Marketing generic products: A transatlantic comparison

Generic animal health products are accounting for a greater proportion of animal health industry sales. In this article, Joshua Forster, Regulatory Executive of Cyton Biosciences, a Knoell Consult company, and Hope Baird Regulatory Consultant from Shotwell and Carr, LLC, also a Knoell Consult company, compare and contrast the different marketing authorization procedures for generic products in the EU and US markets

A competitive market

The common objective for any Marketing Authorization Application (MAA), after a positive opinion is granted of course, is to ensure that a product is as competitive as possible. This is especially true for a generic product. This process begins by scouting the competition, but is practically applied when choosing between similar products which could act as a viable reference product in the generic application.

When considering this decision I would emphasise the word 'similar' in similar products, due to the fact that there will inevitably be subtle differences between given similar products and even dis-harmonization between different EU member states (MS) for the 'same' product. Differences between similar reference/pioneer products include product labelling; claims (albeit only slightly different in most cases); pack sizes and target species. The final choice understandably relies heavily on compliance with the applicant's intended marketing strategy.

Reference/pioneer products

The number of available reference/pioneer products varies, but in general the choice tends to be narrower in the US than in the EU. This is a reflection of the numerous national authorizations within the EU, where dis-harmony is present between the 'same' product authorized in different territories. This is further compounded by the opportunity to cite a reference product which is no longer authorized in the EU or is not authorised in the EU member states in which the application is submitted, options which are not available across the Atlantic.

In the US, Abbreviated New Animal Drug Applications (ANADAs) must have reference to an approved product. The product in question needs to be approved, but not necessarily marketed. However, it is often difficult to obtain labelling for a product which is not present on the market. This would create difficulty when assessing the product's viability as a reference product – a generic label has to be identical to the Reference Listed Drug (RLD) label and can only differ in items specific to the drug itself – trade name, logo, name and address. Another difficulty would be sourcing of the product for bioequivalence studies.

In the US an ANADA can only reference one product. However in the EU generic companies have a competitive advantage in that it is possible to have a single generic product based on more than one reference product. The reference products in this case can be a part of the same global Marketing Authorization (MA) or be different (but similar) products. Note that bioequivalence must be demonstrated between the generic product and all cited reference products. It is also important to ensure that the most recent (approved) version of the reference product SPC is being used, as the reference product SPC could have been amended recently as a result of any variations which may have been submitted.

In the EU, the list of potential reference products must be scrutinised as to their legal base and must have been authorized as a "complete dossier" in accordance with Articles 12(3), 13a, 13b, 13c or 13d of Directive 2001/82/EC as amended. It is also worth noting at this point that although it is legally possible, it is not always advisable to choose a reference product which is not (or was not) authorized in the Reference Member State (RMS) of the chosen generic MAA procedure. It is possible that a competent authority may refuse to act as RMS in such cases.

In the US, ANADA applications, much like in the EU, must refer to complete applications – an ANADA cannot act as a reference product. In addition to this an interesting specific requirement is that an ANADA

Continued on page 12

EU data exclusivity –

In the EU, pioneer products have 8 years data protection and 10 years marketing protection (note this is increased to 13 years marketing exclusivity for products indicated for use in fish or bees). Extension of a pioneer product to include a new food producing species within the first 5 years of the product's authorization will result in an additional years' worth (one year per food producing species) of marketing exclusivity (not exceeding a total of 13 years).

I is of note that some 'old' products may not have been re-assessed by the member states according to current legislation. Even though they have been on the market for 10 years, they cannot be cited as reference products (this would need to be confirmed by the relevant National Competent Authority (NCA). This may also be true of products which are authorized in EU member states that have only recently joined the EU. As mentioned above, it is possible for a generic application to cite data from an authorized product which is still within its data exclusivity period, if this chosen reference product is part of a global MA where the data exclusivity of the initial authorization has elapsed (Refer to Article 13.1 of 2001/82/EC and Co-ordination Group for Mutual Recognition and Decentralised Procedures Veterinary (CMDv) Q&A 115/2009). Overall, this diversity shows how important it is in the EU to thoroughly research an intended reference product.

Expert Opinion

US data exclusivity –

In the US, an original New Animal Drug Application (NADA) which contains a new active will have the benefit of 5 years exclusivity, whereas a NADA which contains an active that has been approved in another application will receive 3 years exclusivity. In addition, supplemental applications or original hybrid applications which contain new data (studies conducted or sponsored by the applicant) will also yield 3 years exclusivity. As in the EU, a generic application will not be entitled to any data exclusivity.

