Regulatory Approval of Pharmaceutical Products

The requirements for obtaining regulatory approval for a pharmaceutical is essentially the same in all major developed countries. Some uncertainty exists regarding the requirements for obtaining regulatory approval of pharmaceutical products comprising generic versions of biological products.

For the purposes of this paper we concentrate on the Australian regulatory requirements as a general representation of the requirements in major developed countries.

Regulatory Approval or Marketing Authorisation

The Australian *Therapeutic Goods Act* 1989 (**TG Act**) establishes a framework for the regulation of therapeutic goods including pharmaceuticals which has as its objective to ensure the quality, safety, efficacy and timely availability of therapeutic goods.

The TG Act requires that pharmaceuticals for import into, supply in or export from Australia be included in the Australian Register of Therapeutic Goods (**ARTG**). A pharmaceutical included in the ARTG is approved for marketing in Australia.

1.1 New pharmaceutical product

For a pharmaceutical to be included on the ARTG the sponsor must make application to the Therapeutic Goods Administration (**TGA**). The sponsor is the importer, exporter or manufacturer of the pharmaceutical or the person who has the pharmaceutical imported or manufactured on their behalf. The application usually consists of a duly completed form accompanied by data and other information in support of the quality, safety and efficacy of the pharmaceutical product for its intended use. The supporting data and other information typically comprises 10,000s of pages.

The data requirements are based on the European Union (**EU**) requirements and the TGA will accept data packages in the EU version of the international Common Technical Document (**CTD**). The European Medicines Evaluation Agency (**EMEA**) has issued a series of guidelines regarding the data requirements which the TGA has adopted.

The data accompanying an application is included in an extensive 5 module dossier and comprises data relating to:

- Quality or CMC data (being Chemistry, Manufacturing and Quality Controls data);
- Animal studies;
- Clinical studies and biopharmaceutical data; and
- Local product information, labelling, consumer information and package inserts.

The TGA undertakes an initial administrative assessment of the application to ensure compliance with basic guidelines. Provided the application is not deficient it then proceeds to the evaluation phase. Theoretically the applicant (the sponsor) may indicate at this point that additional information will become available which although not required to substantiate

the product claims may nevertheless enhance the product's assessment. However, in practice the TGA tends not to look favourably on the provision of such data following application other than if the data is ongoing data related to safety or stability etc. The TGA has taken the view that the provision of data following application lodgement is an attempt by the applicant to "jump the queue" ahead of other applicants who have provided complete data dossiers.

Once accepted for evaluation the data packages are allocated to specific sections within the TGA for evaluation:

- The Pharmaceutical Chemistry Evaluation section evaluates the chemistry, manufacturing and quality control aspects of the application;
- The Drug Toxicology Evaluation section evaluates the pharmacological and toxicological aspects; and
- The Clinical Evaluation section evaluates the various clinical data.

All evaluation sections may ask questions of the applicant during the evaluation process to clarify issues or request further data.

Evaluation reports are prepared and provided to the applicant. The applicant is permitted to provide corrections and comments on the views in the report. The applicant may submit supplementary data to address points raised in the pharmaco-toxicological or clinical evaluation reports. Once the evaluations are complete a document is prepared outlining the key issues on which advice is sought by the TGA from the Australian Drug Evaluation Committee (**ADEC**) or the Peer Review Committee (**PRC**).

A delegate within the TGA makes a decision on whether to approve or reject a product taking into account the advice provided by ADEC or the PRC.

The time taken to gain marketing approval can vary considerably from product to product. A significant amount of the time is taken up in the evaluation and in the applicant clarifying questions raised by the TGA. The amount of time taken is largely dependent on the quality of the original application and the supporting data and the preparedness of the sponsor to work with the TGA. An application to the TGA for approval of a new pharmaceutical product should take approximately 12 months from the time of application to the grant of marketing approval. However, recent applications have taken up to 24 months to process and grant approval.

1.2 Abbreviated Regulatory Pathway

An abbreviated regulatory pathway is available for generic chemical pharmaceuticals being pharmaceutical products that are comparable with the originator product in respect of the active ingredient, strength, dosage form, route of administration, quality, performance characteristics and intended use.

The application for marketing approval of a generic chemical pharmaceutical, unlike that for a new compound, does not require preclinical data from animal studies and clinical data from human clinical studies to establish the generic chemical pharmaceutical's safety and effectiveness. Rather the application must include data that demonstrates scientifically the

generic pharmaceutical is bio-equivalent with the originator product. The application for marketing approval of a generic chemical pharmaceutical must include the other data and information required for and must undergo the evaluation process described in respect of an application for a new pharmaceutical product.

