At the Frontiers of Animal Health: A European Perspective

In animal health, as in human health, scientific discoveries and technological innovations are constantly presenting new possibilities for the prevention and treatment of disease. Harnessing, commercialising and eventually reaping the benefits of these innovative products, however, poses particular challenges. A large proportion of such discoveries originate in academia, research organisations or SMEs – which, in contrast with large established companies within the industry, often do not have any experienced regulatory personnel nor dedicated internal processes to bring their discoveries into development. There is also the very real issue of legislation and guidance not 'keeping step' with innovation. Directive 2001/82/EC (the EU Directive which both sets out standards for veterinary medicinal products and outlines the authorisation procedures) focuses on the established pharmaceutical and immunological product types, and has no scope to provide a framework for innovative products that fall outside these categories. It has also been the case for a considerable time that so-called 'borderline' products in the EU face regulatory uncertainty where no relevant legislation for certain product types exists on the veterinary side. Although some member states have nominated experts, and some competent authorities have dedicated national review and registration processes for borderline products, it is still the case that opinion on the same product (usually as medicinal versus non-medicinal) can be dramatically different from member state to member state. This can often frustrate and confuse companies wishing to market a product, and may be a block to useful products becoming available to veterinarians, farmers, and pet owners.

The bulk of the other animal health-related legislation and guidance is also in the rather restricted pharmaceutical vs. immunological products vein. The situation is such that, at present, legislative development is largely being driven by scientific progress: novel products are often coming to market with regulation being applied on a case by case basis. In recognition of this complicated state of affairs, the EU regulatory agencies have put in place various networks, working groups and informal consultative procedures. The aim is to maximise dialogue between the regulators and industry, from as early a stage as possible. Initiatives are in place that recognise the challenges faced by researchers and SMEs wishing to develop a novel therapy, in negotiating the regulatory landscape and meeting costs. Innovators can be guided towards obtaining data that could support an eventual product authorisation. Early dialogue also enables regulators to become aware of new kinds of treatment as they appear on the horizon.

The scope of this article is two-fold. We wish to identify the particular regulatory infrastructure that currently exists to support innovation in animal health products in the EU, and how this may be used most productively by innovators. We also discuss some of the product types which have come into being more recently; the potential benefits that they could offer if eventually made available on the market, and what difficulties are faced by innovators and regulators in trying to achieve this.

The EU Innovation Network (EU-IN), and the EMA Innovation Task Force (ITF)

Although some of the EU national competent authorities (NCAs) have had their own innovation offices for a number of years, in 2015 the EU Innovation Network (EU-IN) was established with the stated aim of supporting medicine innovation and early development of new medicines in the EU. These innovation offices, and the EU-IN generally, are open to enquiries and discussion around applying new technology in both human and animal health, in recognition of the fact that such innovations may eventually be applied in either or both fields. Meetings of the innovation offices occur a few times a year via telephone conference, and annually face-to-face.

The EU-IN mandate[8], adopted and published in September 2016, encourages dialogue between the individual innovation offices and across the network. Those in the process of developing new therapies can engage with the network in a couple of ways. They can contact the innovation office in their own country, on an informal basis to have meetings and discussions, if they are based in an EU member state which has such an office (it is not compulsory to have an innovation office and not all member states have one, but the majority now do[5]). This can certainly be a useful first step, especially for initial dialogue, since travelling to a meeting is less arduous within one's own country and speaking one's own language! It may well be the case that a meeting with the European Medicines Agency's (EMA) Innovation Task Force will be more productive, however, since the ITF can draw on the scientific expertise of its members across the EU. Although scientific knowledge and experience of emerging trends are shared throughout the network, as well as discussion of case studies (only with sponsor permission, of course), the relevant expertise for the product in question may not necessarily be available within each national innovation office.

