict requirements on impurity control even if adopted. Meanwhile, relevant technical guidelines published by the International Conference of Harmonization (ICH) and its member countries are often claimed inapplicability to antibiotic products. This situation has not been improved until recently when significant modifications have been made in updated versions of several technical guidelines and pharmacopeias, thanks to the advancement of analytical technologies. As a significant milestone, the European Medicines Agency (EMA) issued the Guideline on Setting Specifications for Related Impurities in Antibiotics in 2010 [1], which formally took effect in 2013.
Consistent with the principles of ICH and the US Food and Drug Administration (FDA) guidelines for impurities in other chemical drugs, this document signifies a substantial promotion of the requirements on impurity control in antibiotic products. Likewise, technical requirements for antibiotic impurity characterization and control in China have witnessed a comparable evolution. Currently, the China Food and Drug Administration (CFDA) has elevated the registration requirement gradually, accepting the technical guidelines and principles issued by ICH, FDA and EMA, as well as the USP, the European Pharmacopoeia (EP) and other pharmacopoeias. Over time, our antibiotic impurity control requirements have become more consistent with those promulgated by the ICH.

This report aimed at introducing the recent progresses in antibiotic quality control in China, especially with regard to impurity control. We will first analyze the FDA requirements on impurity characterization and control in generic drugs, considering that antibiotic products on Chinese market are mostly generic drugs and thus the registration review of impurities in antibiotics often adopts FDA guidelines on generic drugs. We also highlight the existing technical requirements on impurity research and control for antibiotics in China, pointing out the existing problems and possible solutions.

**Technical guidelines and principles for characterization and control of antibiotic impurity**

The ICH formulated the technical guidelines of drug substances and drug products in 1994 and 1995, respectively (ICH Q3A and ICH Q3B). The current version was published in 2006\(^{[10-11]}\). While these guidelines are prepared primarily for new chemical entities, their principles are extended further to generic drugs, with adjustments being made appropriate to the latter. Examples include “Abbreviated New Drug Application: Impurities in Drug Substances” and “Abbreviated New Drug Application: Impurities in Drug Products” developed by FDA in 2005\(^{[12-13]}\).

These technical guidelines establish a foundation for impurity characterization and control in small molecule chemical drugs (including new and generic drugs) and the underlying principle for these guidelines is that the reporting, identification, and quality control thresholds of related substances should be developed based on the daily dose\(^{[10-13]}\). When exceeding the relevant thresholds, impurities should be reported, identified, and controlled, as shown in Tables 1 and 2. Another key reference on impurity control is the drug monographs in USP.

<table>
<thead>
<tr>
<th>Maximum daily dosage</th>
<th>Reporting threshold</th>
<th>Identification threshold</th>
<th>Quality control threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 g</td>
<td>0.05%</td>
<td>0.10% or 1.0 mg (minimized)</td>
<td>0.15% or 1.0 mg (minimized)</td>
</tr>
<tr>
<td>&gt; 2 g</td>
<td>0.03%</td>
<td>0.05%</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

**Table 1 Identification, reporting, and quality control thresholds for related drug substances in ICH Q3A**

<table>
<thead>
<tr>
<th>Reporting threshold</th>
<th>Maximum daily dosage</th>
<th>≤ 1 g</th>
<th>&gt; 1 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold</td>
<td></td>
<td></td>
<td>0.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Identification threshold</th>
<th>Maximum daily dosage</th>
<th>≤ 1 mg</th>
<th>1–10 mg</th>
<th>&gt; 10 mg–2 g</th>
<th>&gt; 2 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold (minimized)</td>
<td>1.0% or 5 μg</td>
<td></td>
<td>0.5% or 20 μg (minimized)</td>
<td>0.2% or 2 mg (minimized)</td>
<td>0.10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality control threshold</th>
<th>Maximum daily dosage</th>
<th>≤ 10 mg</th>
<th>10–100 mg</th>
<th>&gt; 100 mg–2 g</th>
<th>&gt; 2 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threshold (minimized)</td>
<td>1.0% or 50 μg</td>
<td></td>
<td>0.5% or 200 μg (minimized)</td>
<td>0.2% or 3 mg (minimized)</td>
<td>0.15%</td>
</tr>
</tbody>
</table>

