Marketing applications for biopharmaceuticals: Considerations for different jurisdictions – Part 1

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Abstract
Pharmaceutical and biotechnology companies planning to obtain marketing authorisation approval for biopharmaceutical products (including biosimilars) often initially file in the EU/US before targeting other key markets such as Australia, Canada, New Zealand, South Africa and Switzerland. Applicants, when possible, will prepare "global documents" based on the common technical document (CTD) and International Council for Harmonisation (ICH) requirements, which can be used in multiple jurisdictions. Increasingly, applicants such as biotechnology companies are registering products that are manufactured at sites located in emerging markets, which may have limited or no experience with manufacturing products for licensing in the more regulated ICH regions. Due to the potential challenges in these markets, it is imperative that these sites are made aware of the requirements such as ICH quality standards and US/EU/mutual recognition agreement (MRA) good manufacturing practice (GMP) requirements, as early as possible during manufacturing process development. This two-part article highlights the similarities and differences between the submission requirements for the EU, US, Australia, Canada, New Zealand, South Africa and Switzerland. In addition, it highlights points to consider when the active substance and drug product manufacturing sites are located in an emerging market with a focus on biopharmaceuticals.

Introduction

It is well known that the US FDA, the European Medicines Agency (EMA), Health Canada, Australian Therapeutics Goods Administration (TGA), New Zealand MedSafe, the South African Health Products Regulatory Authority (SAHPRA) and SwissMedic view biopharmaceuticals differently than chemical drugs. This is evident in the information provided on agency websites and in the guidelines issued. Preparing a marketing application (MA) for a biopharmaceutical can be more challenging than for small molecules and if an applicant proposes its product as a biosimilar, this adds another level of complexity to the development process.[1]

For biosimilar products, the "regulatory bar" is set higher because a biosimilar is not regarded as a generic of a biological medicine. This is because the natural variability and more complex manufacturing of biopharmaceuticals by cell culture in a bioreactor preclude an exact replication of microheterogeneity. Therefore, more studies are required for regulatory approval of biosimilars than for a generic version of small molecule products.[2,3]

The aim of this two-part article is to provide guidance on the requirements for applicants planning to submit MAs to the regulatory authorities in the EU, US, Australia, Canada, New Zealand, South Africa and Switzerland. Part one focuses on pre-submission and submission considerations and highlights the similarities and differences in Module 1 – administrative information of the CTD. Part 2 will provide insights on GMP and chemistry, manufacturing and controls (CMC) considerations when the manufacturing sites for the active substance and drug product are located in an emerging market.

Pre-submission and submission considerations

An overview of pre-submission and submission requirements for the EU, US, Australia, Canada, New Zealand, South Africa and Switzerland is provided in Table 1. Further details on specific requirements follow, while Part 2 will expand on ICH, Module 3 and GMP requirements.

- **Scientific advice.** It is recommended that applicants planning to submit a biologics license application (BLA) or new drug application (NDA) in the US and a marketing authorisation application (MAA) in the EU seek scientific advice from the FDA and EMA throughout development of the product to discuss quality, as well as nonclinical and clinical aspects of the proposed data package. If an applicant has no previous experience of filing MAs for biosimilars in the EU, US and other major markets, then a meeting with the respective agency would be recommended to ensure the applicant is fully conversant with the data requirements and nuances of the submission process. The proposed reference product (RP) for the clinical studies and the quality biosimilarity exercise should also be discussed. Applicants should be aware that even though the EMA and FDA biosimilar guidelines refer to the "totality of evidence" regarding the quality, nonclinical and clinical data packages,[2,3] the EMA and FDA will expect the applicant to demonstrate similarity with the RP at the quality level. Having very comprehensive and robust clinical and nonclinical data packages will not compensate for having a limited quality data package.

  For the EU, an applicant could consider discussing its proposed data package with an EU national regulatory authority (eg, the UK Medicines and Healthcare products

  Regulatory Agency (MHRA) or the Paul-Ehrlich-Institut (PEI) in Germany) before submitting a request to the EMA. This gives the applicant the opportunity to refine and hone questions

Table 1: Overview of pre-submission and submission requirements.