The ITF encourages future applicants, particularly those which are SMEs or are within academia, to engage with the regulators early on: both to assist the innovators in finding the appropriate road to market, and to flag to the ITF and its associated network what regulatory challenges are emerging with the development of new technologies. For truly innovative products, the ITF offers briefing meetings, free of charge, where scientific, technical and regulatory issues can be discussed informally. Following receipt of a request, they will confirm when a meeting can be arranged, and identify the experts recruited to attend. The actual meeting can take place in person or by video conference.

Ad Hoc Expert Group on Veterinary Novel Therapies (ADVENT)

'Novel therapies' in the context of ADVENT refers to therapies that are new to the veterinary domain, although they may already be well-known in research, and possibly in the context of human medicine; equally they may be *entirely* novel to both the human and veterinary fields. ADVENT is a small core group drawn primarily from the EMA's Committee for Medicinal Products for Veterinary use (CVMP). Its purpose is to provide scientific guidance on novel therapies, which it does by releasing problem statements for consultation, consulting topic experts, and following up with published question and answer documents.

The group has recently published its first guidance documents on extraneous agents and sterility of stem cells for veterinary use. Current problem statements at the time of writing include target animal safety for allogenic stem cells products, and monoclonal antibodies for veterinary use. ADVENT invites not only opinions and comments on the published problem statements, but also suggestions on novel therapy-related subject areas that would benefit from the provision of scientific guidance. The guidance documents, problem statements and contacts for comments and suggestions to the group are all available on the "Novel therapies" page, which can be found using the search function on the EMA website.

Scientific Advice from EMA/CVMP

For innovative products, applicants often face the situation that there is no relevant guidance available. Occasionally a human guideline is published on the topic, but it may not be feasible to follow it due to divergent risk factors in animal health, target species differences, or cost issues that are much more prominent when developing veterinary products. Moreover, when experience is lacking, the assessors become risk-aversive and may be overly cautious in their assessment.

To increase the predictability for applicants and to reduce the risk early in the development process, the CVMP can give scientific advice on specific products, studies, and processes. An application with questions and the applicant's background and suggested solutions is submitted to CVMP's Scientific Advice Working Party (SAWP-v). Within 2–3 months an answer is returned with acceptance or proposals that the applicant can work on. Occasionally a meeting is held between the applicant and the SAWP-v, primarily to clarify the topic before the final answer is given. Although the advice is not *legally* binding, the rule is that it is adhered to by all assessors and regardless which authorisation route the applicant pursues, i.e. centralised, decentralised, mutual recognition, or national.

The fee for scientific advice may be waived or reduced for specific applications, or if the applicant is a registered SME.

Scientific advice can be of huge benefit for innovative products to clarify the necessary data package, for example if the manufacturing resembles a vaccine production, but the mode of action resembles a pharmaceutical product. In general, applicants must be ready to explain the science in detail to assure the assessors of the properties and risks of the intended product.

DNA Vaccines

DNA vaccines have been researched for more than two decades for their positive potential, with limited breakthroughs, although the first one was authorised in Canada in 2005 against infectious hematopoietic necrosis virus in fish.

A DNA vaccine consists of a genetic sequence, typically circular bacterial DNA, with inserts of single genes from a pathogenic organism. After injection, the genes are translated to proteins directly inside the cells of the vaccinated animal. These proteins resemble the pathogenic organism and stimulate the host's immune system to create an immunological response (for example antibodies), enabling the host to fight off a subsequent infection with the pathogenic organism itself.

Clynav was the first veterinary DNA vaccine to be recommended for marketing authorisation in the EU. It is authorised to protect farmed Atlantic salmon against salmon pancreas disease (SPD) caused by an alphavirus, which damages the heart, pancreas and skeletal muscle and can lead to death of the salmon[6].

Due to the innovative nature and the content of the product (genetic material), and because it is used in fish-farms in open water cages, a complex environmental assessment was performed. Moreover, an evaluation of safety for the consumer of vaccinated salmon was drawn up based on input from the European Food Safety Agency, as was an assessment of the possibility of integration/non-integration of the DNA from the vaccine into the genome of the salmon.

Despite the general understanding in the scientific community that DNA vaccines are very safe, the authorisation of the first one of these vaccines in the EU proved to be a very lengthy and demanding procedure[3].

