Marketing applications for biopharmaceuticals: Considerations for different jurisdictions – Part 2

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Abstract
Increasingly, applicants such as biotechnology companies are registering products that are manufactured at sites located in emerging markets such as India, which may have limited or no experience of manufacturing products for licensing in the more regulated International Council for Harmonisation (ICH) regions. This article, which is the second in a two-part series, focuses on Module 3 and good manufacturing practice (GMP) requirements and discusses issues and challenges when working with active substance and drug product manufacturing sites located in emerging markets. Part 1, published in Regulatory Rapporteur in October 2017, focused on the pre-submission, scientific advice and Module 1 requirements for the EU, US, Australia, Canada, New Zealand, South Africa and Switzerland.

Introduction

In the second decade of the 21st century it is becoming increasingly common for applicants developing new biopharmaceuticals to use manufacturing sites based in emerging markets. These manufacturers may have been successful at licensing products in their own domestic market and other emerging markets; however, they often have little experience developing products for ICH jurisdictions (US, EU and Japan) and mutual recognition agreement (MRA) markets such as Australia, Canada and Switzerland. For example, EU legislation imposes strict requirements for the manufacture of all medicines. If some or all of the manufacturing steps take place outside the EU then these manufacturers must follow the same stringent requirements and are also regularly inspected.

Lack of experience working to required local GMP standards and ICH requirements may mean when an applicant wants to prepare a filing for ICH and MRA markets, the manufacturing site may encounter a "steep learning curve", and have to make a major investment in order to comply with the required GMP standards, satisfy a third party qualified person (QP) responsible for batch release and perform the necessary studies (eg, process validation) to satisfy regulatory authorities such as the European Medicines Agency (EMA) and pass other agency GMP inspections.

The aim of this article is to provide guidance on the Module 3 and GMP requirements for applicants planning to submit marketing applications to the regulatory authorities in the EU, US, Australia, Canada, New Zealand, South Africa and Switzerland. The information provided highlights the similarities and differences for Module 3. Furthermore, insights are provided into GMP considerations when the manufacturing sites for the active substance and drug product are located in an emerging market.

Module 3 considerations

There are several aspects for applicants to consider in relation to Module 3:

- **Compliance with ICH and agency requirements.** Stability studies, process validation, viral clearance studies and validation of analytical procedures should be performed in accordance with the applicable ICH guidelines. Characterisation of the active substance should be performed using state-of-the-art techniques and clearance of process related impurities such anti-foam reagents needs to be demonstrated and data provided in the submission.
- **Compliance with pharmacopoeias.** Where monographs are available for specific types of products, for example the European Pharmacopoeia (*Ph Eur*) monograph for Monoclonal Antibodies for Human Use (2031), the specification for the active substance should be in accordance with the monograph. Other considerations such as development of the master cell bank should also be in accordance with the recommendations provided in the monograph.

  Raw materials used during the manufacture of the drug substance and excipients used in the drug product should comply with *Ph Eur* and United States Pharmacopoeia (USP) requirements. Moreover, when manufacturing products for marketing in the EU and US, applicants should ensure that water for injection used during the manufacturing process complies with the *Ph Eur* and USP respectively.

  If applicants are partnering with manufacturing sites located in China where the product is already marketed in China, then the active substance and drug product would need to comply with the requirements of the Chinese Pharmacopoeia (CP). For some tests, eg, bacterial endotoxin, the specifications in the CP are tighter than the *Ph Eur* and USP. This may be a point to consider when deciding to have "global" or "regional specific" specifications as batches that may be out of specification with respect to CP requirements could comply with *Ph Eur* and USP requirements.
- **Description of pharmaceutical form.** When preparing the drug product section and labelling for the product, applicants should ensure that the pharmaceutical form proposed for a particular jurisdiction complies with local requirements. For example, for EU markets, the pharmaceutical form specified in applicable quality

Table 1: Overview of Module 3.2.R regional information requirements.

