Vet Meds Legislation: How Far Will The Commission Go?

PEER REVIEWED

The review of the veterinary medicines legislation started in 2010. More than four years later all of us with a stake in how veterinary medicines are regulated in Europe are still waiting for the Commission's proposals to be published. Some general images have emerged from the mists of the consultations, discussions and exchanges between the stakeholders and the Commission and gained some substance from the IFAH conference, but at the time of writing – and I suspect of publication – we are still left wondering.

It is widely believed that the legislation will be in the form of a Regulation rather than a Directive. This will enforce harmonisation and remove the scope for member states to nuance implementation to suit their interests. Industry in general supports a Regulation, but unless it is carefully written and properly scrutinised we may find ourselves strait-jacketed in unexpected areas that demand some flexibility and with no prospect for further change before 2030.

The current regulatory framework is defective in some major areas and we are labouring under a heavy administrative burden that is double that for human medicines. We have an internal market that is not free and far from harmonised, particularly with respect to medicines availability. On top of this, there is pressure on our use of antimicrobials which is, rightly or wrongly, perceived as a threat to public health. All of these aspects feature in the Commission's objectives for the new legislation.

In my mind the central issue is improving veterinary medicines availability. Our industry exists to provide medicines to improve animal (and human) health and welfare and all of the other aspects affect how well this is achieved in Europe. There are around 160 products with European Marketing Authorisations (MAs) through the centralised procedure, but while veterinarians in France or the UK have access to almost all of these, smaller states such as Iceland have relatively few. There are 10 times this number of mutual recognition / decentralised MAs listed in the VMRI index, but of these around 10 % list one to five concerned member states and only ~20 % have 24 or over. The availability across the Community is far from uniform – one can only agree with the statement that farmers do not understand why a colleague on one side of the border can use a certain medicine and they can't.

The Commission has stated that availability may be improved through reducing the administrative burden and stimulating innovation and competitiveness; both sides of industry consider the administrative burden as a factor in availability. There are currently four routes to obtain an MA. This is over-complex, highly administrative, costly and inefficient.

As the Commission has said, in the context of this regulatory review, there is nothing as complicated as simplification. IFAH Europe has proposed the famous 1-1-1 concept, an ambitious plan where all current procedures are replaced by a single 'one dossier, one assessment, one EU-wide authorisation'. While attractive in principle and well adapted to the larger companies, it is less well suited to the smaller and particularly local companies with limited financial and human resources and which are active in one or few member states. These are well adapted to meet local needs and niche markets. In response, EGGVP proposed an alternative, simpler 1-1-1 process with a single assessment leading to multiple separate MAs. The general expectation is that IFAH Europe's 1-1-1 proposal will not see the light, but some of its principles may be adopted into a much wider extension of the centralised procedure, which would allow all-EU authorisation for more products.

But what of the smaller, single-market companies? It appears that the decentralised and national procedures may also be retained permanently, rather than for a transitional period. If so, have we really simplified the regulatory environment? Will the proposals allow a new, simplified DCP to lead to authorisations that will be effectively EU-wide, without the inevitable disagreements clogging the system with referrals as they do now? Decision by majority voting would go a long way towards this goal. Will retaining these routes in a simplified form tempt companies to apply for more MAs, in more countries – or will the right to choose the concerned member states be restricted?

Whatever the new routes for new products, we have a legacy of around 30,000 nationally-authorised existing products with SPCs that differ significantly between countries. Tentative attempts to harmonise a handful have been resource-consuming and less successful than hoped. Bringing these into some form of harmonised, EU-wide authorisation will significantly improve availability. However, unless the majority of well-established, safe and effective products can undergo some administrative (industry would say, voluntary) process, the administrative burden would be massive. Of course there are products, including antimicrobials, where a scientific assessment is necessary but assessment should be limited to where there is an identifiable serious risk to human or animal health.. Harmonisation must not be to the lowest common denominator – that would mean losing indications and species and our veterinarian clients are justifiably very nervous of such unintended consequences.

Currently, maintaining the existing authorisations is a significant drain on the MA holder's resources. Product defence absorbs 35 % of the EU R&D budgets, double that in the USA. The finance and resource costs of making variations are significant, and, according to industry, disproportionate to the work involved. Reducing – even removing – the

administrative burden of changes which do not affect quality, safety or efficacy and bringing back the 'umbrella' Type II concept (combining unrelated minor changes within a single process) are two 'easy wins' which could release resources without detriment.

One area in the variations envelope expected to be addressed is the disproportionate cost and effort of changing the pharmacovigilance system. Currently the described PV system DDPS is linked to each MA, so every minor change must be changed by variation for each product, in each country. The concept of a pharmacovigilance Master File has been widely discussed and must be adopted if the proposals are to have credibility.