Nonetheless, caution is warranted when these guidelines are applied to antibiotic products. Specifically, most antibiotics are produced through, or partially through, fermentation, a biological process that features with a greater variability and a lower controllability, compared to a chemical synthetic process. Consequently, antibiotic impurity profiles are often more complex and unpredictable that that of small molecule drugs. Thus, it is noted that the ICH Q3A, ICH Q3B, and other technical guidelines do not directly apply to fermented products and semi-synthetic products\(^{[10-11]}\).

In line with ICH Q3A and ICH Q3B, the CFDA published *Research Technical Guidelines on Impurity in Chemical Drugs* in 2005\(^{[14]}\); it is noted that antibiotic products manufactured through fermentation are generally beyond the scope of the guideline. Thus, global regulatory guidance for impurity characterization and control was essentially absent for antibiotic products. Specifically, minimal impurity control or no harmonized impurity control strategy for antibiotic products existed worldwide prior to 2011. To work around this deficit, some countries resorted to a case-specific approach, which led to different impurity controls for the same antibiotics (e.g., cephalosporin) or for antibiotics in the same category, and this prompted acceptance for various antibiotic impurity specifications in the USP and EP.

Antibiotic products in China are mainly generic versions of overseas products. The defects in impurity control are transferred inevitably to these generic antibiotic products in China. This in return enhances the difficulty of developing unified and appropriate industrial impurity control standards.
for antibiotics in China.

To change this undesirable situation, the EMA officially implemented the Guideline on setting specifications for related impurities in antibiotics (herein after referred as the EMA Guideline) in 2010 [1], aiming at developing consistent impurity thresholds for antibiotics. This is the first global technical guideline for impurities in antibiotics.

The EMA Guideline points out that impurity profiles are to a great extent subject to the manufacturing processes. For instance, the same microbial strains may generate different impurity profiles. Research of impurity profiles in antibiotics should be conducted according to the ICH guidance; thresholds for related substance should be developed based on specific impurities with known structures and those with unknown structures, non-specific impurities (for non-specific impurities, the acceptable standard should not exceed the identification threshold), and the total impurities, respectively. For specific impurity with unknown structure, it should be fully verified that it comes from the drug substance. It should also be identified and controlled by suitable methods, such as high performance liquid chromatography (HPLC). The technical guidelines also provide the identification, reporting and quality control thresholds for antibiotic drug substances and drug products, as shown in Tables 3 and 4 [1].

**Table 3 Identification, reporting and quality control threshold of related antibiotics substances proposed by the EMA Guideline**

<table>
<thead>
<tr>
<th></th>
<th>Reporting threshold</th>
<th>Identification threshold</th>
<th>Quality control threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semi-synthetic products*</td>
<td>0.05%/0.03%</td>
<td>0.10%/0.05%</td>
<td>0.15%/0.05%</td>
</tr>
<tr>
<td>Fermented product, single component</td>
<td>0.10%</td>
<td>0.15%</td>
<td>0.15%</td>
</tr>
<tr>
<td>Fermented product, multi-component</td>
<td>0.10%</td>
<td>0.15%</td>
<td>0.50%/0.2%</td>
</tr>
</tbody>
</table>

**Table 4 Impurity research threshold of antibiotics products proposed by the EMA Guideline**

<table>
<thead>
<tr>
<th></th>
<th>Reporting threshold</th>
<th>Identification threshold</th>
<th>Quality control threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semi-synthetic products*</td>
<td>0.1%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Fermented product, single component</td>
<td>0.15%</td>
<td>0.2%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Fermented product, multi-component</td>
<td>0.15%</td>
<td>0.2%</td>
<td>0.5%/0.2%</td>
</tr>
</tbody>
</table>

* If semi-synthetic products are multi-component compounds, reporting threshold could refer to multi-component fermented products; ** Quality control threshold of substances closely related to the structure of parent compound was 0.50%.