Regional section	US	EU	Australia	Canada	New Zealand	South Africa	Switzerland
Executed batch records	Required	Not required	Not required	Required	Not required	Required	Not required
Biosimilarity exercise (biosimilars only)	Required. Compare with US sourced reference product (RP).	Required. Compare with European Economic Area (EEA) sourced RP.	Required. Compare with US or EEA sourced RP. Need to justify equivalence to product marketed in Australia.	Required. Compare with US or EEA sourced RP. Need to justify equivalence to product marketed in Canada.	Required. Compare with US or EEA sourced RP. Need to justify equivalence to product marketed in New Zealand. The chosen RP must be an innovator biological medicine that has consent for distribution in New Zealand. Medsafe does not cite any specific New Zealand guidelines for biosimilars, but refers biosimilars manufacturers to both the FDA draft guidelines and the EMA guidelines for more information.	The RP must be registered in South Africa on the basis of efficacy and safety data; however, samples of the RP used in comparability studies do not need to be procured from the South African market but can be sourced from a country with which South African Health Products Regulatory Authority is aligned. These include countries generally recognised to have stringent regulatory systems such as those forming part of the ICH regions eg, EU, US and Japan as well as Australia, Canada and Switzerland.	The comprehensive comparability studies on quality, biological activity, safety and efficacy of the candidate biosimilar must be carried out using a RP obtained from the Swiss market. Alternatively, comparability studies may be performed using an RP with the same active substance that is obtained from EEA and authorised there. In the latter case, it is also necessary to demonstrate equivalence (sufficient similarity) between the EEA RP and the Swiss RP, since the documentation for the latter is the reference for the biosimilar.
TSE/BSE certification suitability for raw materials of animal origin	Required	Required	Required	Required	Required	Required	Required
Lot release documentation	Not required	Not required	Not required	The proposed test protocol format for the release package, including Certificate of Analysis (CoA) for the active substance or drug product, and safety certification for any biological excipient used, if applicable (eg, a Plasma Certificate), should be provided. The documentation should include the name and title of the delegate with signing authority for lot release.	Not required	Not required	Not required
Medicinal products containing or manufactured with materials of animal and/or human origin. All ingredients of animal origin (excluding products from porcine origin) should be declared and specified BSE/TSE free	Required	Required	Required	Required	Required	Required	Required

Table 1: Overview of Module 3.2.R regional information requirements (cont'd).

Regional section	US	EU	Australia	Canada	New Zealand	South Africa	Switzerland
Parent active substance manufacturer with various sites	Not required	Not required	Not required	Not required	Not required	1. If an identical route of synthesis, or manufacturing process of the primary production lot (PPL), including the purification step is used by each site of the same parent company; a statement to this effect will suffice with regards to this route. 2. In this case include valid CoAs from the active substance manufacturer or manufacturer of the PPL for two batches issued by each site.	Not required

overall summary sections, Module 3 sections, summary of product characteristics and in the mock labels should be an approved European Directorate for the Quality of Medicines & HealthCare (EDQM) term. Information about which pharmaceutical form terms are acceptable in the EU can be found by searching in the EDQM standard terms database.[1]

- **Raw materials of biological origin.** Wherever possible, applicants should work with their manufacturing sites to ensure that the use of raw materials of human or animal origin is avoided during the active substance and drug product manufacturing processes.

  If a raw material of animal origin is required during the manufacturing process then manufacturers should, where possible, source a supply that has a certificate of suitability issued by the EDQM. For bovine serum it is recommended that it complies with the *Ph Eur* monograph on bovine serum (2262) and US 9CFR113.53. Furthermore, where possible manufacturing sites should look for alternative reagents, for example instead of using porcine trypsin manufacturers could consider using invertebrate (eg, Accutase® from shrimp), plant derived and recombinant bacterial sources.[2]
- **Container closure system components.** The container closure components for the active substance and medicinal product should comply with the compendial standards such as USP and *Ph Eur* monographs.

  For the US and Canada, a letter of access to the drug master file (DMF) that has been filed by the manufacturer should be included in the biologics license application (BLA) and new drug submission (NDS) respectively. In the absence of a DMF, additional information on the container closure components will need to be submitted in Module 3 Section 3.2.S.6 for active substance and Module 3 Section 3.2.P.7 for drug product.
- **Use of raw materials approved for use in the EU and US.** For biopharmaceutical products that are chemically modified (eg, pegylated), applicants should ensure that where possible the chemical (eg, activated PEG) used for the modification complies with local requirements: for example a DMF is filed with the US and Canada. For the EU, the applicant needs to demonstrate that it is manufactured in accordance with EU GMP requirements and its synthesis needs to be described in the dossier. In addition, it is recommended that the activated PEG manufacturer is included on QP declaration as a part manufacturer of the drug substance and compliance with EU GMP shown to be established on an appropriate basis.
- **Excipients of human origin.** If the medicinal product contains an excipient of human origin such as human serum albumin (HSA) then the applicant should ensure that it is manufactured in accordance with the requirements for the US, EU and other markets. For example, in the EU the company that manufactures the HSA from human plasma should have a plasma master file registered with the EMA. Furthermore, the manufacturer should have a DMF filed with the US FDA, Health Canada and other applicable jurisdictions.
- **Process validation for active substance and drug product.** It is recommended that an applicant performs a regulatory compliance review at least 12 months prior to the planned submission date to ensure that necessary studies have been performed satisfying ICH requirements, eg, active substance/drug product shipping studies and extractables/leachables studies of container closure system. In addition, the latest guidelines issued by the regulatory authorities where submissions are planned should be provided to the manufacturing sites and the applicant should ensure that the necessary studies are performed.