In the EU, major changes (new species/claim/dosage) made by the pioneer company can quickly be added to the generic product. Conversely, this transference of product characteristics cannot be conducted in the US. For example the addition of a new target species to a reference product cannot be as easily adopted by a generic product, due to the data exclusivity which has been granted for the submission of new data. For now, it seems that EU legislation favours the generic companies, although this may not last as it is anticipated that the data protection provisions in the EU will be strengthened when the EU legislation is updated.

Continued from page 11

must contain certification that a patent for the reference drug either does not exist, has expired or will soon expire. In general, approval of the ANADA will not infringe on a patent. In some cases, the sponsor of the ANADA must notify the sponsor of the reference drug that they are pursuing a generic copy.

It is also worth noting that labelling in the US must also be identical between a generic and the RLD, but strength, dosage form and route may be different if a suitability petition is filed. In the EU, a full quality section of the dossier (Part 2) is present, and therefore various quality-related characteristics (if sufficiently justified in the application dossier) can differ in the generic product compared to the reference product.

Characteristics specifically highlighted in the US and EU definitions of generics must remain identical between the reference and the generic products. But in the product characteristics that are not covered by these definitions, lies the potential for subtle diversity and a possible advantage over the reference product. In the EU, examples of potential deviation from the reference product include; pack size, shelf-life, approval region (you can apply to MS where the reference product is not authorised), distribution category and packaging to name but a few.

It is worth noting that distribution categories in the EU are regulated on a national level, with MS having different systems in place which employ various levels of distribution category. This dis-harmonisation allows for discussions to take place on a national level regarding distribution of a given product. Some MS are more willing to discuss justifications for the change of distribution category than others (which can be raised during the national phase of a MAA procedure, but often needs to be implemented via a national variation).

Application procedures for generic products

When it comes to application routes, there are a greater number of options in the EU compared with the US. As stated previously, there is only a single application route for generic products in the US (ANADA)[1] which, if successful, would result in a single authorization applicable to the whole of the US (all States). In the EU, generic product applications have to be applied under the Article 13.1 legal basis, but can be submitted via the National Procedure (NP), Mutual Recognition Procedure (MRP), Decentralised Procedure (DCP) or Centralised Procedure (CP) (under certain conditions) application routes.

The CP is most comparable to the US ANADA, as it consists of a single application, submitted and assessed under a single procedure, resulting in a single authorization throughout the European Economic Area (EEA). But as a limitation, a generic application can only be submitted via the EU CP if the reference product was also authorised via this route.

Apart from the CP, the other application routes offer greater diversity and choice. With the NP, MRP and DCP the applicant is able to choose which MS to include in the application. Although the up-front cost to prepare the application dossier is not affected by the choice of MS, when it comes to submission the applicant can omit regions/territories which are not significant to their marketing plan, and subsequently reduce the overall regulatory assessment costs for the application. This is especially beneficial for products which may have geographical limitations.

It is possible to roughly compare the assessment timetables for EU procedures and the US ANADA, but it is worth emphasising that the conditions of the procedures are different (for greater details refer to Bate *et al* (2013)). EU MAA procedures are rigidly defined, which supports an accurate project schedule as there is a finite timeline where the time to reach a decision can be accurately estimated. In the US, the ANADA is more dynamic in terms of assessment, and it is therefore more difficult to predict the total time required (number of cycles) for the Food and Drug Administration (FDA) to assess the dossier and provide an opinion. But comparing the assessment timelines alone does not tell the whole story.

In the EU, unless an applicant has formally requested Scientific Advice from the CVMP, there is less assistance that can be provided in the development of a product dossier. To compound this, the more rigid timelines also set a finite amount of time to respond to major issues/concerns raised during the assessment phase of the procedure (clock-stops).

In the US, the FDA begins assessing the product during the development phase of the project, which can be a great advantage in ensuring the dossier is compliant with the current requirements at an early stage. A US sponsor will submit the technical sections which are typically filed in a phased format to the FDA. This contrasts with the EU where the entire 'compiled' dossier is submitted at a single time-point (with the exception of the Maximum Residue Limit (MRL) dossier).

At first glance the EU procedural timelines appear shorter and easier to estimate (which I am sure gets a thumbs up from commercial colleagues in a company) but the rigid timelines can work against an applicant if major issues are raised during the procedure.

The EU CP has a 210 day assessment phase (note that this timeline does not account for the development phase or

[1]This discussion does not cover veterinary medicinal products which are governed by the US Environmental Protection Agency (EPA), such as ectoparasiticides. The EPA does, however, award generic product licenses in the form of Identical/Substantially Similar products (formerly known as "Me too" products).

the national phase. The national phase is the period between issue of the approval at the end of the procedure and issue of the MA documentation by the relevant NCAs). The assessment phase for a US ANADA is less finite. It will be comprised of a minimum 180 days, but it is unlikely that an approval will be issued in the first cycle. Therefore a sponsor is looking at upwards of 210 days to reach an approval for an ANADA.

