Global Regulatory Strategy for Veterinary Medicines

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A good regulatory strategy should cover all aspects of pharmaceutical or vaccine development and life-cycle management, not only the brief registration period that marks the transition from development project to commercial product. This is particularly important in the animal health arena where development and manufacturing costs may be high and market value may be low; good strategic planning can help to redress the balance.

Know Your Market

Before any development takes place it is important to define the product type and its potential markets as this will, in turn, determine the registration route and final label indications. A classical pharmaceutical for the treatment of a physiological disease in animals will be considered to be a veterinary medicinal product by most regulatory authorities around the world and will often be assessed in a way very similar to pharmaceutical products for humans. However, there are many product classes that are assessed differently in different countries, for example a topical ectoparasiticide (*e.g.* to kill fleas or lice) would be assessed under pharmaceutical legislation in the European Union, under agrochemical legislation in South Africa and by the Environmental Protection Agency in the US.

Where vaccines are concerned, veterinary medicine legislation in the EU contains specific paragraphs for immunological veterinary medicinal products (IVMP), but in the US assessment of pharmaceuticals and vaccines is divided between the Food and Drug Administration (FDA) and the US Department of Agriculture (USDA), respectively. Furthermore, the definition of an IVMP or vaccine differs between the EU and the US, meaning that the same product can be an immunological in one region and a pharmaceutical in the other (*e.g.* Improvac®/Improvest® in the EU and US). In South Africa, vaccines are exempt from the normal scheduling procedure which classifies over-the-counter and non-registered (schedule 0) products as agrochemicals and prescription medicines and drugs of abuse (schedules 1 to 8) as medicines. Thus vaccines are automatically schedule 0 and are registered as agrochemicals, regardless of the target species.

Even within one region, the assessment of the same formulation can vary according to the proposed product indications. For example, a coccidiostat for use in pigs or poultry in the EU is assessed by the European Food Safety Authority (EFSA) as a feed additive, whereas the same product for use in cattle or sheep is assessed by the European Medicines Agency (EMA) or the National Competent Authorities as a veterinary medicinal product. In fact, borderline products can often be some of the most challenging to fit into established regulatory procedures and the final decision can be determined by one or more factors, such as mode of action (*e.g.* local *vs.* systemic), route of
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administration (*e.g. in vitro vs. in vivo* diagnostics), or label claims (*e.g.* pharmaceuticals *vs.* nutraceuticals *vs.* nutritionals).

But the role of the regulatory affairs professional is not to bombard the research scientists with so many alternatives and problems, which could only serve to confuse and demotivate them, and ultimately stifle innovation. Instead, it is to listen with an open mind to the potential uses of the new molecule and then to outline the pros and cons of each of the registration options available in each geographic region to aid the decision making process. It is important to also involve marketing colleagues at this early stage as they will inevitably have expectations for label indications and markets, which need to be validated by both the scientists and the regulatory managers.

Know the Limitations

Given the diversity of registration procedures across the world and the constantly evolving technology in research and development, it should not be surprising to learn that guidance and precedent for some veterinary medicines and/or regions is not available or, in some cases, states that registration is simply not possible.

Taking the European Union as our example, the best known cases of products banned for use in food-producing animals are those of substances having a hormonal or thyrostatic action and beta agonists (Directive 96/22/EC, as amended by Directive 2008/97/EC), antimicrobial growth promoters (Regulation (EC) No 1831/2003) and substances prohibited for reasons of consumer safety (Regulation (EC) No 37/2010, Table 2). China also bans the use of beta agonists and Brazil limits their use according to species. In such cases, the guidance to development teams is obviously that these products cannot be registered in certain markets, but there are other cases, which are far from clear.

Current concerns about increasing resistance to the antimicrobials used in human and animal health has led to a plethora of new (draft) guidance for the animal health industry, particularly in the EU and US, which makes it extremely difficult to predict the registration requirements that a new molecule entering the development phase now will face in the future. Australia is one of the few markets with a clear position on at least some classes of antimicrobials, having never allowed the use of fluoroquinolones in livestock, but the situation globally is one of constant change. With precedent no longer being a valid predictor and with sound scientific principles being subject to intense political and media pressure, the development of new antimicrobials is no longer an area where regulatory affairs professionals can give meaningful advice to the development teams.