  For applicants considering marketing authorisation in the EU, the active substance and drug product manufacturing sites should conduct the process validation in accordance with the EMA process validation guidelines for biotechnology-derived active

When applicants are partnering with a manufacturing site located in an emerging market, it is imperative that the appropriate due diligence to ICH and GMP compliance is performed as early as possible during product development

substances[3] and finished products.[4] If the recommendations in these guidelines are not followed by the manufacturing sites, then the applicant can expect to receive questions regarding process validation for active substance and drug product at Day 120.

- **Appendices.** Information about the manufacturing facilities provided in Module 3 Section 3.2.A.1 of a US BLA or new drug application (NDA) is far more detailed than what is required in other jurisdictions, such as the EU, Australia, Canada and Switzerland. The requirement to provide very detailed information in US marketing applications can sometimes result in a heavy translation burden for applicants when manufacturing sites are located in an emerging market because qualification reports for key equipment (eg, autoclaves) may only be available in the local language.
- **Regional requirements.** An overview of regional information requirements is provided in Table 1. From the information provided, it can be seen that there are many similarities in respect to requirements across the different jurisdictions.

GMP considerations

The following points outline the key considerations for the applicant in relation to GMP:

- **Compliance with US and MRA GMP requirements.** As mentioned previously, it is becoming increasingly common for active substance and drug product manufacturing sites to be located in an emerging market, as companies in these countries may want to partner with a company located in the EU or US when planning clinical trials in ICH countries for product licensing. Very often these manufacturing sites have not previously been inspected by an EU national regulatory authority, Health Canada, Australia's Therapeutic Goods Administration (TGA) or FDA. Therefore, the site may not currently operate to US and MRA GMP standards and not have a GMP certificate issued by an EU national regulatory authority such as the UK's Medicines and Healthcare products Regulatory Agency (MHRA). Moreover, the manufacturing site may not be familiar with the often onerous requirements of complying with ICH requirements, as currently the site may only be manufacturing products that are licensed in other emerging markets such as Africa and some Latin American countries where ICH standards do not apply. The manufacturing site also needs to work in accordance with the recommendations of applicable GMP guidelines for the markets where the applicant is planning to request marketing authorisation. For example, from an EU GMP perspective, the active substance and drug product manufacturing sites need to comply with the requirements specified in applicable EU GMP guidelines.[5]

When submitting a marketing authorisation application (MAA) in Australia, the GMP status of the manufacturing site must be confirmed in the application. The applicant should confirm that the site has been assessed via the TGA's GMP clearance process.

Reports drafted at the manufacturing site may only be available in the local language. It is therefore imperative that English translations of reports, for example, to support the authoring of Module 3 documents are prepared by an accredited translation agency and are thoroughly checked by the manufacturer's quality assurance group to ensure they are an accurate representation of the original report prepared in the local language. Good and accurate translations are crucial as source documents used for the preparation of high quality Module 3 sections need to be available for review when the site is inspected by the FDA and other regulatory authorities. If reports are provided in Module 3 as supporting documentation, regulatory agencies expect them to be prepared to a high standard and in English. Potential applicants should note that it is not recommended to include bilingual reports in EU MAA submissions. Some regulatory authorities such as Health Canada may visit the active substance and drug product manufacturing sites to ensure the manufacturing process is performed in accordance with the information provided in Module 3. Therefore, reports generated at the sites and provided as source documents for Module 3 sections should accurately summarise the current manufacturing process.

For an MAA being reviewed by the EMA, where a manufacturing site of the active substance and/or drug product is located in a European Economic Area (EEA) member state, it is normally not necessary to request an inspection to confirm its GMP status as it is required by Directive 2001/83/EC[6] to be regularly inspected by the relevant authorities by virtue of holding a manufacturing authorisation for that classification of product and type of manufacturing operation.

An inspection will normally be requested to confirm the GMP compliance status of manufacturing sites in a third country eg, China, India, South Korea, Malaysia and Turkey. This is unless satisfactory information is available from an inspection of the same or similar category of product carried out during the last 2 to 3 years by an EEA competent authority, or by the competent authority of a country where an MRA is in operation, when applicable.