Even though it is possible to have an ANADA approved in a single cycle, generally this is not common. Therefore the overall assessment timeline for generic applications in the US are longer than in the EU. However, depending upon the EU member state involved in the procedure, it is not uncommon to receive the final MAs 6-12 months after the end of the assessment phase (day 210). Suddenly the figures do not seem so far apart.

Timelines

In summary it is very difficult to make a direct comparison between the EU and US assessment timelines, as discussed in greater detail by Bate et al (2013).

The FDA assessment begins at an earlier stage of development, which may be a benefit that outweighs the potential difference in timeline. Although the EU regulatory framework allows greater flexibility in submitting the dossier to various Member States, there is a thorn to this rose. With the segmentation of member states comes a substantial national administrative burden: national documentation requirements; the payment and management of regulatory fees on a national level; national labelling requirements ('blue box'); national language translations and distribution requirements.

To take a step back and look again at the comparison of the assessment timetables is to focus on the word 'assessment'. Following the decision in an EU procedure is the national phase, where the applicant must translate the approved labelling text into the relevant languages for the member state involved in the procedure. This can be a laborious part of the procedure which demands a great level of management to simultaneously submit, respond and finalise the product literature texts in a number of different languages, followed by the submission, review and finalisation of labelling and packaging mock-ups in selected member states.

The total time required for the aforementioned actions and for the NCA involved to issue the MAs can take a significant amount of time (6-12 months in some cases). It is important that the length of the national phase, which does not have a finite timetable and is often difficult to estimate, be considered in the estimation of the overall timeline, from submission of the product dossier to the issue of the MA in the EU.

It is also worth noting that some US states have specific requirements, such as administrative registration and inclusion of particular statements into the product labelling, but the administrative burden of these actions is insignificant compared to the national phase in the EU.

Application fees in the EU and US

From a procedural aspect the assessment fees are also criteria which can be compared between the EU and US. The assessment fee for a US ANADA is $148,300 (€108,800) and the assessment fee for an EU CP is €68,400 ($93,300).

Looking at the respective assessment fees, it is apparent that the US costs for assessment are significantly greater than the EU costs. But the EU cost stated is relative to the CP only, and as previously mentioned a generic application via the CP can only be approached if the reference product was also authorized via the CP, significantly reducing the pool of reference products available to the applicant.

Therefore, it is more likely that an applicant would be looking at a DCP. It is difficult to provide an estimate of the assessment costs for a DCP as each Competent Authority manages its own assessment fee, and the number of member states involved is at the discretion of the applicant. But considering that the most used Reference member states for DCPs in the EU demand fees of around €25,000-€35,000 (dependent upon the number of product strengths), if a large number of member states are involved, the assessment fee for the procedure would likely surpass the US fee.

Other points of consideration include the costs involved in the EU national phase, whereby the applicant is responsible for the maintenance and translation of the product labelling and literature into the national languages of the Member States involved in the procedure.

That the fees are significant on both sides of the Atlantic is not in doubt, but to provide perspective we should remember that the US and EU each account for one third of global animal health sales (IFAH global benchmarking survey from 2011).

Conclusions

The take-home message is that, from a generic perspective, each regulatory framework has its positives and negatives, but for many reasons a direct comparison is difficult to present.

In the EU, there is a greater choice of reference products and application routes in which to approach submission to the competent authorities.

In the US the FDA, through phased submission of product dossiers, offers greater support to the applicant during the development phase of the project. To carry on the theme, direct comparability is not possible when looking into the timelines and costs involved. This is due to the greater choice (in reference product and procedure) present in the EU, meaning that any direct comparison can only be made on a product-specific basis.

At first glance there appear to be more negatives in the US regulatory framework – limited reference products; limited application routes; unpredictable timelines and high assessment costs. However, the advantages of a harmonized assessment and approval should not be taken lightly, and the significantly lower (comparably) administrative burden bears considerable weight. The greatest advantage in the EU is choice; choice of reference product; choice of application route and choice of member state. The presence of these options allows applicants to tailor their products and applications to a specific marketing strategy.

The management of a generic MAA in the EU can be a huge task. The variety of submission and procedural options are an advantage strategically, but can be a challenge if not managed stringently. Great emphasis should be placed on project planning and management, which seems obvious, but is justified considering that it is very difficult (and costly in time and in monetary terms) to change a strategy once it has been followed up to submission.

In the EU, we would urge any applicant to take their time and get the planning right the first time. Thoroughly research the market for intended reference products and explore all viable options before progressing into development. At the end of the day, the target is to come out with an approval - on time and to budget.

Procedure timelines and fees are all important considerations when planning a submission strategy. But just as important are the actual data requirements for the chosen route to market and we will consider this in a future article. ●