The CVMP's guideline for DNA vaccines is currently under review, with expected release in 2018.

Monoclonal Antibodies

Monoclonal antibodies (mAbs) are immunoglobulins (Ig) with a defined specificity derived from a single clone of cells. Their biological activities are determined by a specific binding characteristic to an antigen.

Monoclonal antibodies may be produced by recombinant DNA technology, hybridoma technology, B lymphocyte immortalisation, or genetically engineered animals. Since 2014, several mAbs have been authorised in human medicine against e.g. cancer or rheumatoid arthritis.

ADVENT recently identified areas that would benefit from further consideration and guidance in the form of question and answer documents, specifically regarding quality specifications, target animal safety, and reproductive safety.

In April 2017, Cytopoint was authorised as the first monoclonal antibody for veterinary use in the EU. It contains Lokivetmab that attaches to interleukin-31, a protein that plays an important role in triggering atopic dermatitis in dogs, a common allergic skin disease. By blocking this protein, Lokivetmab reduces itchy skin and inflammation associated with atopic dermatitis.

Stem Cells

Stem cells are non-terminally differentiated, self-renewing cells that harbour the ability to produce mature, diffe-

rentiated daughter cells. Stem cells serve to regulate or participate in normal tissue homeostasis and embryonic and foetal development. The use of stem cell-based products in the veterinary sector is raising questions for manufacturers, authorities, and users. In 2016, ADVENT issued four problem statements regarding stem cells; stem cell sterility, extraneous agents, tumorigenicity, and target animal safety. At the time of writing, the Q&As on extraneous agents (EMA/CVMP/ADVENT/803494/2016) and sterility (EMA/CVMP/ADVENT/751229/2016) were adopted. Because stem cell-based products are novel therapies, different from both pharmaceutical and immunological products, relevant and feasible parameters in relation to different safety concerns need to be considered. When tackling the challenges of stem cells, the deficits of the current veterinary legislation become obvious.

In human medicines in EU, stem cells entered the scene in 2014, where Holoclar was recommended as a treatment for burns to the eye(s), and later with, e.g. Zalmoxis, aiding in the treatment of blood cancer. The initial assessment of human advanced therapy medicinal products (ATMP) is typically carried out by the Committee for Advanced Therapies (CAT) in EMA. A similar committee does not exist on the veterinary side.

Bacteriophages

Bacteriophages are virus-like agents with antibacterial properties. They have been used to treat bacterial infections in humans for almost a century in some parts of the world. Bacteriophage therapy is used in some parts of Europe, but there are currently no authorised bacteriophage medicinal products. In 1923, the idea of bacteriophage therapy was developed as prophylactic and/or therapeutic use of selected bacteriophages in the destruction of pathogenic bacterial cells, while being harmless for the host's cells.

In recent years, the rise of bacterial resistance to many antimicrobial drugs has spurred renewed interest in bacteriophages, and voices increasingly state that bacteriophage therapy has a place within the therapeutic armamentarium against bacterial infections.

However, legislative change and regulatory flexibility will be required to address the unique aspects of bacteriophage development, because bacteriophage therapy is usually adjusted to the individual infection. To our knowledge, no specific guideline is available as yet, but in the US, bacteriophages are generally regarded as safe (GRAS), and have been approved as food additive or food ingredient in human food by the FDA[9].

Efforts should be joined to develop this area and not to burden a promising approach to treating antibiotic resistant microorganisms. This may require innovative solutions, as are available for autogenous vaccines or multistrain dossiers.

