DRUG APPROVAL PROCESS VARIES BETWEEN USA, UK AND EUROPE

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Robin Fearon reviews the work of UK directorates, EU regulatory agencies, and the US administration in the process of pharmaceutical drug approval

CLIENTS benefit from a massive arsenal of pharmaceutical treatments to keep healthy.

Dispensary shelves hold a dizzying array of commercially available creams, tablets, liquids and suspensions, and there are more than enough drugs in development to keep regulatory agencies on constant rotation, but what do you really know about how medicines make the grade?

Pharmaceutical companies collectively sink billions into development, without any guarantees of market share or profitability. Efficacy and safety studies provide crucial barriers to market and there is a large burden of proof placed on companies looking to register new or reformulated drugs, monitored by an active legislature.

How do regulatory agencies work?

Each EU country has its own national veterinary medicines agency; the UK has the VMD, supported by the central European Medicines Agency (EMEA) and its committee for medicinal products for veterinary use (CVMP). Both agencies stress the need to balance manufacturers’desire to get a product to market, using minimal cost and time, versus consumer safety.

There are three main ways to register medicines in Europe – nationally, centrally and through mutual recognition. The VMD plays a dual role in assessing applications for the UK market and, through mutual recognition, of products registered in other countries. The CVMP grants centralised authorisation for products registered Europe-wide in EU and EEA countries, but relies on expertise from national authorities, such as the VMD, to advise its licences.

“The safest thing we can do is not license any product, because then there is no risk to the consumer,” says the EMEA’s head of veterinary medicines and inspections, David Mackay.

“That is undesirable and obvio usly totally impractical, but, on the other hand, you cannot let unsafe or ineffective products on to the market,” he adds.

Promoting corporate innovation is an essential part of the CVMP’s role, he says, and by giving manufacturers the opportunity to ask questions and get scientific advice throughout the development process, the CVMP hopes to minimise risk.

David admits: “The uptake has not been as good as we would like. But, we are promoting it and have published guidelines on our risk-benefit assessment of new products.”

The European product dossier is a four-part document – for “document” read “multivolume book”. It requires serious attention to detail and a publishing arm to produce. The document’s first part deals with administration, including all labelling, certification and the manufacturer’s legal rights; the second part is the chemistry and manufacturing process, costing a company anywhere between £500,000 and £2m; the third part is efficacy, based on animal trials, preferably using clientowned animals under “field” conditions; and the last part is safety testing, which may require “terminal” studies in animals – the least popular component.

Susan Longhofer is product development and regulatory affairs director at Dechra. Her department of 21 people is spread across the UK, Europe and the US, but she initially worked on clinical trials in her native America before moving on to product development.

She says: “I tell our CEO that my job is to keep him out of jail. That is why regulatory agencies do all this auditing.”

In trying to develop a “soup-to-nuts organisation” for pharmaceutical development, Dechra moved away from using external consultants and university professors to provide technical knowledge on development.

That decision means heavy investment and creative pharmaceutical applications to ensure a pipeline of useful medicines flowing into veterinary practices.

The real costs

Making that leap can be costly. It is product specific, but when you figure in manpower, manufacturing and the technical challenges of ensuring efficacy and safety, then the real costs of producing a companion animal medicine can be anywhere between £3m and £12m.

“If you’re going into a food animal, then quadruple that number because of testing to prove animal tissue residues are not a problem. You have to establish safe levels for humans, then set residue limits and a withdrawal period,” says Susan.

In her opinion, the cost of the chemistry and manufacturing controls (CMC) part of the dossier has led to more liquid medicines in the UK. Each separate tablet size requires a CMC section, stability testing for each size and separate registration fee.

“Every year, for every country, we are billed for each registered tablet size,” Susan reveals.

“With liquid solutions, there is much more flexibility and convenience, so it can be more cost effective,” she adds.

Manufacturers monitor competitors’ product applications to determine any advantage. The UK and European public assessment reports are “huge” in Susan’s estimation: “I don’t think the average veterinary surgeon knows about them, but that information is of massive interest to industry competitors. We want to level the playing field, so we find out what another pharmaceutical company did to get a drug study approved. For example, do we have to do the same study and, if they used MRIs in their study, do we have to or can we use CT scans?

“It helps us understand what is going on in the industry, and you pick up on unfair advantages sometimes and let the regulatory agencies know about it. If they offer certain conditions to one company, then they have to offer them to others,” she adds.

On and off the clock system

In the UK and Europe, companies live by the clock system of registration. Every aspect of a dossier must be complete on submission. Depending on whether it is a full product registration, or a manufacturing change, it receives a clock time of, say, 120 or 210 days. Regulatory agencies must then submit any queries about the dossier on day 54 after submission.

Susan says, “They are very good at sticking to the clock system. If you can respond to those questions by the next day, then the clock starts again and you can have approval in 210 days. Sometimes, it might take a month to get the responses because you have to undertake another study or reorganise some data, but you live by the clock.”