Another example of an area with little regulatory guidance is that of biopharmaceutical products, but the outcome here is far more positive. In the EU at least, there is recognition by the regulatory authorities that precedent set for similar molecules in human health may not be directly applicable to animal health and furthermore it would be counter-productive to write rigid guidelines for an area that is still evolving. In this case, where good science remains paramount, seeking scientific advice from the regulatory authorities early in product development can enable the regulatory manager to give valuable feedback to the development team.

Global Development Plan

Having considered the possible registration routes in each market, it is important to decide at an early stage if the target is to have a single, global formulation supported by global safety and efficacy

data, or if a series of regional products is preferred. The structure of the manufacturing and supply organisation will most likely determine the company's preference, but there are also regulatory factors to be taken into consideration.

Good Manufacturing Practice (GMP) standards are not harmonised globally, so product manufactured in one region may not be suitable for marketing in another. For example, the EU recognises the GMP standards of New Zealand as being equivalent to its own, but not those of the US, so a US manufacturing site will need an EU GMP inspection if it is to supply product to that region. Rules concerning excipients are also not harmonised and may even be contradictory. For example, EU guidance requires that all excipients, including preservatives, are justified, but US precedent is that all multi-dose injectable products should contain a preservative regardless of the stability data. It is in cases such as this where the regulatory affairs professional must negotiate a compromise between the regulatory authorities of the two regions in order to avoid the development of parallel formulations, and the additional costs which would accompany it.

Development of global products is becoming easier with the adoption since 1999 of VICH guidance. VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) is a trilateral (EU-Japan-USA) programme aimed at harmonising technical requirements for veterinary product registration, with input from regulatory authorities and industry. There are currently 51 guidelines published on the VICH website (www.vichsec.org) covering many aspects of quality, safety and efficacy, and the inclusion of "observer countries" and the "outreach program" facilitates adoption of those guidelines in many key markets. That said, it is important to understand the scope of each VICH guideline when relying upon it to propose a global development plan. For example, VICH GL 38 on environmental impact assessment makes it clear that there may be regional interpretation and for the EU that interpretation is provided in an EMA guideline (EMEA/CVMP/ERA/418282/2005-Rev.1) which is, incidentally, longer than the original VICH document.

Most VICH guidelines are concerned only with study design and data generation, not data interpretation, so whilst this facilitates a global product development programme, the resulting product labels may not be harmonised and it is important that the marketing team appreciate this. One example where this is most pronounced is in the setting of withdrawal periods, which ensure that unsafe amounts of drug residues in the meat of treated animals do not enter human food. VICH GL 48 has established the study design for residue studies, but fundamental differences in the interpretation of the data generated can lead to vast differences in withdrawal periods between regions (*e.g.* withdrawal periods for Draxxin® in cattle are 18 days in the US and 49 days in the EU, based on the same data set).

Another example, but one which is more easily explained, is that of different clinical indications between regions. There are a number of VICH guidelines concerning the design of efficacy studies for various product classes and species, but there is normally regional guidance that the studies should be conducted under local conditions in order to reflect the differences in animal breeds, animal husbandry, infectious agents and climate. Thus, whilst there may be a global protocol which allows for consistent statistical analysis of the data, it is usually necessary to conduct regional field or veterinary patient studies. On occasions, the regulatory authorities may specify particular breeds or

strains of animals to be used, *e.g. Bos taurus* and *Bos indicus* for cattle products in Australia, so careful attention must be paid to this before the studies are commissioned.

Laboratory studies are not generally subjected to regional requirements as standardised animal breeds, husbandry procedures *etc*. are used regardless of the location of the facilities. However, particular breeds may be specified if there is a known variability in the safety or efficacy of a therapeutic class, *e.g.* susceptibility of collie dogs to avermectin toxicity.