Probiotics and Alternative Products

Antimicrobial resistance (AMR) continues to be a hot topic, and there is a great deal of pressure for the quantities of antimicrobial substances currently used in veterinary medicine (particularly with respect to food-producing/farm animals) to be reduced. Use of antimicrobials for growth promotion has been banned in the EU since 2005[4] and restricted in the US recently[7]. Treatment with antimicrobials in cases of disease outbreak is now closely monitored in many countries. It is generally accepted that antibiotics should remain as an option for treatment in animal health; there are, however, many difficulties and limitations associated with their use. It is recognised that the dose rate that appears on the label of older veterinary antimicrobials is not always adequate, since antimicrobial resistance may have increased and better understanding of the antimicrobial's mechanism of action may have emerged since the time of initial authorisation. This creates knock-on problems, since administration of a higher-than-recommended dose may impact on the withdrawal period in the case of a food-producing animal, and may also affect tolerance in the treated animal and an altered environmental impact[11]. It is very burdensome in regulatory terms to revise all the recommendations linked to posology. Older antimicrobial substances do not offer very big profit margins for manufacturers, and it is unlikely that any new classes of antibiotics will become available for veterinary use in the near future: it is almost certain that they will be reserved for treating humans. Given all of the above, antimicrobial veterinary medicines are looking less and less attractive to manufacturers and licence holders as time goes on.

Farmers, of course, still need to be able to protect their livestock from disease too, and be able to treat them should they become severely infected; they also want to maximise production from their animals. This drive to divest from the use of traditional antimicrobials has meant an increased interest in products that may have been seen as 'alternative' until quite recently. An ingredient derived from pineapple stems, Anatara's 'Detach'[1] has shown much promise in clinical trials in preventing scour (diarrhoea in piglets), which is currently treated with antibiotics. A US firm is focusing their research efforts on algae, having found a candidate compound in it that they hope to develop as an alternative to antibiotics used for growth promotion[2]. Probiotics ('live microorganisms that, when administered in adequate amounts, confer a health benefit on the host', according to the FAO/WHO definition) are becoming more mainstream in animal husbandry globally, with certain substances having proven results in lowering disease susceptibility, improving productivity[10].

Summary and Conclusions

It is clear that the regulatory bodies in the EU/EEA are well aware of the need for the Community legislation and guidelines – and the practical procedures involved in authorising new therapies – to be in close dialogue with those at the cutting edge of innovation in animal health. The continuing expansion and development of the Innovation Network, and its remit of sharing experience gained and identifying need for training or recruitment of specific expertise, is a recognition of the fact that regulation is often lagging behind research and academia. Animal health is also often secondary to human health, with legislation for some technologies entirely absent on the veterinary side (medical devices, for example). Scientific innovations usually break into human healthcare first too; but it is nevertheless quite common for companies that have managed to obtain a licence for an effective new therapy in humans to then consider widening their market to include animals, where the treatment is relevant.

The shift away from use of antimicrobials, with continued reduction anticipated, has created an incentive for companies to develop new products with similar functions that have the potential to replace them. Multi-faceted

approaches to combating disease are also being explored, with innovative classes of products showing promise, but as yet not being widely trialled or applied, nor giving consistent results.

Looking ahead from the current frontiers of animal health, there are clearly some emerging 'front-runners' amongst the new and innovative treatments, some of which have been identified in the discussion. It is safe to say though – as with everything in life – the only certainty is change.

Glossary

ADVENT	Ad-hoc expert group on Veterinary Novel Therapies (ADVENT)
AMR	Antimicrobial resistance
CAT	Committee for advanced therapies
CVMP	Committee for medicinal products for veterinary use
EC	European Commission
EEA	European Economic Area
EFSA	European Food Safety Agency
EMA	European Medicines Agency (the central agency for human and veterinary medicines regulation for the EU)
EPAR	European Public Assessment Report
EU	European Union
FAO	Food and Agriculture Organisation
FDA	Food and Drug Administration (the agency for human and veterinary medicines regulation for the USA)
GRAS	Generally regarded as safe
HMA	Heads of medicines agencies
IN/EU-IN	European Union Innovation Network
ITF	Innovation Task Force
MS	Member state
NCA	National competent authorities (the national agencies located in the EU Member States)
SAWP-v	Scientific advice working party (veterinary)
SME	Small or medium-sized enterprise
VMP	Veterinary medicinal product
WHO	World Health Organisation

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