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Regulatory pathways to enable the licencing of alternatives to antibiotics

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ABSTRACT

Effective alternatives to antibiotics (ATA) such as vaccines, antibodies, phage therapies, prebiotics, probiotics and herbal medicines can be used in place of traditional antibiotics in a way that does not compromise animal health as means of tackling the growing threat to both animal and human health from antimicrobial resistance (AMR). This paper reflects the key points on the approaches that were discussed during the 2nd International Symposium on ATA between regulatory agencies, veterinary product companies representing largely the pharmaceutical and feed-additive sectors, academia and other stakeholders on regulatory pathways to enable the licensing of alternatives to antibiotics for food producing animals. The need to demonstrate compliance with generally accepted standards for quality, safety and efficacy is considered a pre-requisite for all veterinary medicinal products receiving an authorisation including ATA, irrespective of the region in which they are approved. ATA are often based on novel technologies, with complex mechanisms of action; therefore, early and close communication with regulators is encouraged. In addition, strategic use by ATA applicants of all regulatory tools available to support innovation is highly recommended. The veterinary product manufacturers consider that the regulation of veterinary medicines should evolve to accommodate innovative ATA technologies and incentives from regulatory agencies provided to stimulate further ATA development.

1. Introduction

The emergence of antibiotic resistance has created a growing global threat for both animals and humans [1]. At the same time the contribution of antibiotics in treating animal diseases and thus improving livestock health and animal welfare has been significant. Considerable interest is now focussed on developing products that represent alternatives to conventional antibiotics that have the potential to play an important role in allowing farmers and veterinarians to reduce the use of antibiotics in a way that does not compromise animal health, welfare and production. Veterinary medicines regulators across the world are exploring ways to support the access to market of a wider range alternatives to antibiotics (ATA). Many categories of ATA are based on novel technologies with mechanisms of action that have not yet been subject to regulatory scrutiny and therefore requiring careful evaluation of their quality, safety and efficacy. The pace of innovation is rapid and covers a wide range of different type of products that sometimes do not fit the traditional definition of a veterinary medicinal product, creating the need for clarity over the appropriate regulatory framework and standards under which they should be evaluated.

The discussion below reflects the approaches discussed and the main conclusions drawn during the Regulatory Session of the 2nd International Symposium on ATA, Challenges and Solutions in Animal Production, held December 12–15, 2016, at the World Organisation for Animal Health (OIE), in Paris, France. The Symposium was attended by representatives of regulatory agencies with oversight of some of the largest pharmaceutical and biological markets globally, veterinary product companies, academic and research bodies. During the regulatory session special emphasis was given to describing the regulatory pathways now in place to enable the licencing of ATA for food animals, and the experience from the veterinary industries developing ATA.

2. European Union

2.1. European Medicines Agency (EMA)

In the context of current European Union (EU) strategies there are a number of initiatives aiming to facilitate the authorisation of alternatives to antibiotics as part of the wider approach to combatting antimicrobial resistance (AMR). With respect to the European Medicines Agency, the Committee for Veterinary Medicinal Products (CVMP) strategy on antimicrobials for 2016–2020 [2] adopted in October 2016 foresees actions for EU regulators encouraging the development of alternative products. The strategy calls for a close international collaboration with a view to promoting the international harmonization of regulatory requirements for these types of product requirements. The strategy points out that developers of ATA are able to access the same range of support measures as are available for applicants seeking to authorise any other new type of product, namely:

- Scientific advice to companies on the appropriate tests and studies the EMA will need for the process of reviewing applications for veterinary medicine [3].
- Pre-submission meetings for applicants to obtain procedural, regulatory and legal advice from EMA.
- The Minor Use/Minor Species (MUMS) scheme to address the lack of veterinary medicines for the treatment of minor animal species and uncommon diseases in major animal species. Applicants who seek approval for an ATA intended for a limited market in the EU may seek classification by CVMP under the MUMS/limited market scheme with the benefits of having to meet fewer data requirements and/or the financial incentives that this implies [4].
- The Small and Medium Enterprises (SME) scheme provides financial incentives and other benefits to companies designated as SMEs. This

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is particularly relevant for an SME that carries out initial research and discovery for an ATA [5].

In addition, for novel veterinary therapies and taking into account that most ATAs fall in this category, the following groups already generate advice and guidance, also in line with the latest CVMP strategy:

- Innovation Task Force (ITF), which acts as a forum for confidential early dialogue with applicants on innovative aspects in medicines development [6].
- Ad Hoc Expert Group on Veterinary Novel Therapies (ADVENT) providing general publicly available advice guidance on specific aspects related to the requirements for authorisation of therapies that are new to the veterinary domain (novel therapies) [7].