It is also worth noting the vast range of routes of administration used in the animal health sector. In general, products that are administered by veterinarians are often injectable as this is easiest for the vet and the least stressful for the animal, but for products administered by farmers and pet owners other solutions need to be found. Dogs and cats may be persuaded to take tablets, chewable tablets or oral liquids, or to submit to topical solutions, powders or creams. Oral or intranasal dosing of farm animals is also possible on an individual basis, but for herd treatment pour-on, in-feed or in-water administration may be more appropriate. Mastitis products for dairy cattle are administered as teat dips or intramammary infusions, poultry products can be sprayed over the whole flock and poultry vaccines can be injected *in ovo*. The options are seemingly endless, but in every case it is important to ensure that the safety and efficacy studies reflect the intended route of administration. It is also essential to comply with the rules and regulations regarding field and veterinary patient studies and animal welfare, which differ in every country. It can take from one week to 6 months to obtain a permit to conduct studies depending on the country chosen and that variability needs to be taken into account in the global development plan, particularly if the condition to be treated is a seasonal one.

A general point to note about any medicinal product development programme, whether it concerns human or animal health, is that the terms and conditions of the registration granted will depend upon the data submitted for assessment. Thus it should be the role of the regulatory affairs professional, or the experts to whom they delegate, to objectively review each study protocol and report. The draft product label may be aspirational in that it represents the best case scenario, but every efficacy claim and every warning statement (or its absence) must be supported by data and a poorly designed study is unlikely to be useful in this regard. In addition, any changes in the regulatory environment need to be taken into account as and when they arise. By continually amending the label and, if necessary, the development programme, it is possible to manage the expectations of the team on the likely outcome of the registration procedure.

Safety Considerations Unique to Veterinary Medicinal Products

To those experienced in the development and registration of medicines for human health, much of the discussion above and below will seem very familiar, barring a different set of acronyms. However, there are two considerations that are specific to, or more important to, the animal health sector.

The first point is that of human food safety. For a human medicinal product, the patient is a person and the healthcare professional or carer is also a person, so although they may be exposed to the product by different routes (*e.g.* oral or intravenous *vs.* dermal), the target is always human and any data generated in laboratory species can be extrapolated accordingly. For a veterinary medicinal product, the patient is an animal which may or may not be the same species as that used in

laboratory safety studies. However, the user is a person, *i.e.* the veterinarian or the animal owner or handler, so the safety data must also be extrapolated to humans as well as to the target species.

But there is another group of people to consider for some products – the consumers of meat, offal, milk, eggs and honey. In this case, the focus is on the potential for pharmacologically or microbiologically active residues of medicines to be in the tissues or products of treated animals at the time of slaughter or collection, which may subsequently be ingested by the general public. Whilst the exact methodology varies across the world, the general principle is to use laboratory safety data to establish an acceptable daily intake (ADI) of the drug residues (parent compound and/or metabolites) for people. Given that consumers can be of any age, weight, ethnic origin, or health status, and that it is impossible for them to know the identity and quantity of the residues they might unwittingly be consuming, setting of the ADI is a very conservative (risk averse) process with the inclusion of multiple safety factors and worst case assumptions.

Once the ADI has been established, maximum residue limits (MRLs) or tolerances are set for each edible tissue such that any consumer could ingest a generous amount of animal-derived food products every day without fear of exceeding the ADI. The withdrawal period is the time that must elapse between treating the animal and slaughtering it for meat, or collecting milk, eggs or honey for human consumption to ensure compliance with the MRLs.

It is noteworthy that MRLs are being developed in Europe and globally for different product types such as biocides, pesticides, *etc*. In the EU Regulation 470/2009 proposes the CVMP as the main MRL regulator in Europe, but on the global scene JECFA, the Joint FAO/WHO Expert Committee on Food Additives, is the norm. Furthermore, there seems not yet to be complete alignment globally on how to link MRLs and human exposure through animal derived food (TMDI or Theoretical Maximum Daily Intake versus the EDI or (median) Estimated Daily Intake). As the current EU MRL legislation only requires recognition by the European Union of the global (JECFA) standards when no objection was raised during the global procedure, the risk of misalignment between MRLs for the same active ingredient in different product types and/or geographies is high.