Bioequivalence means the rate and extent of absorption of the generic pharmaceutical is not statistically different from that of the originator when administered to patients at the same "molar" dose under similar experimental conditions.

Bio-equivalence may be demonstrated by measuring the time it takes for the generic pharmaceutical's active ingredient to reach the blood stream of healthy human volunteers. This provides data on the rate of absorption, or bioavailability, of the generic chemical pharmaceutical's active ingredient which may then be compared with that of the originator product approved for marketing in Australia. For the purposes of gaining marketing approval the generic chemical pharmaceutical must possess a rate and extent of absorption that is not statistically different to that of the originator product. That is, the generic chemical pharmaceutical must deliver the same amount of active ingredient into the bloodstream of a given patient in the same amount of time as the originator product. In other words bioequivalence indicates the generic chemical pharmaceutical performs in the same manner as the originator product.

The theoretical basis underlying the grant of a marketing approval utilising the abbreviated regulatory pathway is that if the generic chemical pharmaceutical is chemically identical, has the same formulation and is bioequivalent with the originator product then the generic chemical pharmaceutical is assumed to produce the same clinical outcome as the originator product. That is, the generic chemical pharmaceutical that is granted marketing approval utilising the abbreviated regulatory pathway is assumed to produce the same clinical outcome as the originator product and is therefore considered "clinically equivalent" with the originator product. On that basis the generic chemical pharmaceutical maybe interchanged with or substituted for the originator product approved for marketing in Australia.

The preclinical animal studies and human clinical studies required for the purpose of an application for marketing approval of a new pharmaceutical product are invariably costly and usually take a considerable amount of time to complete. Therefore, the abbreviated regulatory pathway offers significant cost and time savings in obtaining the data required to support an application for marketing approval for a generic chemical pharmaceutical.

The time taken for the TGA to process an application utilising the abbreviated pathway is usually less than the time taken for a new pharmaceutical product but nevertheless the time taken cannot be predicted with absolute certainty.

1.3 Regulatory Pathway for FOBs

Biological pharmaceutical products are highly complex molecules often containing between 5,000 to 50,000 atoms and will usually also have complicated folding molecular structures. On the other hand the traditional generic chemical pharmaceuticals for which the abbreviated regulatory pathway was developed usually contain 20 to 100 atoms in a well defined molecular structure. Further, biological products are derived from unique biological materials and are generally affected by the product's manufacturing process and as a result a generic biologic product or follow-on-biologic products (**FOBs**) will inevitably not have a

molecular structure that is identical in all respects with that of the originator biological pharmaceutical product.

Unlike the traditional generic chemical pharmaceutical, generic versions of biological pharmaceutical products or FOBs are almost never chemically identical with the originator biological pharmaceutical product and are unable to establish the precise bioequivalence that is required to utilise the abbreviated regulatory pathway outlined in section 1.2 above. In other words, the assumptions underlying the abbreviated regulatory pathway for traditional generic chemical pharmaceuticals do not readily apply to FOBs. In addition in the US most FOBs are considered ineligible to utilise the abbreviated regulatory pathway under the applicable US law.

Most of the discussion concerning the regulatory pathway for FOBs has centred on the extent and detail of the clinical studies required such that a regulatory authority may confidently grant marketing authorisation for an FOB. It has always been generally accepted that FOBs will require significantly greater clinical testing than the testing required for traditional generic chemical pharmaceuticals under the abbreviated regulatory pathway.

☎🗁🕗 Europe

In late 2007 the European regulatory authority, the EMEA, announced a series of guidelines that set out the procedures which, if followed could lead to the grant of marketing approval for an FOB in Europe. The EMEA guidelines provide for a comparison to be undertaken of the pharmacokinetic and pharmacodynamic data from studies conducted on the FOB with the published data on the originator product. If the data on the FOB and originator are "similar" then the EMEA will grant marketing approval for the FOB on the basis that it produces a "similar" clinical outcome to the originator product.

Significantly the EMEA does not consider the data generated by the required clinical studies statistically significant enough to permit the FOB to claim "clinical equivalence" with the originator and on that basis may not be interchanged with or substituted for the originator product. Further, the EMEA has required those FOBs granted marketing approval in Europe to have a different name to that of the originator. For example Epoetin Alfa and Epoetin Beta etc.