Pre-submission and submission requirement	US	EU	Australia	Canada	New Zealand	South Africa	Switzerland
Local name for MA	BLA and NDA	MAA	New Chemical Entity (NCE)/New Biological Entity (NBE)	New Drug Submission (NDS)	New Medicine Application (NMA)	MAA	MAA
eCTD	eCTD mandatory submission via the FDA Electronic Submission Gateway.	eCTD mandatory submission via the EMA eSubmission Gateway.	eCTD accepted submission via electronic media (CD-R, DVD-R). TGA also accepts NeeS format.	eCTD mandatory from 1Jan 2018. Submission via the Common Electronic Submissions Gateway.	Preferred format is ICH CTD submission via DVD. Medsafe does not require dossiers to be prepared with eCTD software or in NeeS format.	Preferred format is eCTD submission via DVD.	Preferred format is eCTD submission via the SwissMedic eGov portal. Submissions can also be in the eDOK format or on paper.
Scientific advice meeting	Recommended	Recommended	Not available	Not essential	Not available	Not essential	Not essential
Pre-submission meeting	Recommended 6–7 months before the planned submission date.	Recommended 6–7 months before the planned submission date. In addition, it is recommended to have a follow up meeting with the rapporteur at least 3 months before the planned submission date.	Recommended 2–3 months before the planned submission date.	Recommended at least 6 months before the planned submission date.	Not available	Recommended at least 3 months before the planned submission date.	It is possible to hold a pre-submission meeting with SwissMedic; however this is not typically required.
SME benefits	Yes	Yes	No	Yes	No	No	No
Legal entity	US law requires that MA holders are established in the US.	EU law requires that MA holders are established in the EU or EEA.	Australian law requires that product sponsors are established in Australia.	Canadian law requires that MA holders are established in Canada.	New Zealand law requires that sponsors or licence holders are established in New Zealand.	An application for registration of a medicine in South Africa may be made by any of the following: an Applicant residing and doing business in South Africa; a close corporation incorporated in South Africa; or a company in South Africa with at least a responsible delegated person residing in South Africa and an authorised person residing in South Africa authorised to communicate with the SAHPRA.	Applicants for MA in Switzerland must be locally based and must hold a pharmaceutical establishment license from SwissMedic in order to file a MAA. The licence is required for both companies headquartered or affiliated in Switzerland, and companies based outside the country that apply for MAA in Switzerland.

Table 1: Overview of pre-submission and submission requirements (Cont'd).

Pre-submission and submission requirement	US	EU	Australia	Canada	New Zealand	South Africa	Switzerland
Invented name	A proprietary name request must be submitted to the FDA for approval.	Two proposed invented names must be submitted to the EMA for approval.	Submitted as part of the application.	Submitted as part of the NDS.	Submitted as part of the NMA.	Submitted as part of the MAA.	Submitted as part of the MAA.
Eligibility	Biopharma-ceuticals that consist of more than 40 amino acids use the BLA process.	An eligibility request for submitting via the CP must be submitted to the EMA.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
Compliance with ICH requirements	Required	Required	Required	Required	Required	South Africa is an observer of ICH.	Required
GMP inspection of active substance and drug product manufacturing sites	Required	Required	Overseas manufacturing sites require a GMP pre-clearance certificate.	Required. Health Canada performs an "on-site evaluation" regulatory compliance review to ensure the manufacturing process for the drug substance and drug product matches the description provided in Module 3.	New Zealand will typically accept GMP certificates from recognised agencies such as EU national regulatory authorities or FDA.	SAHPRA will typically accept GMP certificates from recognised agencies such as EU national regulatory authorities or FDA. When acceptable evidence of GMP compliance is not available, overseas manufacturers are inspected by the GMP Inspectorate before registration of the medicine is approved.	Overseas manufacturing sites that are not part of MRA require GMP certificates or an inspection report confirming the manufacturer satisfies GMP requirements and has been inspected by a recognised agency such as EMA or FDA or a copy of an audit report and GMP certificate issued by the authority of the country in which the manufacturer is located.
Competent person for batch release	Not required. Onus is on applicant to identify a person responsible for ensuring compliance with FDA regulations. Batch analysis data from the manufacturing site is acceptable.	Required. Batch release must be performed in the EU or EEA by a qualified person. Batch release testing in the EU or EEA is required where the site of manufacture /testing is not an MRA country.	Each batch of finished medicinal product must be released for supply by an authorised person (AP) before being sold or supplied in Australia. Batch analysis data from the manufacturing site is acceptable.	Canada will accept batch release testing from an MRA country. If the site of manufacture is not an MRA country, Canada requires an ID test to be conducted and confirmed before the product can be distributed in Canada. This testing site should be established and indicated in the application prior to submission of the application.	Each batch of finished medicinal product must be released for supply by an authorised person (AP) before being sold or supplied in New Zealand. Batch analysis data from the manufacturing site is acceptable	Post importation testing required.	Required. QP needs to be based in Switzerland.
Qualified person for pharmacovigilance (QPPV)	Not applicable	Required. The QPPV must be based in an EU or EEA country.	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

Table 1: Overview of pre-submission and submission requirements (Cont'd).

