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Biologic medicines and biosimilars

Assessment of biosimilars – Is Australia leading, following or going its own way?

The ongoing lack of certainty about what is required to obtain biosimilar registration in Australia extends to three key issues:

- Comparability – is the new product sufficiently similar to permit it to rely on the reference product's safety and efficacy data?
- Extrapolation – for which of the indications of the reference biological will the biosimilar receive marking authorisation?
- Interchangeability – should the new product be substitutable for the reference product in clinical practice and, if so, in what circumstances?

  (On the linkage between interchangeability and reimbursement in Australia, see our separate paper *Costs before Caution – Australia's unique approach to the interchangeability of biosimilars*.)

When coupled with the high investment required, these uncertainties explain why the business of bringing biosimilar products to market is very different to promoting generics, and why the cost savings from generic entry are unlikely to be replicated for biosimilars.

Assessment of follow on products

In general, the requirements to demonstrate safety and efficacy are remarkably similar throughout the major developed economies for the first approval of a new medicine, as are the processes for obtaining approval for follow-on products. The relevant National Registration Authority (***NRA***) – the Therapeutic Goods Administration (***TGA***) in Australia, the Food and Drug Administration (***FDA***) in the US and in Europe, the European Medicines Agency (***EMA***) – needs to be satisfied that the product is safe and efficacious and manufactured to a sufficient quality for it to receive marketing authorisation.

For small molecule medicines, the follow-on product can usually be shown to be identical to the reference product, making the assessment of generic products relatively straightforward. It is not so simple for follow-on biologics.

Biological manufacturing processes dictate that it is not possible to make precise copies of a biologic medicine. Accordingly, the NRA needs to decide when and to what extent the sponsor of the follow-on biologic should be able to rely on the detailed clinical and non-clinical studies provided by the sponsor of the original medicine. Reliance on an originator's clinical data is normally an important part of a follow-on business model. Aside from the ethical issues associated with the repetition of clinical studies, the studies and the preparation of the detailed documentation required to demonstrate safety and efficacy are expensive and time consuming. This provides particular barriers to biosimilar entry, which is exacerbated further by the uncertainty about the particular requirements in Australia explored below.

Biosimilar assessment in the EU and US

The EMA has been influential in shaping the biosimilar policies of many NRAs, as it has had the longest experience with processing biosimilar applications. From 2005, the EU implemented an expedited approval pathway for biosimilars. This allowed clinical data relating to a previously approved reference biologic to be used in support of the biosimilar application. Many other countries, including the US and Australia, have used the EMA's biosimilar approval framework as a reference point for developing their own processes.

The EMA system allows for biosimilars that are comparable to their reference products (as supported by sufficiently sensitive analytical data) to be approved on less non-clinical and clinical data compared to the full dossier required for a new biologic entity. The biosimilar may refer to the non-clinical and clinical data previously generated for the reference product, although some additional non-clinical and clinical data specific to the biosimilar will usually be required. The extent to which this is required will depend on whether safety and efficacy can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and pharmacokinetics and/or pharmacodynamics profiles of the biosimilar and the reference product.

Biological activity and potency are important issues for establishing comparability. Arguably, comparability can only be shown in those indications for which the biological activity and potency of the follow-on product has been studied. Whether that can then be 'extrapolated' to assume similarity to other untested indications is a further issue that is addressed in the assessment process used by the EMA and adopted in various ways by other NRAs.

Despite use of the EMA's framework as a reference point, the introduction of biosimilars into the US health system has not been smooth sailing. In 2010, after years of debate, President Obama enacted the *Biologics Price Competition and Innovation Act of 2009* (***BPCIA***). Under the BPCIA, manufacturers of biosimilars can file 'abbreviated' applications for FDA approval, similar to the EMA process. Yet, six years on, it is far from settled as to exactly how and when access should be granted, and the proper interaction of patent protection and data (and marketing) exclusivity.

The most recent guidance from the FDA released in April 2015[1] recommends a 'step-wise' approach to access this 'abbreviated' pathway. This requires:

- structural and functional characterisation;
- toxicological studies (in animals);
- clinical pharmacology;
- immunogenicity; and
- clinical efficacy and safety.

The FDA guidance indicates that a failure at any of these steps, particularly at the initial structural and functional characterisation step, is likely to mean that the process does not continue.[2] In practice, it may be possible, but additional work would then be required in the subsequent steps.[3]

Moreover, at first blush, the BPCIA system does not appear to be particularly abbreviated. Indeed, for the first step, some commentators consider the studies required go beyond the work that was required for the biologic reference product.[4] This may be because, for example, the reference biologic may never have been characterised in any detail, at least in publically available documents. This could mean that the requirement for approval of the biosimilar is to characterise ***both*** the biologic reference and the biosimilar to show that there are no relevant differences. Similarly, it may be that the biologic reference product is known to work but the mechanism of

1 U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. 'Scientific Considerations in Demonstrating Biosimilarity to a Reference Product'. April 2015. Available online at www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.