The FOBs with marketing approval in Europe have not gained market share to the levels typically experienced with traditional generic chemical pharmaceuticals and the originators have not been forced to lower price. The lack of market share is thought to relate to the FOBs not having the same name as the originator product and the inability in the FOB to claim "clinical equivalence" with the originator product and on that basis permit it to be interchanged with or substituted for the originator product. Competition between the originator product and those FOBs for which marketing approval has been granted is akin to "brand" to "brand" competition which is not that typically experienced in the traditional generic chemical pharmaceuticals market.

☎🗎🕗 United States of America

In March 2010 legislation was enacted in the US establishing a regulatory pathway for FOBs. The pathway provides for the grant of marketing approval for an FOB as "bio-similar" or as "interchangeable" with the originator biologic. The first FOB to achieve

“interchangeability” will also receive market exclusivity as against other FOB’s for at least 12 months. The criteria listed for obtaining a “biosimilar” marketing approval indicate that the data and information the US regulator (the FDA) will likely require will be in similar terms to that required in Europe. Clinical data in addition to the requirements for a “bio-similar” marketing approval will be required to obtain an “interchangeable” marketing approval. Precise detail of what data and other information will be required for each approval type for a particular FOB remains to be determined.

☎▤◑ Australia

In Australia the TGA typically follows the EMEA and in that regard has adopted the EMEA guidelines on registration of FOBs. Importantly from BGA’s perspective this does not prevent a sponsor making application to the TGA for marketing approval of an FOB supported by data and information establishing “clinical equivalence” with the originator and a claim that the FOB is “interchangeable” with or may be “substituted” for the originator product.

As with an application for marketing approval of a generic chemical pharmaceutical utilising the abbreviated regulatory pathway an application for marketing approval of an FOB must include the other data and information required for and must undergo the evaluation process described in respect of an application for a new pharmaceutical product.

The regulatory pathway for FOBs in Australia is a new procedure for the TGA and remains untested. Associated with this is the potential for some uncertainty on the part of the TGA regarding precisely how the pathway will operate including in respect of establishing “clinical equivalence” and any associated claim that the FOB may be “interchanged” with or substituted for the originator.

Further each of the various regulators in the major developed markets including the US, European, Canadian and Japanese authorities and the TGA typically seek to adopt similar requirements and implement similar approaches to pharmaceutical product registration to the extent relevant governing legislation will permit. In this regard there is every indication that the TGA in developing its requirements and procedures for obtaining marketing approval of FOBs will seek to take account of developments in other major developed markets. In other words, it is unlikely TGA will adopt requirements and implement procedures in isolation or out of step with the requirements and procedures in other major developed markets.

BGA’s Approach to FOB Registration

BGA concluded prior to the EMEA issuing its guidelines that establishing “clinical equivalence” of the FOB with the originator product, which would permit it to be interchanged with or substituted for the originator, was critical to the FOBs success in the market. BGA notes that the European experience with FOBs to date supports this conclusion. It is also noted that the marketing approval for a generic chemical pharmaceutical obtained utilising the abbreviated regulatory pathway permits it to be interchanged with or substituted for the originator product and the generic chemical pharmaceutical is not merely considered “bio-similar” to the originator product. In BGA’s view, establishing “clinical equivalence” of an FOB with the originator product will be critical in the context of the FOB gaining market share (refer to the discussion in section 1 above).

1.4 The BGA Clinical Study

BGA's focus in developing its clinical study methodology (**BGA Study Methodology**) was specifically on ensuring that the study could produce a data set that proved the BGA FOB was clinically equivalent with the originator product and thereby permitting it to claim that it may be "interchanged" with or "substituted" for the originator product.

The BGA Study Methodology comprises a non-inferiority study. BGA has commenced a clinical study in Australia that utilises the BGA Study Methodology and compares the BGA FOB with the originator product (**BGA Study**).

BGA has engaged a specialist clinical study manager who is dedicated fulltime to managing the BGA Study including its co-ordination, liaising with the principal investigator and ethics committees, monitoring study participant recruitment and ensuring the study otherwise runs to schedule. The study manager also drafts relevant study protocols for other clinical studies on BGA's FOBs and works closely with BGA's regulatory compliance specialist to ensure that BGA's application for marketing approval of the FOB contains all necessary data and information.

BGA understands that the BGA Study is the first of its kind conducted anywhere in the world. Importantly, the US legislation provides that the information or data provided in support of an application for "interchangeability" in the USA must be sufficient to establish that the FOB "can be expected to produce the same clinical result as the reference product (originator product) in any given patient". This is a primary objective of the BGA Study Methodology and BGA Study.