Compared with ICH Q3, the EMA Guideline fully considers the special characteristics or features of antibiotics when developing impurity control thresholds. For semi-synthetic antibiotics produced by starting materials with a relatively high purity, the guideline states that impurity concentrations in these antibiotics are relatively low, and therefore ICH Q3 could be adopted for their impurity control. For example, penicillin and cephalosporin, synthesized from 6-amino-penicillanic acid (6-APA) and 7-amino-cephalosporanic acid (7-ACA), should be based on ICH Q3 Guideline. For fully fermented products, on the other hand, corresponding thresholds are properly loosened. As such, the guideline considers on one hand those antibiotics with relatively mature processes and clear impurity profiles and on the other those with large clinical doses and poor manufacturing controllability.

Currently, this guideline is also taken as reference when submissions of antibiotic products are evaluated in China.

**Progresses of pharmacopoeia in different countries with respect to antibiotic impurity control**

Comparisons of pharmacopoeia published during different periods in different countries indicate that, with the advancement of analytical technologies, the understanding of physical and chemical properties of antibiotic products and their production processes have been continuously improved [15-22]. Consequently, guidelines for antibiotic impurity controls established in pharmacopoeias in various countries have been progressively improved, in line with the advent of related technical guidelines. Tables 5–7 show the impurity control schemes of azithromycin and cefazolin sodium [23], two typical semi-fermented antibiotics in various pharmacopoeias published in different periods and different countries, indicating that the trend of requirements for tightening impurity control of these two drug substances are progressing.

As can be seen from these tables, earlier versions of pharmacopoeias imposed few requirements on impurity control in antibiotics. While in some cases the less sensitive Thin Layer Chromatography (TLC) method was adopted for impurity testing, the impurity test items were even left absent for others. In the later versions, however, tighter requirements on impurity control were gradually developed, with more attentions being paid to the control of known impurities. It should be noted that Chinese Pharmacopoeia provides a limited number of known impurities for these two products, and there is limited availability of impurity reference standards.

**Progresses in FDA’s requirements on impurity research and control in antibiotics**

As generic drugs may differ from the reference drug products in Active Pharmaceutical Ingredient (API) synthetic routes, formula, and processes of drug products, impurities that are absent in reference drug products may appear in generic drugs. Thus, in various countries, it is generally required that, after consulting with the impurity control information of the reference drug products, new impurities should be studied.
### Table 5  Drug substances of azithromycin and cefazolin sodium recorded by USP at different stages

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azithromycin</strong></td>
<td>Impurity test items excluded</td>
<td>HPLC/UV, gradient elution, relative retention time for positioning known impurities, correction factor for calculating impurity contents; impurity threshold in %: Azithromycin N-oxide 0.5 3-(N, N-Dimethyl)-3-N-formylazithromycin 0.5 3-(N, N-Dimethyl) azithromycin (aminooazithromycin) 0.5 Azithromycin related compound F 0.5 Desosaminylazithromycin 0.3 N-Demethylazithromycin 0.7 Azithromycin C (3&quot;-O-demethylazithromycin) 0.5 3-De (dimethylamino) -3-oxoaazithromycin 0.5 Azaeerythromycin A 0.5 Azithromycin impurity P 0.2 2-Desethyl-2-propylazithromycin 0.5 3-N-Demethyl-3-N-[ (4-methylphenyl) sulfonyl]azithromycin 0.5 3-Deoxiazithromycin (azithromycin B) 1.0 Any Unspecified Impurities 0.2 Total Impurities 3.0</td>
</tr>
<tr>
<td><strong>Cefazolin Sodium</strong></td>
<td>Impurity test items excluded</td>
<td>HPLC/UV, gradient elution, relative retention time for positioning known impurities, correction factor for calculating impurity contents; impurity threshold in %: Tetrazolylacetic acid 1.0 Tetrazolylacetamidicetacetal 1.0 Cefazolin open-ring lactone or Cefazolin 3-hydroxymethyl 0.5 Methylthiadiacetylthiol 1.0 7-Aminocephalosporanic acid 1.0 Cefazolin 3-methyl analog 1.0 Cefazolin lactone 1.0 Cefazolinacetoxyl analog 1.0 Cefazolindeacylated 1.0 Cefazolol acid isomers 1.0 Cefazolinpimiper 1.0 Cefazolinpivaloyl 1.0 Any Unspecified Impurities 0.1 Total Impurities 3.5</td>
</tr>
</tbody>
</table>

