



IPEC Federation Position Paper

Good Manufacturing Practices for Atypical Actives

Date: 14 Feb 2019

Contact: info@ipec-federation.org

<p>Background</p>	<p>Most countries have legislation equivalent to ICH Q7 Good Manufacturing Practice (GMP) Guide for Active Pharmaceutical Ingredients requiring that APIs are made under the prescribed conditions. However, many prescription and non-prescription (i.e. Over-the-Counter) medicines have ingredients designated as active substances that were not manufactured as Active Pharmaceutical Ingredients (APIs), but rather are excipients, food additives, cosmetic ingredients or even industrial grade products. These materials are not manufactured in accordance with ICH Q7 GMPs nor are they likely to be because the materials that are defined as the “active” are not what would be considered to be therapeutic substances. The term “Atypical Actives” has been used to describe these starting materials. Atypical Actives are usually associated with medicinal products that have been used for a long time and with a good history of patient safety.</p> <p>Other characteristics of Atypical Actives are that they are chemicals which are manufactured and sold to other industries in much larger volumes than are used in the pharmaceutical industry. Since their use as an Atypical Active may be a small part of a supplier’s business, most manufacturers of these substances would rather not continue to supply these products for API uses than face the regulatory requirements and costs of implementing ICH Q7 requirements. Finding a supplier who is compliant is not usually possible for the same reason, and many suppliers would not seek this business because of the perceived and actual liabilities caused by not meeting the regulatory and GMP requirements. This leaves the pharmaceutical manufacturer with a difficult choice: either to withdraw a safe and effective product from the market or to continue to supply their product in the full knowledge that they are in a not compliant with regulations for APIs.</p> <p>Accordingly, the IPEC Federation advocates, in the form of this position paper that for certain materials used as Atypical Actives in drug products, their manufacture should be conducted according to appropriate GMP based on risk assessment rather than ICH Q7 GMP compliance or its equivalent. This paper could be used to discuss Atypical Actives with regulatory authorities globally to establish a harmonized approach for their control, always ensuring that patient safety is not compromised.</p>
<p>Regulatory Perspectives</p>	
<p>European Union</p>	<p>In Europe, Articles 46 and 47 of Directive 2001/83/EC as amended and article 50(f) of Directive 2001/82/EC as amended, require that marketing authorisation holders use active substances manufactured in compliance with Good Manufacturing Practices (GMPs), as described in Part II of the GMP guide (ICH Q7).</p>

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	<p>Additionally, the Falsified Medicines Directive (FMD) Directive 2011/62/EU requires the Qualified Person (QP) must issue a signed declaration that the API has been made in accordance with Part II of the GMP Guide (“the QP declaration”), which presents a dilemma if the QP knows that the supplier of an Atypical Actives does not manufacture the material according to Part II GMP.</p> <p>In the mid to late 2000s industry brought this situation to the attention of the European Authorities. These concerns were recognized and the existence of Atypical Actives was acknowledged. The European Medicines Agency issued a Guideline (EMA/196292/2014) which provided guidance for the QPs declaration. The guideline stated: <i>“Exceptional circumstances, when an on-site audit is not practical (e.g. atypical actives¹), are out of scope of the declaration template.”</i></p> <p>However by not having a declaration, there would still be a regulatory gap and so the EMA Guideline goes on to require:</p> <p><i>“Specific guidance addresses the case of non-traditional (or atypical) active substances and..... in these exceptional circumstances, the QP declaration should be supported by:</i></p> <ol style="list-style-type: none">a) <i>the justification for assessment of GMP compliance in lieu of on-site audit;</i>b) <i>a listing of the documents forming the basis of the off-site audit, for example - questionnaires, review of documents, ISO 9000 certification, results of analytical testing and historical experience with the supplier, and risk analysis.</i> <p>Clearly, the QP can justify using an Atypical Active by following the guideline, and will no longer be non-complaint to the regulations as these materials are no longer in scope of the parent legislation.</p> <p>Bullet b) of the guideline requires that a risk analysis is conducted to support the justification. A “one size fits all” approach for GMP for excipients was not enacted in Europe, and in 2015 the European Commission published guidelines (EC Guidelines 2015/C 92/02) to apply a risk assessment for ascertaining the appropriate GMP for excipients. The risk assessment methodology is applied to the excipient, how it is made, how and where it is used in the drug product and potential impact on patient safety. From this risk assessment the drug product manufacturer could determine the suitability of the ingredient for its intended use. This is a pragmatic approach which</p>
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¹ 11 European Medicines Agency: Inspections: Q&A: Good Manufacturing Practice (GMP)

EU GMP guide part II Basic requirements for active substances used as starting materials: GMP compliance for active substances