2 U.S. Department of Health and Human Services, above n1, page 10.

3 Chow, Shein-Chung. (2015) 'Challenging issues in assessing analytical similarity in biosimilar studies'. Biosimilars 2015:5, 33-39.

4 Donniger et al. (2012) 'Key considerations in biosimilars development'. *BioPharm International*, 25(10). Available online at www.biopharminternational.com/key-considerations-biosimilars-development.

action and the functional aspects of the product that make it effective are not fully understood. It may therefore be difficult to determine which characteristics and functional aspects are important. However, where structural and functional characterisation can demonstrate no relevant differences, it is likely that the most expensive aspects of drug approval – clinical trials – can be minimised. The growing number of marketing authorisations for biosimilars supports this.

The Australian registration process

In Australia, the TGA's assessment approach is still evolving and differs from other countries. When compare with some of Australia's key trade partners, the statutory approval framework used by the TGA is relatively unstructured. It is risk based, with different approaches taken for different medicines according to their perceived safety risks. There are no separate pathways for different types of applications such as new drugs, generics, new biologics and biosimilars under the Australian statutory scheme. The process follows an assessment of Category 1 and 2 applications.

However, the TGA, in non-binding guidance on its assessment processes, makes clear that concessions are made that can allow a biosimilar product to rely on data from the reference product. This has been borrowed and adapted from the EMA, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (***ICH***) and, to a lesser extent, the FDA. The TGA's current approach is set out in its guideline, *Evaluation of Biosimilars*, most recently updated in December 2015. The revisions from the preceding July 2013 version – including the removal of application flowcharts – reinforce that the TGA's flexible, risk-based approach applies to biosimilars.

Nonetheless, the overall approach is similar to that taken by the FDA and the EMA. Where the biosimilar shows appropriate similarity to a reference biologic, the TGA will consider the detailed non-clinical and clinical studies for the reference biologic can be relied on for the purpose of approving the biosimilar. However, the TGA guidance makes plain that evaluation in Australia may require different and more detailed clinical data than applications made in the US or Europe. This approach has been criticised, with stakeholders questioning the need for the TGA to evaluate products independently where they have already been approved by reputable overseas NRAs, such as the FDA and the EMA.

Category 1 Applications

Category 1 is the pathway used in the vast majority of cases. This is the pathway used for new chemical and biological entities, new generic products, new dosage forms and new extensions to indications, as well as biosimilars. Category 1 products are assessed de novo, with the TGA independently evaluating the complete application dossier.

Category 2 Applications

Category 2 is open to medicines which have been approved by the NRA in two other acceptable countries, have the same formulation, directions for use and indications as approved in those other two countries and for which two un-redacted independent evaluation reports are available. If the sponsor is able to provide this information as part of their biosimilar registration application, Category 2 drugs are afforded accelerated market entry compared to Category 1 applications.

Like the US and the EU, demonstrating comparability of a biosimilar product to the reference biologic product is an additional element to the normal requirements of the quality dossier requirements, and must be dealt with separately when presenting the data to the TGA. In this respect, the TGA is more similar to the EMA.

The EMA guidance referenced by the TGA requires comparability to be demonstrated between the reference product and the biosimilar using the same criteria that are used for determining whether a change to the manufacturing process for a biologic medicine produces any relevant difference in that biologic product. This can pose significant difficulties for biologic medicines where the reference product may not be well characterised (or at least the detail of that characterisation may be closely guarded proprietary information belonging to the original manufacturer), and where the relevance of differences may not be apparent.

The TGA makes it clear that the comparability and the relevance of any differences in physicochemical characteristics, biological activity/potency, and pharmacokinetics and/or pharmacodynamics profiles of the biosimilar and the reference product are critical to determining the extent to which the biosimilar product will be permitted to rely on the data for the reference product. This is similar to other jurisdictions, especially the EU. However, the TGA notes that its requirements for the *Common Technical Document Module 3 – chemistry, manufacturing and quality control data* – a key aspect of the required comparability studies – will require significant modification from the EU document, particularly in relation to in-house standards, studies that bridge between the chosen reference standard and the Australian registered product (if any), shipping stability, and labelling. The result is that evaluation in Australia may require different and more detailed clinical data than in other major markets.