### Table 6  Drug substances of azithromycin and cefazolin sodium recorded by BP at different stages

<table>
<thead>
<tr>
<th></th>
<th>BP Version 2002</th>
<th>BP Version 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azithromycin</strong></td>
<td>Impurity test items excluded</td>
<td>HPLC/UV, gradient elution, relative retention time for positioning known impurities, correction factor for calculating impurity contents; impurity threshold in %: —Impurity B: 2.0 —Impurity A, C, E, F, H, I, L, M, N, O, P: not exceeding 0.5 respectively; —Sum of Impurity D and J: not exceeding 0.5; —Impurity G: not exceeding 0.2; —Any Unspecified Impurities : 0.2; —total impurities : 3.0; —Impurities less than 0.1% were not included.</td>
</tr>
<tr>
<td><strong>Cefazolin Sodium</strong></td>
<td>Impurity test items excluded</td>
<td>HPLC/UV, gradient elution, relative retention time for positioning known impurities, correction factor for calculating impurity contents; impurity threshold in %: —Any Unspecified Impurities : 1.0; —total impurities : 3.5; —Impurities less than 0.1% were not included.</td>
</tr>
</tbody>
</table>

### Table 7  Drug substances of azithromycin and cefazolin sodium recorded by ChP at different stages

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Azithromycin</strong></td>
<td>TLC: Known impurities not controlled; Maximum impurity percentage not exceeding 2.0%; and other single impurity not exceeding 1.0%.</td>
<td>TLC: Known impurities not controlled; Maximum impurity percentage not exceeding 2.0%; and other single impurity not exceeding 1.0%.</td>
<td>HPLC: Drug substancesfor Injection: Known impurities with correction factor positioning: Impurity B, Q, R, S not exceeding 0.5%; Single impurity: not exceeding 0.5%; Total impurities: not exceeding 2.0%. Drug substances for Oral Administration: omitted.</td>
</tr>
<tr>
<td><strong>Cefazolin Sodium</strong></td>
<td>Impurity test items excluded</td>
<td>HPLC/Gradient. Single impurity not exceeding 1.0%; Total impurities not exceeding 3.5%.</td>
<td></td>
</tr>
</tbody>
</table>
and controlled, following the requirements of relevant technical guidelines on impurity control in chemical drugs. When possible, new impurities should be controlled under the identification threshold or their control levels should be justified [22-23].

The US FDA Generic Drugs Office has illustrated the similarities of and differences in impurities between generic drugs and new drugs, emphasizing the importance of impurity control in the development and technical review of generic medicines [26]. In this front, FDA mainly follows the basic principles outlined below:

1. Impurity information of new drugs can be obtained through published literatures, such as published data from the originators, the USP, the EP, and other monographs;
2. ICH Q3A, ICH Q3B and the Draft Technical guidelines “ANDA: Impurities in Drug Substances” and “ANDA: Impurities in Drug Products” can be taken as primary references;
3. If a medicine is included in USP, FDA also takes the monograph as the primary reference for the impurity information;
4. In addition, to avoid inconsistent quality of products where impurity controls were present, TLC was the most frequently used method, of which the low sensitivity was a great hurdle to an accurate detection and quantification in place. Purity control methods were conventional microbial-based potency tests with little specificity. For some antibiotics in China, FDA proposed to set up reference drugs in 1979, and issued the first catalogue of reference drugs (reference listed drug, RLD) in 1980, or the so-called “Orange Book” [27]. The catalogue is updated annually, with most RLDs being from the originators. In the research of impurities of generic drugs, a comparison of formula and quality between the generic drugs and RLDs in the Orange Book is required. When a RLD is not available, FDA recommends that a comparison to a different drug product containing the same Drug Substance and for the same administration route (e.g., using a capsule product as the reference for developing a generic tablet product) can be adopted.