These groups have complementary roles. The ITF provides product-specific advice to applicants in response to a request. ADVENT identifies priority areas in the field of veterinary novel therapies and publishes advice, generally in the form of Question and Answer documents.

There are therefore clearly benefits to be gained from an early and close communication between regulators and developers. Nevertheless when it comes to technologies new to veterinary medicine, ATA represent particular challenges for the regulator highlighting the need for new regulatory paradigms to reflect new approaches such as establishing the approach and data requirements to support claims for reducing the need for antimicrobials in the absence of a disease-specific claim, clarifying the requirements in terms of MRLs for novel active substances presented as ATA, the difficulties in classifying products that could be categorised as medicines, feed additives or even biocides depending on the claims made and the way in which they are presented and used, and the need for close cooperation between different agencies and bodies within the European regulatory network (such as EMA, the European Food Safety Authority and the European Commission) to agree on a clear and consistent approach to regulation of the wide range of products presented as ATA [8]. Work has started to define an approach addressing these issues with respect to veterinary medicines but a longer term, and wider, strategic approach will be needed if the objective of promoting access to market of a wide range of ATA is to be achieved.

In recognising the global nature of Antimicrobial Resistance (AMR) the use of ATA has been included as a topic for action within the workplan of the Transatlantic Task Force on Antimicrobial Resistance (TATFAR). Recognising that development of novel veterinary medicines now takes place at global level, the objective is to identify where international cooperation can facilitate the development and access to market of ATA in the most efficient way for both regulators and developers.

3. United States

In the United States, the mechanism of action and the intended use of an alternative product determine which agency has authority to regulate it. Alternative products can be classified as drugs, which are regulated by the Food and Drug Administration (FDA); food additives (regulated by FDA); biologics (e.g., vaccines), which are regulated by the U.S. Department of Agriculture (USDA); or pesticides, which are regulated by the Environmental Protection Agency (EPA).

3.1. Food and Drug Administration (FDA) - animal drugs

A product is determined to be an animal drug if it is intended for use in animals for the diagnosis, cure, mitigation, treatment, or prevention of disease; or if it is a product other than food and is intended to affect the structure or any function of the body of animals. This includes any drug intended for use in animal feed, but not including the animal feed itself. For any drug, including an alternative to an antibiotic, to be approved it must demonstrate safety (for the target animal, human food, and the human user), effectiveness, quality manufacturing, and proper labelling. The environmental impact of each new animal drug must also be assessed. How an ATA meets these requirements can be different from a traditional antimicrobial, but the regulatory requirements must still be met.

The FDA's Center for Veterinary Medicine (CVM) has created several mechanisms to foster the development of innovative technologies and approaches. As with the EMA, these measures are available to all who seek approval of animal drugs and includes:

- Submission of early information - CVM has a process whereby sponsors may submit information very early in the review process, thereby giving CVM detailed information on a product early in the regulatory process. This allows CVM to identify any issues early in the development process and helps develop the most efficient and effective pathway for approval for that product.
- Technology teams - These teams are groups of internal and external experts who can be assembled to address scientific concerns about a new technology.
- Focus groups - These groups are internal teams that can address broad topic areas (e.g., biomarkers) or process improvements.

In addition, CVM staff are willing to meet with ATA developers before establishing an investigational new animal drug file to convey what will be needed to gain approval for the ATA. They are also involved in various international initiatives regarding licensing of ATAs, including the Transatlantic Task Force on Antimicrobial Resistance.

CVM recognises the benefits of international harmonization and works closely with other international regulatory agencies to facilitate the concept of global approvals.

3.2. FDA - food additives

Any substance that is intentionally added to food is a food additive and is subject to premarket review and approval by FDA unless the substance is generally recognized as safe (GRAS). Determination of GRAS status requires the same quantity and quality of scientific evidence as that needed for approval as a food additive.

3.3. USDA - biologics

The Center for Veterinary Biologics (CVB), a division of the United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), may issue a conditional product licensure that can be used for ATA and biologics to meet emergency conditions, or for a limited market or local or special circumstances. This licensure allows sponsors to submit fewer requirements for proof of efficacy (“reasonable expectation”), but otherwise, a product must meet all licensing requirements for full licensure. Upon collection and acceptance of efficacy and potency test studies, full licensure is granted. In addition, the CVB has evaluated various methodologies to facilitate a more rapid interchange of vaccine strains and genetic sequences in licensed products to meet new challenges.

4. China

4.1. China institute for veterinary drug control

In China, farmers often use herbal medicines as ATA, especially because of their extensive and historical use in traditional Chinese medicine. Even though traditional medicine has been used for thousands of years in China, herbal medicines must be fully characterized and undergo an evaluation for safety, efficacy, and quality to be authorised as veterinary medicines. They must also be reviewed for their