Not only are residue studies expensive and time consuming to conduct, but differing MRLs between countries hinder international trade in food products. Furthermore, differing withdrawal periods between similar products can seriously impact their competitiveness, since no farmer wants to discard milk or eggs for a week after using product A when he could use product B and only have to discard milk or eggs for a day. The economic impact of long meat withdrawal periods is even more significant if animals need to be treated just prior to their intended slaughter date and then have to be fed and housed for additional time to meet the requirements of the withdrawal period. In such cases, farmers will necessarily balance economic concerns against animal welfare, so there is an onus on the pharmaceutical industry to develop formulations with the shortest possible withdrawal periods (and on regulatory authorities to approve them) so that neither animal welfare nor consumer safety are jeopardised.

The second area of particular importance in the development programme of a veterinary medicinal product, again primarily for farm animals, is environmental safety. Treatment of individual animals has negligible environmental impact, but herd treatment can potentially result in significant amounts of drug residues being present in manure or urine that is either spread on the land or washed into watercourses. Many parasiticides are known to have acute toxic effects on terrestrial

and aquatic organisms and various models can be used to predict the environmental impact of these and other veterinary medicines. Unfortunately, complex and dynamic ecosystems are notoriously difficult to model and ultimately a balance needs to be struck between risk management measures such as storage of manure to allow degradation of drug residues, and therapeutic need to ensure animal welfare. With regard to the product development programme, the normal practice is to predict the environmental fate of the drug residues and then to conduct acute or chronic ecotoxicology studies only in the areas where exposure is expected to be above particular trigger values. Analogous to the way in which field efficacy studies are conducted locally and laboratory studies are conducted globally, environmental fate calculations must be done locally to take account of different climates and soil types, but a single battery of laboratory-based ecotoxicology studies can be used globally if the test organisms are chosen carefully.

Registration Procedures

With regard to the registration procedure, we are again faced with a range of systems around the world. Some regulatory authorities such as the US FDA accept phased submissions, but others (*e.g.* EMA in Europe) require all parts of the registration dossier to be submitted together. Nonetheless, the general principles of making an assessment of the quality, safety and efficacy of the product in order to reach a conclusion on its benefit-risk balance are used in all regions.

Special attention needs to be paid to products intended for use in food-producing animals as it is often, but not always, necessary to make a separate application for the assessment of human food safety and MRLs. That application may or may not be made to the same regulatory authority as the product registration application. In the EU, all MRL applications must be submitted to the EMA, but Marketing Authorisation applications can be made to either the EMA or to the national authorities. In Australia, the registration dossier is submitted to the Australian Pesticide and Veterinary Medicines Authority (APVMA), which is responsible for the elaboration of MRLs (and ultimately the product licence), but this agency must first obtain an assessment from the Office of Chemical Safety (an independent and separate organization) which is responsible for establishing the ADI. By all accounts, Japan has probably the most convoluted registration process as three separate agencies are typically involved. The Food Safety Commission (FSC) reviews and sets the ADI, the Ministry of Health Labour and Welfare (MHLW) sets the MRLs and the Japan Ministry of Agriculture Farm and Fisheries (JMAFF) ultimately sets the final withdrawal times. These additional steps/agencies can have a significant impact on registration timelines, either because the steps must be done sequentially, or because of lack of alignment between the different parties involved.

To add further complexity, the European Union currently maintains four different procedures and multiple regulatory authorities for the registration of veterinary medicinal products. Historically, each EU Member State maintained its own National Procedure (NP) which required national assessments and resulted in licences valid only in one country. However, as mentioned previously, individual assessment of the same data set can result in different label claims so the concept of harmonisation between Member States was introduced in the early 1990s via the Mutual Recognition Procedure (MRP). Shortly afterwards, the European Medicines Agency (EMA) was created to enable the European Commission to issue pan-European marketing authorisations valid in all Member States; this is the Centralised Procedure (CP). In 2005, a fourth procedure was added (Decentralised Procedure, DCP) which has many similarities with MRP in that it aims to harmonise assessments and label claims between the Member States included in the procedure.