By comparison, there is no clock in the US, and the Food and Drug Administration (FDA) statutory requirement of 180 days to registration has not been met in years, says Susan. However, one

advantage is the ability to phase-file – submit parts of the dossier as they are completed.

“Another good thing about the FDA is that you can speak to them about any inconsistencies between reviewers and they will sort it out. I think Europe needs to work a little harder on that, but it“s difficult with 27 different countries to consider,” she adds.

Harmonious operations

Smoothing out those differences is a large part of the medicines agencies’ workload.

The VMD seeks to harmonise operations through its representation in the European Heads of Medicines Agencies (HMA), and through processes such as mutual recognition.

According to a VMD spokesman: “The HMA is engaged in developing coordinated training, and the EMEA organises a number of assessor training sessions each year, intended to ensure a consistent approach in the interpretation of guidelines and data.

“Harmonisation in certain areas, such as data requirements between the EU, US and Japan, is carried out by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (or VICH).”

The UK, along with other member states, contributes to the development of the EU position, and David Mackay of the CVMP believes anything that harmonises markets has direct benefits for vets and owners.

“The market for veterinary products in Europe, and the free movement of pets, mean it doesn’t make sense to have separate territories for each product,” he says.

Because all member states contribute experts to the CVMP, they buy into its guidelines and agreed standards. The VICH works on a similar footing for global harmonisation.

David explains: “Over time, there is a lot more emphasis going into VICH. It has taken nearly 10 years to make much progress, but because multinational companies do most of the development, there is pressure to harmonise between regions. Tension arises where smaller companies say that we risk raising standards to a higher level than they can afford to reach for their national markets.

“You can understand that point of view, but these fears have not been realised in practice. Generally, VICH guidelines are moving ahead constructively and the EU sees a greater need for international standardisation,” he adds.

For pharmaceutical companies, that means potentially fewer costs, wider acceptance of their products and faster registration.

“VICH guidelines have levelled the playing field, so you don’t have to duplicate studies multiple times,” says Susan.

“There are still different levels and gradations according to product type. Sterile-fill suspensions, such as insulin, are the toughest products to manufacture to either EU or US standards,” she adds.

Definite trends in medicines manufacture may influence production methods in Europe. Sustained release and chewable products aimed at owner compliance offer greater flexibility, for example a six-month heartworm preventive in the US and a 12-month injection in Australia.

Susan comments: “You have two-career families looking for reasons not to pick up prescriptions and give the dog pills twice a day. I would be very surprised if a once-a-month NSAID does not do well, because there is a market for convenience over price. If once-a-month costs me 30 times one tablet, maybe not, but if it’s 20 times one tablet then it looks like a good deal. I think there will be a move towards sustained release [treatments] and products that give more compliance.”

Market forces

There are approximately 65 million dogs and 85 million cats in the US, roughly 10 times the UK population. That means there are either more pets per household or, more likely, more households with a cat or dog. The US market is a lucrative one for companies with enough capital and tenacity to break through.

“Where there’s more affluence, there’s more understanding, and I“d say, in general, that US pet owners are fairly astute,” says Susan.

“For love of their animals I don’t know if they’d beat the Brits and their dogs, but Americans love their animals as well. It’s driven by socio-economic and educational factors, but veterinary salaries on the east and west coast reflect what people are prepared to pay,” she adds.

Every new product that Dechra develops is considered as part of a worldwide programme. It does the majority of clinical studies in the US because the level of scientific rigour required is also acceptable in Europe.

Susan says: “We are going to try to do one study over here with a key opinion leader or someone who has a large practice, because it’s good to have a European voice, but in the diseases we’re dealing with there is no difference.

“If you are combating parasites, you really have to do local studies because there may be different species or patterns of resistance,” she adds.

The single biggest difference between FDA trials and the rest of the world seems to be the amount

of documentation – US registration results in costly studies. On one study, the company totalled 6,000 data entry hours.

Susan asserts: “The reason for this is a past history of fraud in pharmaceutical development – you are guilty until proven innocent. One company was caught falsifying data because the data entries were too similar, written by the same person with the same pen. So now the FDA wants to see your raw data, the original documentation as it was written down.”

Dechra is now upgrading its production plant in Skipton for FDA inspection, and has set up an American operation to deal with the huge customer base and large US distributor chains. One thing it could not influence was US legislation. Under the Animal Medicine Drug Use Clarification Act, there is more scope for American vets to use human medicines off-label, a situation mitigated against in Europe by the cascade.

Susan believes “preference should be given to a veterinary drug if it is available”, but adds:

“There is absolutely no enforcement in the US. It is something you must contend with in the US market – readily available human generics that may be substituted for a veterinary product.”

Asked whether the cascade helps veterinary medicines manufacturers in the UK, a VMD spokesman said: “The cascade provides a legal basis for veterinary surgeons to use a medicine that is not authorised for the species or condition being treated. It is not designed to help medicine producers, but presumably they get increased sales for those products used under the cascade.”