Pharmacovigilance is the most rapidly growing administrative sector. The value of properly monitoring the safety and efficacy of veterinary medicines is recognised by all stakeholders, and the confidence that robust surveillance brings may even lead to completely removing the need to renew MAs. This may be facilitated by the completion of a single European product database covering all authorisation routes and maintaining full pharmacovigilance records, with appropriate public access. However, the current reporting system is overly complex and is driven by process, not risk. At least, the routine PSUR reporting in prescribed complex formats could be simplified and focussed on new and higher-risk products, and reduced or removed for established products with known, good safety records.

Several years of effort by industry and CMDv has reduced the requirements for labelling – and so for translation – as far as possible under current rules, and a simplified QRD template is now actively promoted. I'm confident that the Commission's proposals will further facilitate availability through multi-country labels.

IFAH Europe has lobbied hard to increase data protection, to delay generic entry and so stimulate innovation. Cumulative data protection, where additional claims increase protection up to 20 years, has been floated. Unsurprisingly, the generic industry argues that data protection should also promote competition, through increased choice, reduced costs and better availability that they bring to the market. They argue that extensions may benefit from specific protection which would allow a generic authorisation of the original MA, but without the new species or indication. The Commission seems to have accepted the need to adapt data protection to encourage innovation, but will have to find a balance with competition to optimise availability. In any case, we all expect special provisions for the MUMS sector, especially bees and probably fish, where the lack of authorised medicines is so severe.

The traditional pharmaceutical market model has been seen to fail in human medicine in two very public areas; in the Ebola crisis unfolding in West Africa, and in the lack of new antibiotics to offset the relentless march of resistance in hospitals and the community. Governments are now openly discussing how big pharma can be incentivised to develop new antimicrobial molecules that will, by definition, only be used as a last resort. One thing is certain; we will not see these molecules allowed in a species under our care. How can the animal health industry be incentivised to develop new antibiotics when the major source (big pharma) will shut the door, and any relationship with a 'critically important' molecule for human treatment will significantly reduce the probability of regulatory success? I hope to see some innovation from the Commission in this vital area, but I'm not optimistic.

The pressure to reduce antimicrobial use in animal health is intensifying. While it is important we continue to defend

our corner, it is vital that the agricultural sector is seen to be taking action to responsibly use antimicrobials '*as little as possible but as much as necessary*', and we can expect to be encouraged (more probably, mandated) in this by the Commission's proposals. The delay in publishing the legislation is thought to be related, at least in part, to the measures on antimicrobial resistance. The EMA has just published its draft advice to the Commission on the impact on public health of the use of antibiotics in animals, with finalisation anticipated by the end of this year. Perhaps we won't see the proposal until afterwards. At least, I expect the proposal to include enabling measures to restrict and even stop use of specific antimicrobial classes in animals following scientific advice and/or risk assessments, to tightly control or restrict off-label use and to collect detailed data on antimicrobial use and prescribing. I'm also anxious to see what is proposed around 'preventive' (prophylactic) use – will this be banned? If so, how will 'prophylactic' be defined? Will metaphylaxis become a legal concept?

There is pressure on in-feed administration of antibiotics, especially in intensive pigs and poultry, where it is viewed by some as supporting poor husbandry. The Commission is believed to have recognised that it is a legitimate and important route of administration. In member states where in-feed medication is not allowed by local legislation, alternative practices such as top dressing lead to inconsistent dosing which may increase resistance pressures. It is hoped that the related proposals on feed legislation will make in-feed administered medicines available across the community under a clearer and tighter framework, and even allow developments of innovative in-feed medication in new areas, such as companion animals.

One area which has raised concerns with regard to feed medication is carry-over. A zero-tolerance policy on residues in following batches has been suggested. This is impractical, as analytical methods are capable of detecting nano-quantities. Such a policy will effectively stop feed medication overnight as feed manufacturers withdraw from the market. Carry-over might be reduced if pre-manufacture were allowed, with supply only on a responsible and appropriate prescription from a veterinarian for animals under his care. I would expect common sense to prevail in the Commission proposal, but I'm nervous about the European Parliament's amendments.

Veterinarians are rightly nervous about their ability to continue to prescribe off-label. The 'Cascade' currently permits a prescribing hierarchy where there is no authorised medicine for the clinical condition. In most circumstances this is a reasonable and controlled approach that protects animal welfare, human health and the veterinarian's clinical freedom, but there are fears that this may be restricted, particularly with respect to antimicrobials in food animals. In some species (goats and turkeys come to mind) the choice of authorised medicines is so limited that their welfare is dependent on the Cascade. Even if the new Regulation is successful in improving availability, the Cascade or something very like it will be needed to fill in the gaps.

We have been promised these proposals for revised veterinary medicines and feed legislation for so long now, but they are always just beyond the horizon, out of reach. The Commission has said it should be within 2014, but has not given guarantees. My final hope is that they are published soon. There are limits to our patience!

The views expressed in this article are my own and not necessarily those of any organisation with which I am associated.

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