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	<p>allows for the risks to the patient to determine the manufacturing standards needed or the risks that require mitigation.</p> <p>The publication of this guideline to ascertain GMP for Excipients has now provided a structure and approach for Atypical Actives. Indeed, performing the risk assessment for an Atypical Active will identify the most suitable GMP or quality management system which is required to assure the safety of the patient. Having determined the GMP required, the pharmaceutical company then has to gather evidence that the supplier is compliant with the determined standards. With this information, the QP can now comprehensively justify the use of the Atypical Active in accordance with the QP Declaration guidelines.</p> <p>For the most part, this combination of legislation and guidelines, which describe what to do in <i>exceptional circumstances</i>, allows industry to continue to provide safe and effective medicines using Atypical Actives for medicinal products sold in the EU. The IPEC Federation supports this approach which ensures that materials classified as Atypical Actives are manufactured under appropriate GMP conditions as determined by risk assessment.</p>
USA	<p>The USA FDA has acknowledged with the first mention of the term Atypical Actives in the Federal register² concerning the reporting of “Submission of Quality Metrics Data; Draft Guidance for Industry; Availability; Request for Comments”, however, FDA does not have an official definition. Recently, contrary positions have been expressed by FDA whereby a gap analysis referencing ICH Q7 requirements (gaps to be filled) could be performed rather than the risk assessment approach. FDA policy is needed for the use of Atypical Actives.</p>
Canada³	<p>Canada has acknowledged that this category of APIs exists and recently published a notice (DEL Bulletin #4) on how the drug product manufacturer can apply for an establishment license in such circumstances. This application also allows the drug product manufacturer to specify the standard of GMP used for its manufacture. Usefully the Canadian notice includes a comprehensive list of Atypical Actives but currently the list is more focused on ingredients used in Natural Health Products (i.e. mainly OTCs) and does not include those known to be used in prescription drugs.</p>
Brazil	<p>ANVISA is currently working to develop their strategy for ‘Atypical Actives’ and have been open to discussing with industry what an acceptable process might be. Currently, a working group representing</p>

² <https://www.federalregister.gov/documents/2016/11/25/2016-28332/submission-of-quality-metrics-data-draft-guidance-for-industry-availability-request-for-comments>

³ <http://www.hc-sc.gc.ca/dhp-mps/consultation/compli-conform/atypical-active-pharm-notice-actifs-atypiques-pharm-avis-eng.php>



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	ANVISA and Sindusfarma are basing how they handle Atypical Actives by placing the responsibility for identifying what the applicable GMPs should be, as determined by a risk assessment performed by the drug product manufacturer.
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IPEC Federation Position Statement on Atypical Actives	<p>The development and implementation of a specific set of GMP rules for Active Pharmaceutical Ingredients (APIs) (ICH Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients) was a crucial milestone to improve the safety of drug products.</p> <p>By requiring all APIs to be made to this GMP, the authorities inadvertently created Atypical Actives – substances widely used in medicinal products, which would likely, never be made to these standards.</p> <p>A solution to this situation has been found in some countries but ideally, a harmonized approach should be established across global regions. It is hoped other countries will acknowledge the issue and seek their own solutions by considering the following principles which will help to assure the quality of the medicines in which they are used and of course, do not compromise patient safety:</p> <ul style="list-style-type: none">• As part of its supplier management quality system, a risk assessment performed by the drug product manufacturer should be used to determine the appropriate level of GMP for the intended application of the Atypical Active. The risk assessment would determine where further controls might be needed related to the drug product manufacturer’s specific requirements / application. [The use of the EU Ascertaining GMP for excipients risk assessment would be best practice for this.]• The manufacturer of the Atypical Active needs to have a clear understanding of which GMPs they follow (a clear statement to which GMPs they reference).• The stated excipient supplier GMPs need to be the baseline for any drug product manufacturer’s risk assessment. The risk assessment should conclude that the ‘status quo’ is acceptable or if it is not, the drug product manufacturer and supplier should collaborate to address required improvements.• Quality Agreements should be considered to document the appropriate GMP requirements and demonstrate where potential additional controls are necessary and agreed on between drug product manufacturer and supplier. Additional testing (specification parameters) can also be agreed by the parties.• Regulators / inspectorates need to extend a pragmatic approach on a case-by-case basis whether for a given Atypical Active the minimum GMP requirements have been adequately defined and addressed through additional controls, for the specific application, without compromising patient safety.• The Atypical Active manufacturer should have a clear understanding and message about the Atypical Active and its potential uses, and the appropriate GMPs and controls in place.
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	<p>This would have particular relevance for those materials which might also be classified as a novel excipient.</p> <ul style="list-style-type: none">• The use of certification to a GMP standard is a useful tool in the drug product manufacturer's risk assessment process to determine the acceptability of the baseline level of GMPs used by the supplier.• Good communication between the drug product manufacturer and supplier is an essential prerequisite to managing an effective risk assessment process.• Registration and Customs requirements need to have flexibility built-in to allow for different fee structures and registration requirements (defined minimum standards), i.e. need to address GDUFA fees for APIs.• Compendia should establish a clear mechanism to establish which monograph is the compliance reference where an Atypical Active may have both conflicting active ingredient and excipient standards.• To further the aim of establishing a global, harmonised approach to determining appropriate GMP for Atypical Actives, the IPEC Federation would support efforts to add this topic to ICH agenda.
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About IPEC Federation:

Created in 2010, the IPEC Federation is a global organization that promotes quality in pharmaceutical excipients. The IPEC Federation represents the five existing regional International Pharmaceutical Excipient Councils (IPECs) – IPEC-Americas, IPEC Europe, IPEC Japan, IPEC China and IPEC India – and provides a unified voice to promote the best use of excipients in medicines as a means of improving patient treatment and safety. Its global membership extends to more than 200 companies.