Australia's regulatory requirements mean that those seeking to bring biosimilars to the Australian market cannot know with certainty what is required before they commence the process. This is likely to result in very different risk/reward calculations being made about which biologics to copy. It will also significantly increase the costs of bringing biosimilars to market and this may limit which biosimilars come to Australia, particularly as Australia is a relatively small market.

Despite these issues, Australia is nonetheless at the forefront of biosimilar approvals. However, the initial impression is that translation to effective competition between reference products and biosimilars, and uptake of biosimilars once on the market, is not strong.

Reforms in Australia

A recent report by the Independent Panel for the Review of Medicines and Medical Devices Regulation (the ***Sansom Report***)[5] made specific recommendations to improve the biosimilar registration process. These aim to improve efficiency and further harmonise the evaluation of biosimilars with international approaches. Two pathways, similar to existing Categories 1 and 2, for registration of a new biosimilar were proposed. These, along with most of the recommendations in the Sansom Report, were accepted in the government response in September 2016. Since then, the TGA has made a series of announcements about how it will implement the recommendations accepted by government.

Pathway One requires the submission of a complete dossier for *de novo* assessment by the TGA and mirrors the current approach in Category 1. There are however suggestions and recommendations to reduce the target evaluation timeframe for the assessment and to reduce the requirements for the sponsor's dossier. If implemented, these would explicitly allow for work-sharing arrangements between the TGA and a comparable overseas NRA. This could include the partial assessment of parts of the application by different NRAs with a joint evaluation report being used by the relevant decision makers.

The key potential benefits arise from proposed Pathway Two which provides, at least in principle, easier access to expedited assessment. This pathway would require only one positive assessment by an overseas NRA (where that NRA meets a flexible set of criteria). This widens the overseas approvals which can provide the basis for an Australian registration. However, the potential benefits from this approach may in practice be undermined by the finer details.

The recommendations recognise that there will be situations where a product may not be supported by all overseas NRAs. In such situations, it is recommended that the TGA undertake de novo assessment of those aspects of the Australian application that are not supported by the overseas NRAs. This suggests that, in practice, a single positive overseas approval will not be sufficient (at least where there is any negative assessment by a relevant NRA) and that a sponsor will be required to explain and justify any negative assessments from any overseas NRA.

It should be noted that while these recommendations have been accepted, there is no great hope for quick change. Rather, the government response is subject to the caveat that that 'implementation of the multiple pathways [for biosimilars] will only be viable in the longer-term'.

Further, while the accepted recommendations hold promise for a more efficient registration process, they do not address the fundamental problem for approval of biosimilars in Australia – the Australia-specific requirements identified above. These concern whether the new product and the reference product are sufficiently comparable and likely to remain a contentious and uncertain aspect of biosimilar registration in Australia.

These specific requirements may mean that the ability to rely on a single positive NRA assessment is somewhat illusory. Accordingly, sponsors (and given the lack of a specific statutory scheme, evaluators) may not be in a position to determine with any clarity whether the Australian application for the new biosimilar product will be permitted to rely on proof of safety and efficacy from the reference product.

5 *Review of Medicines and Medical Devices Regulation, Report on the regulatory framework for medicines and medical devices*, Emeritus Professor Lloyd Sansom AO, Mr Will Delaat AM, Professor John Horvath AO, March 2015.

Pathway Two

Pathway Two recognises that it can be impossible to provide the TGA with two un-redacted evaluation reports as required for a Category 2 application – some NRAs do not divulge that information and the reports may not be in English. If eligible for the proposed Pathway Two only one un-redacted evaluation report from any comparable NRA will be required together with a copy of the dossier submitted to that NRA and an Australia-specific module.

To qualify for Pathway Two the sponsored biosimilar must:

- be identical in dosage form, strength and formulation to the product approved by the comparable overseas NRA;
- be manufactured using a process which is identical to that assessed by the comparable NRA for the overseas product; and
- have a reference biologic, registered in Australia, that is the same as the overseas reference product.

If the sponsor is then able to satisfy the TGA regarding comparability (ie biosimilarity), then the TGA would undertake an independent assessment of the Australian-specific information only, as opposed to the clinical data and other relevant information already evaluated by an overseas NRA.

However, unlike the current position which would revert to a full Category 1 assessment if the TGA is not satisfied that the sponsored biosimilar is the comparable to the reference biologic, there are two recommended options:

- if the differences are assessed to have minimal impact on product quality, safety or efficacy, the TGA can still recommend that the biosimilar be registered if the Australian production information and labelling are appropriate; or
- if the differences do have the potential to impact quality, safety or efficacy, it is recommended that the TGA undertake further assessment necessary to satisfy itself that any potential impact of the differences has been addressed, and consider whether or not the Australian product information and labelling are still appropriate. If so, it may still recommend that the biosimilar product be registered.