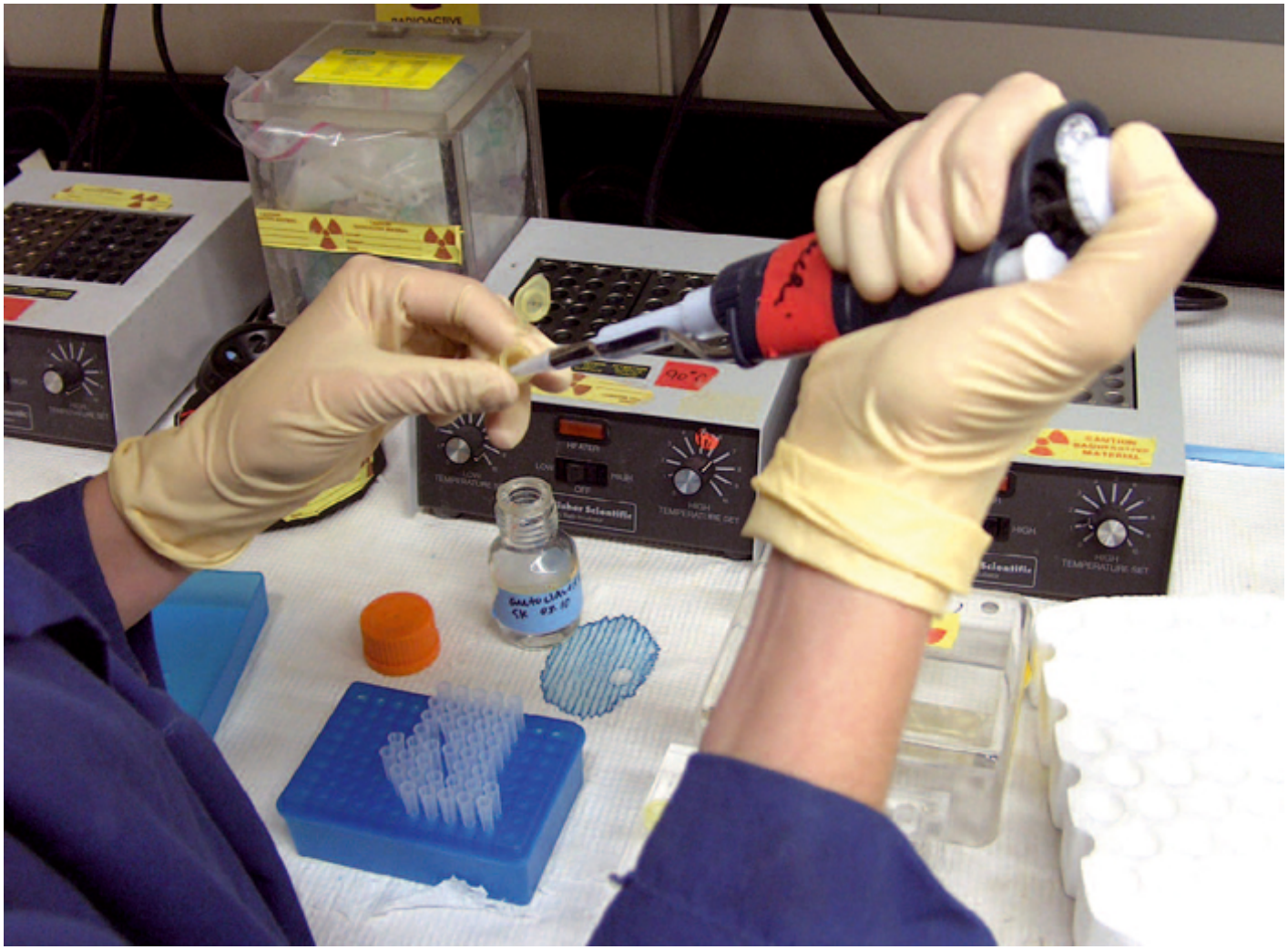
The spokesman added: “When we explain the reasons for the cascade, we get positive feedback from most veterinary surgeons. Some still see it as a limitation on the medicines they are able to use. Compared to many other member states, UK vets have good access to veterinary medicines and the cascade is an important element of this.”

In its own way, the cascade is helping keep the veterinary medicines pipeline open at the entry level for many small and medium-sized companies. There are obvious cost barriers in development and expansion into new territories, and the longterm future for true innovation in medicines is unclear, given the continued rise of generic drugs.

Susan has spent years in product development and knows that competitive advantage is increasingly harder to come by.

She adds: “Regulatory agencies make it tougher each time. Study standards are also being ratcheted up. In the US, the minimum number of subjects is 100 treated animals. In the UK, it is acceptable to use 50 or 60 animal studies, but there will come a point where it is not going to be cost-efficient any more.”

Susan Longhofer.



Heavy investment and creative pharmaceutical applications are required to ensure a pipeline of useful medicines flowing into veterinary practices.

Photo: SXC/DAINO_16.

Due to the number of pets in US households, that market is a potentially lucrative one for companies.

Photo: SXC/RACHEL NESOM.

There is more scope for American vets to use human medicines off-label, which is a situation mitigated against in Europe by the cascade.

Photo: SXC/PAWEL KRYJ.