Pre-submission and submission requirement	US	EU	Australia	Canada	New Zealand	South Africa	Switzerland
Expedited approval process available based on approval in another market	No	No	No. An abbreviated evaluation process is currently under consideration by TGA.	No	Yes. Medsafe offers an abbreviated evaluation procedure in which review of overseas regulatory evaluation reports (eg, EMA) forms the basis of the evaluation. Therefore, the quality and availability of evaluation reports should be a fundamental consideration for applicants wishing to use the abbreviated evaluation process.	No. Due to the large generic load at the SAHPRA, there are many backlogs, with an average time to registration of 2–3 years.	Yes, when the medicinal product is approved in a jurisdiction with a comparable regulatory system, including the EEA, SwissMedic may consider a foreign regulator's assessment, under the Article 13 procedure. If SwissMedic agrees to review a MAA through this pathway, the assessment time and fees may be reduced by one-third.

and the company's positions before contacting the EMA where the cost of requesting scientific advice is high (currently in the region of €42,300 to €84,700 as of August 2017). Furthermore, the timeline for requesting scientific advice from EU national regulatory authorities is shorter and applicants can normally have a face-to-face meeting at the national agency.

The FDA encourages sponsors to submit comprehensive analytical similarity data early in the development process to help better provide meaningful input for a proposed biosimilar development programme once the agency has considered the analytical similarity data.[4]

It is not essential to hold scientific advice meetings with other markets as the advice received from the FDA and EMA will typically cover the most stringent global requirements.

- **Pre-submission and rapporteur meetings.** Pre-submission meetings provide the opportunity for the applicant to discuss topics related to the clinical, nonclinical, quality and procedural aspects of the submission. It is also an opportunity to familiarise the agency with the development strategy and data package for the product and gain feedback on additional expectations and recommendations that are not specified in guidance. It is recommended to have a pre-submission meeting approximately six to seven months in advance of the planned submission date of the MA with the FDA, EMA and Health Canada. When planning submissions in Australia and South Africa, a pre-submission meeting normally takes place two to three months before the planned submission date where positions agreed with other agencies can be ratified with the TGA and SAHPRA.

  When submitting an MAA via the centralised procedure (CP) in the EU, a rapporteur and co-rapporteur are assigned by the EMA. As a follow-up to the EMA pre-submission meeting, approximately four to five months before the planned MAA submission date, it is possible for applicants to meet with the rapporteur and co-rapporteur to discuss any outstanding issues for clarification that were highlighted during the pre-submission meeting. This meeting normally takes place at the national agency where the rapporteur is based (eg, the MHRA) or via teleconference.

  It is not typically necessary to hold pre-submission meetings with national agencies in Switzerland, and pre-submission meetings are not available in New Zealand.
- **Eligibility/submission considerations.** In the European Economic Area (EEA), normally human medicines derived from biotechnological processes including biosimilars must be evaluated by the EMA via the CP. Nevertheless, an eligibility request must be sent to the EMA to confirm that the CP can be used for a MAA submission.

  For most biopharmaceuticals in the US, including biosimilars such as monoclonal antibodies, the application is authorised via the BLA pathway. However, for some products (eg, a recombinant peptide product), it may be considered as a therapeutic equivalent, not as a biosimilar. This is normally the approach that is followed where the originator was granted MA by the FDA under the NDA pathway, instead of the BLA pathway, because it is shorter than 40 amino acids in length. Therefore, for these products, an applicant may pursue the potential approval of its biosimilar product under Section 505(b)(2) of the Federal Food Drug and Cosmetics Act, instead of Section 351(k) of the Public Health Service Act (note that the 505(b)(2) pathway

Table 2: Overview of Module 1 requirements.