All of these procedures continue to co-exist in Europe and many products, particularly innovative ones, have a number of registration procedure options open to them. A typical choice to be made by regulatory affairs professionals is whether to recommend CP or DCP, based on various factors, including for instance eligibility, market size, likelihood of procedural delays and prescription status. MRP is used to extend existing products into additional markets and NP is very rarely used for new applications, although it is estimated that 70% of existing products are still maintained under national licences. The European example highlights the need for having access to regulatory affairs professionals who have experience of the target region(s). In practice, this may mean that several regulatory managers should be involved in a single, global development programme, which has cost and resource implications for companies, but given the potential impact of relying on poor or no regulatory advice (*i.e.* no registration and therefore no opportunity to recover development costs through product sales), it is an investment worth making.

Communication is Key

Communication skills are critical to the regulatory professional. As already pointed out, within a company, the regulatory manager should ensure that the development and marketing teams are onboard with the regulatory context and implications for all the markets where an approval will be sought for the product, and equally important, an effective line of communication has to be in place with the regulatory bodies. When discussing any research and development or regulatory project with the competent authorities, it is essential to set up meetings and/or discussions appropriately. Depending on the project, "appropriate" will have different meanings. For a product line extension to a well-established marketing authorisation, communication will be very much limited to a letter of intent or the occasional conversation in the hallways. For totally new technologies, biopharmaceutical or otherwise, where the existing regulatory framework and paradigm are a mismatch with the nature of the new concept, much earlier and higher level discussions will be needed.

The purpose of the communication can be threefold; sometimes companies simply want to inform authorities of upcoming workload; sometimes the industrial partner seeks scientific advice on specific questions that arise when planning or implementing a development plan for a project within the current regulatory paradigm; at other times the advice requested would be more strategic or political in nature, especially when the regulatory context is unclear or non-existent.

Occasionally, for very early and groundbreaking topics, the purpose of the contact can be education of assessors and dossier managers of the competent authorities on cutting edge technology not yet encountered by the agencies. From a company point of view, such early discussions and an ongoing communication with the authorities worldwide have several benefits. Any new concept is flagged to the agency, allowing regulators to come up with a suitable regulatory route, within or outside of the discussions with the industry partner. Very early strategic advice not only allows companies to have more robust development plans early in the process, but also leads to a much deeper knowledge of the technology from the start. The ultimate goal is to facilitate the scientific assessment later in the process, especially if the future assessors of the main application are involved. In Europe, the EMA is a strong advocate of this practice, both in direct conversations with the companies and in documents describing the Agency's *Roadmap*.

Confrontation of the authorities with new technologies without any time to prepare will result in efforts to squeeze the product into an existing regulatory framework that does not meet its needs. In fact, not only are the authorities surprised, but also any prediction of timelines and probability of success within your portfolio management becomes uncertain. Also, the approach taken by the different regulatory bodies worldwide will likely be different, leading to even more uncertainty. If authorities get the time to explore new concepts in advance, not only will they more readily find a suitable approach, but there is also a higher probability that their respective approaches can be aligned.

It should be acknowledged that the European and the US markets tend to be the key drivers for the definition of global development programmes in many companies. Not only is this true for early-stage projects concerning new technologies or concepts, but also for projects requiring scientific advice later in the process. Advice procedures are well established in the US, not only for development plans, but also to provide protocol concurrence. In Europe however, neither companies nor regulators are advocates of protocol concurrence, which is seen as decreasing the scientific responsibility and freedom of the companies. Furthermore, the details of EMA's proposal for providing early strategic and scientific advice are not yet fully established and both regulators and companies will have to each play their part going forward. That said, the initiative for joint scientific advice between EMA and FDA does offer interesting possibilities for some development projects.

To conclude this point on scientific advice, it should be said that both types of advice combined, *i.e.* the early (more regulatory strategic and less binding) advice and the later-stage (more precise, scientific and binding) advice must surely lead to less attrition and more regulatory approvals for innovative products. Communication between regulatory authorities and companies can be very different in terms of detail, frequency and openness across regions, and even across Member States within the EU. Nevertheless, ongoing communication between the two parties is very important, throughout all stages of development leading up to submission. For all too long the two parties have not valued each other enough as partners with a common goal: to put safe, high-quality, efficacious veterinary medicinal products on the market. Recognising that humans and animals live in "One World" with "One Health" we need to bring new innovation to the market and we must further refine and develop what is available on the market.