FDA suggests that an impurity research decision-making tree be used to study generic drug impurities. Table 8 depicts the thresholds used for detecting impurities. For impurity specifications for generic drugs, sponsors should evaluate daily doses, technical guideline, the USP, and the data from comparison with the reference products. This should ensure that generic products are of the same or better quality than the reference products.

Table 8   Proofs of making impurity threshold for a generic drug substance not listed in the pharmacopoeia (Note: non-antibiotics)

<table>
<thead>
<tr>
<th>Name</th>
<th>Source</th>
<th>Measured value of imitated drug substances</th>
<th>Measured RLD at the end of validity</th>
<th>Threshold of drug substances</th>
<th>Confirmation of rationality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impurity A</td>
<td>Degradation product (hydrolysate)</td>
<td>0.20%</td>
<td>1.5%</td>
<td>NMT 0.5%</td>
<td>Metabolite</td>
</tr>
<tr>
<td>Impurity B</td>
<td>Technical impurity</td>
<td>0.10%</td>
<td>0.01%</td>
<td>NMT 0.15%</td>
<td>ICH Q3 quality control threshold a</td>
</tr>
<tr>
<td>Impurity C</td>
<td>Technical impurity</td>
<td>0.09%</td>
<td>0.07%</td>
<td>NMT 0.15%</td>
<td>ICH Q3 quality control threshold a</td>
</tr>
<tr>
<td>Impurity D</td>
<td>Technical impurity</td>
<td>0.11%</td>
<td>≤ 0.02%</td>
<td>NMT 0.15%</td>
<td>ICH Q3 quality control threshold a</td>
</tr>
<tr>
<td>Impurity E</td>
<td>Degradation product (oxidation)</td>
<td>0.30%</td>
<td>1.0%</td>
<td>NMT 1.0%</td>
<td>RLD-based regulation</td>
</tr>
<tr>
<td>Impurity F</td>
<td>Technical impurity</td>
<td>0.30%</td>
<td>0.50%</td>
<td>NMT 0.5%</td>
<td>RLD-based regulation</td>
</tr>
<tr>
<td>Any unknown impurity</td>
<td>≤ 0.07%</td>
<td>≤ 0.05%</td>
<td>NMT 0.10%</td>
<td>ICH Q3 LOD a</td>
<td></td>
</tr>
<tr>
<td>Total impurities</td>
<td></td>
<td>1.4%</td>
<td>3.7%</td>
<td>NMT 1.0%</td>
<td>Expected acceptable threshold is lower than measured RLD value.</td>
</tr>
</tbody>
</table>

a: Maximum Daily Dosage of RLD was 64 mg·d−1. The recommended drug substances identification threshold and quality control threshold were 0.10% and 0.15% respectively;
b: Impurity F also existed in RLD on the basis of chromatographic peaks with the same retention time, UV chromatography (PDA) and mass spectrum (electrospray mass spectroscopy) of two products in HPLC.

**Progresses and problems in impurity research and control for antibiotics in China**

Similar to advances made in other countries, antibiotic quality control has been evolving in China. This can be viewed at three stages: purity control, impurity control and impurity profile control [3-4, 28].

**Purity control stage**

Prior to 2000, antibiotic quality control was relatively simple as described in various pharmacopoeias, and impurity testing was not included in some product monographs. At this stage, the Chinese Pharmacopoeia (ChP) adopted purity control methods without an effective impurity control being
of β-lactam [18].