US	EU	Australia	Canada	New Zealand	South Africa	Switzerland
1.1 Forms	1.0 Cover letter	1.0 Cover letter	1.0 Cover letter	1.0.1 Letter of application	1.0 Letter of application	1.0 Cover letter
1.2 Cover letters	1.1 Comprehensive table of contents	1.1 Comprehensive table of contents	1.1 Comprehensive table of contents	1.1 Comprehensive table of contents	1.1 Comprehensive table of contents	1.2.1 Application form
1.3 Administrative information	1.2 Application form	1.2.1 Application form	1.2.1 Application form	1.2.1 Application form	1.2.1 Application form	1.2.2 Annexes –forms
1.4 References	1.3 Product information	1.2.2 Pre-submission planning form	1.2.2 Fee form	1.2.2 Pre-submission details	1.2.2 Annexes to application form	1.2.3 Annexes – documents on drug quality
1.5 Application status	1.3.1 SmPC, labelling and package leaflet	1.2.3 Patent certification	1.2.3 Submission certification form	1.2.3 Patent certification	1.3.1 South African package insert	1.2.4 Annexes – manufacturing
1.6 Meetings	1.3.2 Mock-up	1.2.4 Change in Sponsor	1.2.4 Intellectual property information	1.3.1 Data sheet and package insert	1.3.2 Patient Information Leaflet	1.3.1 Information on professionals
1.7 Fast track	1.3.3 Specimen	1.3.1 Product information – clean/annotated and package insert	1.2.5 Compliance and site information	1.3.2 Consumer medicine information	1.3.3 Labels	1.3.2 Patient information
1.8 Special protocol assessment request	1.3.4 Consultation with target patient groups	1.3.2 Consumer medicine information – clean/annotated	1.2.6 Authorisation for sharing information	1.3.3 Human embryo stem cell declaration	1.3.4 Braille	1.3.3 Packaging information
1.9 Paediatric administrative information	1.3.5 Product Information already approved in the member states	1.3.3 Label mock-ups and specimens	1.2.7 International information	1.3.4 Label mock-ups and specimens	1.4.1 Declaration by quality expert	1.3.4 Information for professionals from other countries
1.10 Dispute resolution	1.3.6 Braille	1.4.1 Information about the experts – Quality	1.3.1 Product monograph	1.4 Information about experts and expert declarations	1.4.2 Declaration by nonclinical expert	1.4.1 Information about the expert – Quality
1.11 Information amendment: Information not covered under Modules 2 to 5	1.4 1.4.1 Information about the experts – Quality	1.4.2 Information about the experts – Nonclinical	1.3.2 Inner and outer labels	1.5.1 Literature based submission documents	1.4.3 Declaration by clinical expert	1.4.2 Information about the expert – Nonclinical
1.12 Other correspondence	1.4.2 Information about the experts – Nonclinical	1.4.3 Information about the experts – Clinical	1.3.3 Non-Canadian labelling	1.5.2 Orphan drug designation	1.5.1 Literature based submission	1.4.3 Information about the experts – Clinical
1.13 Annual Report	1.4.3 Information about the experts – Clinical	1.5 Specific requirements for different types of applications	1.3.4 Investigators brochure	1.5.3 Genetically modified organisms consents	1.5.2 Amendments/ variations	1.5 Data of bioavailability studies

Table 2: Overview of Module 1 requirements (Cont'd).

US	EU	Australia	Canada	New Zealand	South Africa	Switzerland
1.14 Labelling	1.5 Specific requirements for different types of applications	1.6 Master files and certificates of suitability	1.3.5 Reference product labelling	1.5.4 Additional trade name declarations	1.5.3 Propriety name application	1.6 Environmental risk assessment
1.14.1 Draft labelling	1.6 Environmental risk assessment	1.7 Meetings and pre-submission process	1.3.6 Certified product information document	1.5.5 Co-marketed medicines declarations	1.5.4 Genetically modified organisms	1.7 Decision of foreign Authorities
1.14.2 Final labelling	1.7 Information relating to orphan market exclusivity	1.8.1 Pharmacovigilance systems	1.3.7 Look-alike/ sound-alike assessment	1.6 Drug and plasma master files and certificates of suitability	1.5.5 Package insert and patient information leaflet amendments	1.8.1 Pharmacovigilance system
1.14.3 Listed drug labelling	1.8 Information relating to pharmacovigilance	1.8.2 Risk management plan	1.3.8 Pharma-covigilance information	1.7 Good manufacturing practice	1.6 Environmental risk assessment	1.8.2 Risk manage-ment system
1.14.4 Investigational drug labelling	1.8.1 Pharmacovigilance system	1.9 Summary of biopharmaceutic studies	1.4.1 PSEAT-CTA (Protocol safety & efficacy assess-ment template – clinical trial application)	1.8 Compliance with meetings and pre-submission processes	1.7 Good manufacturing practice	1.9 Fast track status decision
1.14.5 Foreign labelling	1.8.2 Risk management system	1.10 Information relating to paediatrics	1.4.2 Comprehensive summary: Bioequivalence	1.9 Individual patient data declaration	1.8 Details of compliance with screening out-comes	1.10 Information related to paediatrics
1.14.6 Product labelling for 2253 submissions	1.9 Information relating to clinical trials	1.11 Foreign regulatory information	1.4.3 Multidisciplinary tabular summaries	1.10 Overseas regulatory status	1.9 Individual patient data	1.11 Orphan drug status decision
1.15 Promotional material (promotional-material-audience-type)	1.10 Information relating to paediatrics	1.12 Antibiotic resistance data	1.5 Environmental assessment statement	1.11 Summary of biopharma-ceutic studies	1.10 Foreign regulatory status	
1.16 Risk management plan			1.6.1 Comparative bioavailability information	1.12 References to paediatric development programme	1.11 Bioequivalence trial information	
1.16.1 Risk management (Non-REMS)			1.6.2 Company core data sheets	1.13 Information relating to pharmaco-vigilance	1.12 Paediatric development programme	
1.16.2 Risk evaluation and mitigation strategy (REMS)			1.6.3 Priority review requests	Annex I Antibiotic resistance data	1.13 Risk management plan	
1.17 Post-marketing studies			1.6.4 Notice of compliance with conditions	Annex II Overseas evaluation reports		
1.18 Proprietary names			1.7 Clinical trial Information			