1.5 BGA's FOB Product Marketing Approval Application

As noted above the time taken to gain marketing approval can vary considerably between applications. A significant proportion of the time is taken up in the evaluation process and the time taken by the applicant in answering any questions raised by the TGA. Generally the more questions the TGA asks the greater the time taken to gain marketing approval. In this regard, the amount of time taken is largely dependent on the quality of the original application, the quality of the supporting data and the preparedness of the sponsor to work with the TGA.

As noted above the regulatory pathway for FOBs in Australia is a new procedure for the TGA and there is potentially some uncertainty on the part of the TGA regarding precisely how it will operate. It is unlikely the TGA will wish to adopt requirements and implement procedures in isolation or out of step with the requirements and procedures adopted or proposed in other major developed markets. In view of these observations and the recent events with Pan Pharmaceuticals it is likely the TGA will exercise considerable caution when considering the initial FOB marketing authorisation applications. There is the real possibility that the TGA may take longer to process applications and grant marketing approval for the initial FOBs.

With the above in mind BGA is engaged in active and on-going dialogue and discussion with representatives of the TGA, the Commonwealth government department responsible for the TGA and the pharmaceutical benefits scheme in an effort to identify and address the issues highlighted above in advance of BGA lodging a marketing approval application for its FOB

product. BGA is also now clarifying and settling the required make-up and content of its proposed application for marketing approval with the view to identifying and thereby addressing as many potential issues in advance of its lodgement with the TGA. In so doing BGA is hoping to minimise any potential delays associated with the TGA implementing the FOB regulatory pathway and thereby facilitate the grant of marketing approval for the BGA product as quickly as possible.

BGA's best estimate is that following lodgement of its application the processing and grant of marketing approval for BGA's FOB product will likely take less time than for a new pharmaceutical but may take longer than for a generic chemical pharmaceutical utilising the abbreviated regulatory pathway, although in the current environment even this is extremely difficult to predict with any certainty. Nevertheless, BGA remains hopefully its on-going discussions with government and TGA representatives will result in a reduced processing time. Hence BGA is undertaking considerable lobbying efforts in this regard. Note, BGA cannot realistically lodge its application with the TGA until the BGA Study is complete and it has the results (refer to the discussion paper entitled "The Conduct of Clinical Studies").

BGA has engaged a regulatory compliance specialist who is dedicated fulltime to preparing BGA's applications for marketing approval of its FOBs and is working closely with BGA's specialist clinical study manager and BGA's manufacturing specialist. The application for marketing approval of the first FOB when complete will comprise 10,000s of pages of data and information. The BGA regulatory specialist is collating the data required for the various modules and ensuring the data packages comply with the CTD format and that the application is internally consistent.

The key focus here is to ensure the TGA is provided with all the information and data it requires, in the format it requires and thereby hopefully minimising the number of questions asked by the TGA and thereby enabling the TGA to process the application and grant marketing approval for the BGA FOB product as quickly as possible. In that way BGA is hopeful it will have its FOB product on the market in the shortest possible time.

Manufacturing Requirements

Manufacturers of pharmaceutical products for supply in Australia including overseas manufacturers must comply with the principles of Good Manufacturing Practice (**GMP**). GMP specifies manufacturing standards that if followed seek to ensure pharmaceuticals including biological products satisfy defined standards and that they are manufactured in conditions that are clean and free of contamination. GMP also applies equally to products supplied and used in clinical studies.

The applicant or sponsor of pharmaceuticals manufactured overseas must provide evidence acceptable to the TGA that the products are manufactured to a standard of GMP equivalent to that expected of Australian manufacturers of the same products. If acceptable documentary GMP evidence cannot be provided, the TGA will undertake on-site audits in the same manner as that conducted for the Australian manufacturers.

The obligation to satisfy GMP is not a one off requirement but rather it is ongoing and is mandatory in obtaining and maintaining marketing approval for any product. In this regard BGA has engaged a pharmaceutical manufacturing specialist who is dedicated fulltime to

ensuring the manufacture of all BGA's FOBs and particularly its first FOB to seek marketing approval satisfy and even exceed the relevant GMP requirements. As noted the manufacturing specialist works closely with BGA's regulatory compliance specialist to ensure that BGA's application for marketing approval of its first FOB product contains all necessary data and information to establish the FOB is manufactured in accordance with Australian GMP.

Additional Information

Additional information is available at the following websites:

- Therapeutic Goods Administration – Regulation of Prescription Medicines: http://www.tga.gov.au/pmeds/pmeds.htm
- The US Food and Drug Administration: http://www.fda.gov/
- The European Medicines Agency (EMEA): http://www.ema.europa.eu/