Impurity control stage: Before 2011

The ChP has significantly improved the quality control standards for antibiotics. At this stage, more sensitive HPLC methods were adopted for related substance testing for most antibiotic products listed in ChP, consistent with other pharmacopoeias. Moreover, because macromolecular impurities in some antibiotics (such as β-lactams) were responsible for anaphylactic reactions, study and control of macromolecular impurities were considered critical to product development. Therefore, size-exclusion chromatography based on Sephadex gel columns were rapidly promoted to control these β-lactam macromolecular impurities, leading to the popularization of this method in ChP Versions 2005 and 2010 [19-20, 29].

During this period the concept and methodology of antibiotic quality control in China was harmonized with other developed countries. For the registration review of antibiotics, a comprehensive quality comparison with reference products was required with an emphasis on a comparative analysis of related substances. In setting the specifications a more comprehensive list of testing items was required, with the testing on related substances being a critical component. Furthermore, while a growing attention was paid to the control of impurities such as multi-component and/or optical isomers, in the case of cephalosporin for injection it became routinely required that macromolecular impurities should be studied [19-20]. It is also worth noting that a rapid advancement of analytical technologies was made during this period. For instance, the high performance gel permeation chromatography (HPGPC) with better separation performance was used to investigate macromolecular impurities, such as cefodizime sodium [20] and Cefcapene Pivoxil Hydrochloride [20]. The HPLC methods had also been extensively used to replace the traditional microbial-based potency assay.

However, at this stage, the antibiotic impurity study and control in China did not reached the level of impurity profile controls. Due partially to the global absence of technical guidelines suitable for impurity study in antibiotics, a comprehensive study and analysis on potential impurities originated from starting materials, manufacturing processes, and degradation pathways had yet to be accomplished. A complete impurity profile was therefore unavailable to facilitate the establishment of a comprehensive impurity control strategy including the analytical methods and specifications.

During this period, the ChP was almost the only key reference for the research and control of antibiotic impurities in China. The USP and the EP were used as a reference when needed.

Impurity profile control stage: After 2011

In May 2010, EMA published Guideline on Setting Specifications for Related Impurities in Antibiotics. In the meantime, ChP Version 2010 also took effect in 2011. These developments set the stage for the modernization of impurity study and control for antibiotic products in China.

Currently, the technical guidance on impurity research and control for antibiotics in China not only takes full consideration of ChP, but also is harmonized with the FDA/EMA guidance for generic drugs and/or antibiotics and related technical standards. It is mandatory now that comprehensive studies on impurity profiles are performed based on the structural features and manufacturing processes of the products. Furthermore, the specification on impurities should be established following the scheme recommended by the EMA Guideline, i.e., the impurity control thresholds are based on specific impurities with known structure, specific impurities with unknown structure, non-specific impurities, and total impurities, respectively. For multi-component antibiotics, the control of individual components should be highlighted. Moreover, given that most antibiotic products on Chinese market are generic products, adjustments have been made to the technical guidance. For example, while it is required that quality comparisons between generic products and marketed products are conducted, an official RLD system has not been established in China at this point. To remedy this problem, at least temporarily, it is strongly recommended that the marketed products from the originators are utilized as the reference products. Complementary to this recommendation, products marketed in the ICH member countries may also be taken as references for quality comparison studies, due mainly to the fact that ICH Q3 has been effectively implemented in these countries. Another difficulty is that the number of reference standards of impurities in antibiotics is currently limited in China, which also hinders the impurity study and control in antibiotics. Purchase or synthesis of reference standards for impurities by the applicant is recommended by the Center for Drug Evaluation, China Food and Drug Administration (CDE CFDA); resource legal certification, content data, and photographs of entity and label are needed when reference standards are purchased; the preparation process, identification, and content data (using more than one analytical techniques) are also necessary while the reference standards are synthesized by the applicant.

Current requirements on impurity research and control for antibiotics in China

Quality comparison samples

Products from drug originators should be prioritized as reference listed drug (RLD). If not available, however, products marketed in ICH member countries can be used as references for impurity profile comparisons. Furthermore, to ensure that reasonable impurity specifications are established, it is recommended that the impurity profiles of the RLD should be examined at a time close to the end of shelf-life.