When planning global development and biopharmaceutical submissions, it is important to be aware of any pre-submission and submission requirements to avoid potential pitfalls and legal issues arising prior to or during review of the application

is only available until 23 March 2020). Because the 505(b)(2) approval pathway can reference information from previous nonclinical and clinical studies not conducted by or for the applicant, animal studies or long-term safety or efficacy trials in patients are not necessarily required for approval.

For Australia, vaccines (that do not contain viable human cells), recombinant products, plasma-derived products and blood-products are not currently declared as biologics and are regulated by TGA as either a medicine or a medical device, but are not included in the biological regulatory framework. Biologicals only refer to human cells or human tissues.

For South Africa, a MA dossier for a new biological entity (NBE) is usually submitted following registration by at least one international regulatory authority that the SAHPRA aligns itself with (eg, the FDA or the EMA).

For Switzerland and New Zealand an applicant has the option of either submitting the MA dossier following approval from a reference jurisdiction (eg, the EU) which expedites the approval process or can submit in parallel to EU and US submissions. Moreover, using this approach in Switzerland also results in a substantial reduction in the fees that need to be paid to SwissMedic for the review of the MAA dossier.

In 2016, Australia commenced a consultation process with local industry on the implementation of a similar procedure to expedite approvals for products with recognised overseas registrations.

- **Small or medium-sized enterprise status.** It is possible to register as a small or medium-sized enterprise (SME) with the EMA. The EMA offers several fee incentives for SMEs including:
  - 90% fee reduction for scientific advice for non-orphan products
  - Conditional fee exemption, where the EMA scientific advice is followed and a MAA is not successful
  - Fee deferral until outcome of MAA.

In the US, an applicant is eligible for a waiver of the application fee if it is a small business submitting its first human drug application to the agency for review and does not have another product approved under a human drug application and introduced or delivered for introduction into interstate commerce.

In Canada, an applicant can apply for a fee remission if the full fee is more than 10% of the anticipated gross revenue from sales of the product in Canada during the fee verification period of three years. In addition, if a sponsor has not completed its first full fiscal year on the day that drug submission is filed, the sponsor is eligible for a two-year deferral of payment.

Currently, there are no incentives for small businesses in Australia, New Zealand, South Africa or Switzerland.

Module 1 considerations

An overview of the Module 1 requirements, for the EU, US, Australia, Canada, New Zealand, South Africa and Switzerland, is provided in Table 2. From the information provided, it is evident that there are many similarities in requirements across the different jurisdictions (eg, requirements to provide information about labelling, pharmacovigilance system and declarations by subject matter experts, such as a quality expert. Depending on the product and global regulatory status it should be noted that not all sections in Module 1 may be required. Country-specific requirements include the requirement to provide patent information and a certified product information document (CPID), which is an abbreviated quality overall summary in the Canadian Module 1 and information about antibiotic resistance in the Australian Module 1.

Discussion

When planning global development and biopharmaceutical submissions, it is important to be aware of any pre-submission and submission requirements to avoid potential pitfalls and legal issues arising prior to or during review of the application. Applicants need to consider legal obligations in different regions to ensure they have the appropriate legal entities in place and that the necessary supply chain, batch release and GMP requirements are taken into consideration.

From the information provided here it can be seen that there are many similarities between the MA requirements for the EU, US, Australia, Canada, New Zealand, South Africa and Switzerland.

It is strongly recommended that applicants take advantage of the opportunity to have scientific advice and pre-submission meetings to enhance the development process and account for agency requirements and expectations. This ultimately leads to a more complete dossier, which will reduce the likelihood of questions and potential delays during the review process.

Part two of this article will focus on Module 3 (including regional) requirements and GMP considerations. ■

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