Extrapolation of indications

In relation to generic small molecule products, where the proposed indications and dosage regimen are the same as those of the originator product (and where the safety and efficacy data provided with the originator product are not 'protected'[6], the TGA will generally accept applications to register generic products without requiring further safety and efficacy data. This is because it is possible to achieve an identical product and, where bioequivalence is demonstrated, the product will work in an identical way..

However, because biosimilars are not identical, the activity of the biosimilar may be different to the reference biologic. As is apparent from the approaches outlined above – which require at least some level of functional characterisation and comparative efficacy studies – NRAs are chiefly concerned with the way in which the biosimilar works compared to the reference product in relation to the treatment of a particular disease or indication. This gives rise to concerns about any extrapolation from the demonstrated safety and efficacy of the biosimilar for that indication to other disease states in which the reference biologic has demonstrated safety and efficacy.

Not surprisingly, stakeholders with a focus on the development of biosimilars strongly advocate for wide extrapolation. Given the benefits to society of improved access to medicines and lower drug costs to government, there are sound bases for this approach. In its April 2015 White Paper,[7] Hospira, which has a significant biosimilar business, also highlighted the problems of unnecessary clinical trials and the ethical issues involved in undertaking such trials.

While it could be argued that those opposing wide extrapolation, including manufacturers and sponsors of reference biologic medicines, are opposing extrapolation out of self-interest, there are also real issues that may impact on patient health and public perception of the safety and efficacy of their products. Further, where the biosimilar and the reference biologic are used interchangeably, there may be very real potential for product liability exposure. Similar concerns that have also been expressed by some patient groups and specialist medical practitioners.

Currently, the TGA applies the EMA guidelines which state that if the reference biologic has more than one indication, the efficacy and safety of the biosimilar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. In certain cases, it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference biologic. Justification for this will depend on a range of factors including clinical experience, available literature data and whether or not the same mechanisms of action or receptors are involved in all indications. The TGA has also stated that possible safety issues in different subpopulations should also be addressed. These factors will be considered in light of the totality of the quality, safety and efficacy data.

According to the EMA guidelines,[8] it is expected that the safety and efficacy data for a particular indication can be extrapolated when:

- biosimilar comparability has been demonstrated;
- there has been thorough physicochemical and structural analyses;
- there has been in vitro functional tests; and
- the above information is complemented with clinical data (efficacy, safety and/or pharmacodynamics and pharmacokinetics data).

It is clear that where the reference biologic interacts with several biological or physiological receptors *in vivo*, additional data will be required.

It may also be necessary to provide further data where an immune response, which can impact upon clinical efficacy and safety of a particular product, could differ between indications. The World Health Organisation also has guidelines on this.[9] The TGA makes reference to these guidelines, but has not officially adopted them.

In the US, the BPCIA allows extrapolation of information regarding the safety, purity and potency of a reference biologic in relation to a particular indication to the related biosimilar if sufficient scientific justification is provided. This must be done for each indication for which the sponsor wishes to register the biosimilar. The FDA has stated that this information includes, among other things, data derived from a clinical study or studies sufficient to demonstrate safety, purity, and potency in an appropriate condition of use.

Here again, the lack of clarity about whether a biosimilar will be able to compete with the reference biologic in all indications means that those seeking to bring biosimilars to market cannot know with certainty the potential market they will be entering before they commence the process. The lack of clear guidance about when extrapolation should be allowed is likely to provide fertile ground for challenges to biosimilar registrations from those selling the reference biologic. Again, this is very different from small molecule generics and is another reason that there is expected to be less competition and lower cost savings to payers, even after patent expiry.

6 For a discussion of how data exclusivity protects reference products from competition see our paper *Protecting innovation without patents – data exclusivity and market exclusivity*.

7 Ramanchandra et al. 'Why extrapolation is paramount to achieving the full promise of biosimilars'. Hospira Policy Paper, April 2015. Available online at http://origin-qps.onstreammedia.com/origin/multivu_archive/ENR/201229-Hospira---Extrapolation-White-Paper---April-2015.pdf.

8 European Medicines Agency, Committee for Medicinal Products for Human Use. 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues'. December 2014. Available online at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf.

9 World Health Organisation. 'Guidelines on evaluation of similar biotherapeutic products (SBPs)'. October 2009. Available online at www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf.

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Please contact us if you would like to discuss the challenges and opportunities presented by biologics and biosimilars.

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