For any company it is also critical to keep track of the current status of your application as it progresses through the registration process. Besides the official moments of communications, such as receipt of the list of questions, the previously mentioned ongoing communication will also lead to a better understanding within the company of the progress and will provide more predictability and trust in the process. For instance, once a list of questions or deficiencies has been sent to the applicant, it is of the utmost importance that communication continues to allow a full understanding of the issues, and consequently the preparation of detailed and relevant responses. Any company that fails to engage in open, two-way communication at this stage is likely to be storing up problems for the future.

Final Steps

So by now you have identified the key features of your new product and the markets where you would like to sell it; you have conducted all the necessary studies, avoiding duplication of local

studies in different regions wherever possible; you have selected your registration procedure (if there was a choice), you have assembled your data dossier and you have made your submission. Throughout the whole process you have had more or less communication with the regulatory authorities, so you should also have a good idea of the procedural steps still to be completed, the expected timelines and the likelihood of having the key label claims approved in each market.

It is at this stage that all eyes in the company turn towards regulatory affairs; suddenly it seems that one small group (or even one individual) is solely responsible for answering the question "when can we launch?" Before attempting to give a date, it is vitally important to consider all of the remaining steps, even if they lie outside the scope of regulatory affairs, in order to be able to manage expectations and to justify the date proposed (which, by the way, will never be early enough!). There are four main aspects to consider.

The first consideration is the assessment time required by the agency. In the EU, assessment times for veterinary medicinal products are dictated by legislation and a calendar showing the key dates is shared with the applicant. The biggest unknown will be the time taken for the applicant to respond to questions, which could be from 1 to 6 months depending on the availability of the data required to support the responses. Typically, registration of a new product in the EU takes 12-18 months, but it is best to estimate optimistic, realistic and pessimistic approval dates to facilitate the launch planning. In the US where phased submissions are the norm, assessment of each technical section takes 6 months, but if questions are raised a second review cycle of 6 months is required. Assessment of the different technical sections is often done in parallel, so it is important to determine which one will be rate-limiting and, again, estimate an approval date range for the application as a whole. Other regions may have no defined timelines at all, in which case estimates of the approval date can only be based on precedent. For feed additives the European Food Safety Agency (EFSA) officially has 15 to 18 months in which to give their scientific assessment to the European Commission, but this becomes more and more challenging as the validation period and clock stops seem to prolong the timeline substantially.

The second consideration is to provide an accurate understanding of the notion of "approval" *vs*. product marketability. For example, a positive opinion from CVMP in the EU is often mistaken for an approval, whereas in fact it is merely a recommendation to the European Commission which must make its formal decision before the product can be marketed. In the US, approval of all technical sections must be followed by approval of an administrative section and the product label before a valid licence is granted. Approval of the human food safety section is also a pre-requisite for products for food-producing animals in most regions and it is important to check that this has been granted, especially if it involves separate agencies as in Australia or Japan, for example.

Occasionally there may be other pre-launch commitments that must be met, even though the registration has been granted. Such arrangements are rare, but can be negotiated if the "missing piece" is expected to be available very soon.

The third step is the regulatory approval of product packaging. The approach to this varies greatly between countries, ranging from an "at the company's own risk" approach (*i.e.* no agency review of packaging, but the company is liable if it is subsequently found to be illegible or not in compliance with the registration) to a full review of all packaging mock-ups and/or specimens prior to product launch (although this does not lessen the company's liability for non-compliance). The most

common, and most pragmatic, approach is for the agency to review a "worst case" mock-up (*e.g.* three languages on the smallest pack size) as this gives both parties confidence that all of the packaging will be acceptable without significantly delaying the product launch. Most regulatory authorities will aim to review packaging mock-ups within a specified time and it is a company decision as to when they are willing to start the printing process in earnest, *i.e.* should they wait for approval or go ahead at risk?