In all cases (for sites in EEA and third countries), an inspection may be requested to cover product or process related issues arising from the assessment of the application. In this case the rapporteur and/or co-rapporteur will provide the inspection team with a list of questions/issues, which should be addressed during the inspection.

If deficiencies are identified during a GMP inspection by a national EU regulatory authority on behalf of the EMA, eg, UK MHRA, this can delay marketing authorisation being issued while corrective and preventive actions are implemented at the manufacturing plant. According to the EMA 2016 Annual Report,[7] there appears to be a growing problem with companies in India, as the number of GMP non-compliance statements has doubled (from 6 to 12).

These GMP non-compliance statements can lead to supply stop; removal of a manufacturing site from the dossier; removal/replacement of a manufacturing site during the assessment procedure (prior approval); withdrawal of an application for marketing authorisation and recall of medicinal products.

- **Qualified person declaration.** For a company wishing to market a product in the EU, a QP based in an EU country is required for EU batch release (see Table 1). In Module 1 of an EU MAA dossier, a QP declaration needs to be provided. This is a critical document and if it is not included in the initial filing of the MAA then the dossier will not pass validation. If the active substance manufacturing site is located in a non-ICH jurisdiction, it is recommended to engage a third party QP at least 18 months in advance of the planned MAA submission so the QP has adequate time to visit the manufacturing site to ensure that it complies with EU GMP standards. This will facilitate the corrective actions required are performed well in advance of the planned MAA submission date so the QP declaration can be signed. Applicants are encouraged to make the manufacturing site aware of this EU requirement for a QP to perform batch release as soon as possible when setting up quality agreements. If the QP declaration is not provided in the initial filing of the MAA then the submission will not pass validation and the clock will stop until this is provided to the EMA.

  The manufacturer's authorisation and GMP certificate for the site where importation into the EU and batch release takes place must be included in Module 1 of the MAA.
- **EU and US mutual recognition agreement.** An EU and US MRA[8] on GMP inspections is due to come into effect on 1 November 2017. The agreement encourages international harmonisation, makes better use of inspection capacity and reduces duplication. The EU-US MRA covers certain marketed biopharmaceuticals for human use. It will allow EU authorities and their US counterparts to: rely on each other's GMP inspections; waive any requirements for batch testing of products on entry into their territories after a transition phase; and share information on inspection outcomes and quality defects.

  Given that FDA and EMA are in the process of establishing an MRA regarding each other's GMP inspections, it will be interesting to see whether the decision to withdraw an EMA MAA due to major issues identified during a GMP inspection by an EU national regulatory authority, may impact FDA's decision to approve a BLA for the same biopharmaceutical.

Discussion

From the information provided here it is evident that there are many similarities between the Module 3 regional requirements for the US, MRA countries and South Africa.

Furthermore, if an applicant is partnering with manufacturers or contract manufacturing organisations located in emerging markets then ideally the applicant should perform regulatory due diligence prior to manufacturing of batches of product to be evaluated in Phase III clinical trials to ensure manufacturing sites are operating in accordance with ICH and GMP requirements. Not performing this type of assessment can lead to the applicant receiving major objections and many other comments regarding sections provided in Module 3. Applicants should also ensure that the manufacturing sites are constantly checking agency websites and have a robust regulatory intelligence notification process in place to ensure that they are aware of the most recent regulatory and GMP guidance developments. A robust risk assessment approach should also be implemented to identify deficiencies during the preparation of the dossier and a mitigation strategy should be implemented to address these deficiencies both pre- and post-submission.

Conclusions

From the information provided in this 2-part article, it can be seen that there are similarities in the Module 1 and Module 3 requirements between EU, US, Australia, Canada, New Zealand and Switzerland that allow applicants to prepare certain sections of the dossier that can be classified as "global" and used in multiple jurisdictions. With regards to pre-submission activities seeking scientific advice is recommended in certain jurisdictions such as the US, EU, Canada and Australia, especially if an applicant does not have previous experience with the product in question in these markets. Engaging with regulatory agencies during scientific advice and pre-submission meetings gives the agency the opportunity to become familiar with the product and initiate dialogue with the applicant at an early stage.

Finally, when applicants are partnering with a manufacturing site in located in an emerging market, it is imperative that the appropriate due diligence with respect to ICH and GMP compliance is performed as early as possible during product development. This will ensure potential issues are identified well in advance of a planned filing date, that provides more time for issues to be resolved prior to submission and helps reduce the risk of major objections being raised during review of the marketing application and critical observations raised during regulatory agency GMP inspections. ■

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