Impurity profiling

Impurity profiles can be acquired and analyzed based on the starting materials, the manufacturing processes, and degradation studies, considering the structural features and related literatures [31-33]. The structure and origin of each
impurity should be determined as far as possible [34-40], and it is preferable that impurities are validated with analytical methods using corresponding impurity reference standards. Furthermore, impurities exceeding the identification threshold in long-term stability studies should be identified and qualitatively characterized, with information (e.g., comparative impurity profile data against the reference products) being provided.

**Impurity-detecting methods**

Most antibiotics have now been listed in pharmacopeias of many countries. However, analytical methods and impurity specifications of the same antibiotics often vary among different pharmacopeias. To identify and select the best analytical method for quality control in qualitative criteria, it is currently required that a comparison of impurity profiles generated by different analytical methods should be performed [41-47].

**Setting specifications**

Impurity control should be established based on specific impurities with known structures, specific impurities with unknown structures, non-specific impurities, and total impurities, respectively [1].

For specific impurities with known structures, specification limits can be established according to the respective pharmacopeia limits or the identification threshold recommended by the EMA Guideline. For special impurities such as metabolic impurities, specification limits can be established based on the measured values of the generic and reference products. An exception to this, however, is that, when increased metabolic impurities impact other product quality such as efficacy, specification limits should be reduced to below quality control thresholds, according to the EMA Guideline.

For specific impurities with unknown structures, explanations should be offered as to why the identification could not be accomplished. If it is due to the difficulty of obtaining the impurity reference standards, sufficient evidences should be provided to support that the impurities are attributable to the parent compounds. For instance, LC/MS and/or photodiode array detector can be employed to show whether the fragmentation and/or UV spectra are identical. Additionally, changing the mobile phases or co-elution of mixed samples of the generic and the reference products may also be used to demonstrate whether the retention times are identical. With these evidences, the impurities can be classified as specific impurities with unknown structures, and proper labeling approach, such as HPLC relative retention times, can be employed to identify and control the impurities.

Specifications of specific impurities with unknown structures can be established based on the EMA Guideline, the pharmacopeia limits for the same impurities, or the measured values of the reference products. However, the identification threshold in the EMA Guideline should be prioritized. When the identification threshold is exceeded, the pharmacopeia limits for the same impurities can be implemented. If the impurities are not listed in pharmacopeias, the measured values of reference products at the end of their shelf-life can be referred to. For non-specific impurities, specifications are based on an identification threshold in the EMA Guideline. For total impurities, control specifications are based on the more restrictive limits of various pharmacopeias.

As an example, Table 9 illustrates the comparison of two different quality standards for cephalosporin. The registration specification for this application has followed the guidance as described above, with the limits of non-specific impurities being essentially consistent to the EMA Guideline, and the requirements on product quality have been further improved based on Chinese Pharmacopeia Version 2010.

<table>
<thead>
<tr>
<th>Table 9 The comparison of two different quality standards of cephalosporin</th>
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<tbody>
<tr>
<td><strong>ChP Version 2010</strong></td>
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<tr>
<td><strong>Cefodizime sodium for injection</strong></td>
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<tr>
<td>Cefepime dihydrochloride for injection</td>
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</table>

1: USP, BP and EP did not record this variety;
2: According to EMA Antibiotics Guiding Principles, the reporting threshold of impurities in two drug products should be 0.1%, and their identification threshold should be 0.2%.
Conclusions

Impurity characterization and control of antibiotic products that are challenging global requirements have been strengthened significantly in recent years, and the current trends suggest that these requirements are being extended to other chemical drugs [48–51]. The Chinese regulatory authority is learning from FDA, EMA, and ICH, especially their experiences with generic products. These data have been used to improve antibiotic quality control in China, significantly improving quality standards for antibiotics on the Chinese market (both imported and domestic products). Nonetheless, additional measures are warranted to establish a system of reference listed drugs, expand banks of impurity reference standards, and establish a novel impurity safety database.

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References

[1] EMA. Guideline on setting specifications for related impurities in antibiotics [2010] [S].