This brings us to the fourth and last consideration, which is the availability of finished goods for sale. Many regulatory affairs professionals, particularly in large companies, do not have a detailed knowledge of the manufacturing and supply chain and so are unable to estimate the time required to get product to the market. If this is the case, the estimated timelines provided to colleagues must be given with very clear conditions. For example, "product registration is expected on <date> - any product manufactured before this date is manufactured at risk as product specifications may change", or "packaging approval is expected on <date> - any packaging printed and/or product packed before this date is done so at risk as packaging design and/or text may change". It is also wise to avoid the temptation to only give pessimistic estimates for registration and packaging approval, believing that colleagues will be happy if the process ultimately comes in ahead of schedule. An expectedly early approval can mean that there is no product available for the markets and so additional sales opportunities have been missed. Therefore, as mentioned previously, providing optimistic, realistic and pessimistic dates is good practice.

Because the duration of the registration procedure is different in each market, and internal logistics may also vary, the earliest possible launch date will also be different in each market. Furthermore, some regulatory authorities, for example those in the Middle East, may refuse to grant a registration without evidence of registration in the country of product manufacture or in a major market such as the US or EU, so these markets will always receive their registrations later. The decision of exactly when to launch the product in each market lies with Marketing colleagues and will most likely be based on market size, but communication of the actual date of commercialisation to the agency is normally required and should be done by the regulatory affairs professional.

Ongoing Compliance

The role of the regulatory affairs professional does not stop with the product launch; it is the company's responsibility to ensure compliance of the product with the registration for the lifetime of that product. Exactly how this is done varies between companies with some taking a "cradle to grave" approach (*i.e.* one regulatory affairs team managing a product through development, registration and post-approval), others having separate teams for pre- and post-approval activities, and either having more or less involvement of a separate quality/CMC (chemistry, manufacturing and control) team.

There are pros and cons of each approach, but the key point is that the company must ensure full compliance of the product's manufacture, specifications, packaging, storage and sale. If there were post-approval commitments made at the time of registration (*e.g.* provision of real time stability data), these must be completed in a timely manner otherwise the licence may be revoked. Likewise, there will be a pharmacovigilance plan which specifies the reporting obligations for adverse events. Adverse events include side effects in the target species, off-label use (with or without obvious side effects), human exposure, lack of efficacy and product quality defects (*e.g.* broken vials,

discolouration, or packaging errors). There are many regional differences in pharmacovigilance reporting, but typically serious adverse events must be reported immediately and non-serious adverse events (either from the region concerned, or globally) must be reported according to an agreed timetable.

Inevitably there will also be changes proposed by the company during the lifetime of the product. These may occur because data has been generated to support a new therapeutic claim or a new species; minor changes to the manufacturing process may be desired to make it more efficient; there might be a more radical formulation change or a manufacturing site transfer; or pharmacovigilance reporting may have highlighted a common side effect that should be mentioned on the product label. Whatever the reason, the regulatory affairs professional must decide if the proposed change is: (a) so insignificant that it does not need to be reported to the authorities (*e.g.* a change of solvent supplier where the original supplier was not mentioned in the registration dossier); (b) a minor change that can be implemented immediately and notified to the authorities later (*i.e.* "do and tell"); (c) a "tell and do" variation that requires authority notification before implementation; or (d) a "tell, wait and do" variation that requires authority review and approval before implementation. The categorisation of variations depends entirely on the country concerned, as do the data requirements and assessment timelines, so the company must employ a strict change management system to ensure that all changes are implemented at the correct time for each market.

The final point to note is that the product licences issued by some regulatory authorities are of limited duration, meaning that a renewal application must be submitted to extend its validity. The best example of this is in the EU where all new licences are valid for 5 years. The renewal application comprises a review of post-approval commitments (if any), variations, pharmacovigilance data and an updated benefit-risk assessment. If the product is found to be performing as expected and the benefit-risk is still positive, the licence will be given indefinite validity (subject to ongoing commitments, variations and pharmacovigilance). The rationale behind requiring a separate renewal application in the EU when monitoring of commitments, variations and pharmacovigilance is already ongoing is questionable, but for the time being the requirement remains.

Conclusion

Regulatory affairs is about far more than the submission of a dossier to a regulatory authority. Good planning can lead to the creation of a global development strategy that can minimise costs; good communication can smooth the way through registration and reduce timelines; and good change management can keep compliant product on the market and generating revenues for many years to come. Whilst none of these points are unique to the animal health sector, the complexity lies in the diversity of target species and in getting maximum return on investment from this diverse and fragmented market.

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