Investment in New Veterinary Antibiotics: Barriers, Consequences and Solutions

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Introduction

Three problematic global trends have become apparent. The first is the persistence of bacterial diseases - like swine dysentery or bovine respiratory disease associated with multiple drug-resistant pathogens. The second trend is the challenge of producing enough safe food, especially animal-derived protein, to meet rapidly-growing consumer demand, whilst also maintaining animal welfare standards. The third is antibiotic resistance, which has become one of the major challenges facing human health. In human medicine a range of different bacterial infections have become difficult or impossible to treat, but there are also early signs that problems with antibiotic resistance are arising in veterinary medicine.

One solution that could help address these challenges is the development and application of new antibiotic products for animals that do not easily select for resistance to human-use antibiotics. Yet despite the growing and pressing need for such products, investment in new veterinary antibiotic R&D, like that in human health pharmaceutical company antibiotic R&D, has been decreasing for years. This has resulted in a continuing decrease in the number of new antibiotics entering the market.

Why is there such a gap between the growing demand for these new veterinary antibiotic products, and the disinclination of animal health companies to supply them? This article explains the seven main barriers that prevent or slow development and coming-to-market of novel veterinary antibiotics, and the six negative consequences of this diminishing investment. It also offers solutions to address these barriers.

Barriers to Stimulating Investment in Innovative Veterinary Antibiotics

Barrier 1: Discovery of unique compounds not for human application. Like all companies, animal health companies carefully weigh their investments in new product development. Most new antibiotic compounds come from human discovery and the greatest challenge is to discover unique compounds that do not (or are unlikely to) have future human applications. Discovery and development is expensive, complex and time-consuming, running at least 10 years from discovery to commercialisation. To make such a major investment, companies need a stable and predictable market. The increasing uncertainty of whether market access will be possible in 10 years' time is a serious inhibitor. The decision to advance any given product is based on a careful weighing of the likelihood of technical, regulatory and commercial success. Only a few out of tens of thousands of product candidates make it to the market.

Barrier 2: Changing regulatory requirements. Of the many disincentives for investment, the constantly-changing regulatory requirements create uncertainty. In some markets, political and unscientific reasons are used to justify lack of regulatory progress. It is important to know that analogues of existing antibiotic classes – products modified in some way to achieve a marketing differentiation – have been the most productive and commercially successful pathway for bringing new products to market over the past 10 years. Those products for which society has the greatest need from a public health and food safety perspective – novel, non-human antibiotics – are the riskiest commercial prospects; in large part because they face the most changing regulatory requirements. It is this type of new antibiotic which offers the greatest potential to overcome the three trends mentioned above.

Barrier 3: More challenging requirements than human health. Antibiotics in food animal veterinary medicine have to meet more challenging requirements than those for human use. The basic requirements for manufacturing quality, safety and effectiveness are similar for both sectors, but veterinary antibiotics also have to be affordable for users, unlike those for human use, which are typically covered by government or private health insurance. Veterinary antibiotics get similar patent protection to human antibiotics, but in addition they:

- must offer a return on investment in a much smaller market,
- be differentiated from existing generic products,
- not be on a potential list of antibiotic classes reserved for human-only use,
- need to have international food/consumer safety standards set (Codex Alimentarus),
- face constraints imposed by societal factors like organic food preference.

Barrier 4: Time to recoup investment shortening. It is more and more difficult to make the business case for funding R&D in new antibiotics. A patent lasts 20 years and it takes at least 10 years before launch and sales even start. So most of the R&D investment – US $100 million or more – and a profit to fund ongoing and future research, must to be made in the remaining 10-year period. From a business perspective, companies therefore have to sell as much as they can in those 10 years to have commercial success. This has a perverse effect: instead of using new antibiotics "as little as possible, but as much as necessary" – the definition of responsible use the animal health industry supports – it promotes use of the new antibiotic over a short period to capture market share. Thus, the relatively short period of patent life and

data protection means the financial incentive to invest is diminished.

Barrier 5: Competition for R&D funding. Within companies there is increasing competition for R&D funding for the development of non-antibiotic animal health products – like vaccines, parasiticides, internal medicines, productivity enhancers or immune system enhancers. Investments in these areas can often be comparatively commercially more attractive. Without doubt there is, and will continue to be, demand for new veterinary antibiotics to more effectively treat diseases, but more attractive investment areas make it even more important to have a high probability of technical, regulatory and commercial success.

Barrier 6: Political disincentives. There are political activities that make investment in veterinary antibiotics less attractive. A threat to investment in new antibiotics development is that in some markets, food animal use of antibiotics is becoming greatly restricted. Some organisations have recommended that new antibiotics should be held in reserve to be used only in cases where first- or second-line treatment options have failed. This disincentive makes the development of new products commercially unattractive. Novel animal antibiotic discovery and development is difficult, especially given that the human need for new molecules might "take" the animal-intended molecules for medical applications; though this could be commercially beneficial if out-licensed.

Barrier 7: Changing markets disfavour investment in traditional areas. Only economically significant diseases offer a sufficient return on investment. That means that the US and EU markets – currently about 66% of the global market – essentially drive R&D product decision-making. But this is changing as countries like China and Brazil and others become larger players. There is data which suggests that in 10 years' time, the Latin American and Asian markets may be as large as the EU animal health market, with only the US being larger. As a result, future investment evaluations will likely have a different economic calculation and future products may be designed primarily for non-EU or US markets.

Negative Consequences of Diminishing Investment

Unlike human medicine – where new antibiotics are desperately needed – there is currently not yet a major therapeutic crisis in veterinary medicine. But there is evidence that this is changing, and judging from what happened on the human side, this situation will get worse. Contrary to the experiences on the human side, existing and generic products are in many cases, but not all, still effective and available. So new, usually more expensive, products have a difficult time competing. This will change – if there is insufficient investment in new antibiotic R&D today, there will not be new products in the future when we need them.

Consequence 1: Fewer large companies and new products. Given the 10 years or more needed to identify, evaluate, and perform registration studies and regulatory review of data for new antibiotics, only major animal health companies have sufficient funds to invest in this area. With fewer companies able to generate new antibiotics, there will be fewer new products entering the market.

Consequence 2: Increases in approval times. Industry consolidation means fewer experts are retained in those companies, contract research laboratories and even regulatory agencies. As seen in human pharmaceutical development, this has led to increases in approval times because new drug developers have very few mentors to guide them.

Consequence 3: Coordination with human medicines. It is currently an opportunity cost to the animal health industry to not fully participate in new human antibiotic development and funding initiatives. Many novel antibiotics tested for human use may not be suitable for development but, as they have in the past, be appropriate for animal disease applications. Looking through the One Health lens, new antibiotics for animal health will contribute to human health and food safety. Without better collaboration and partnership, fewer new veterinary antibiotics will be developed.

Consequence 4: Shifting R&D focus leading to therapeutic gaps. The focus of R&D in food animals will shift towards poultry and pigs and perhaps aquaculture, as consumers in developing countries increasingly demand meat from those species. This may result in therapeutic gaps in other species.

Consequence 5: Resurgence of certain disease. Political or other constraints on the use of antibiotics for prevention of disease will further weaken the veterinarians' ability to ensure healthy animals enter the food chain. This may result in certain diseases becoming resurgent because they cannot be treated – a severe impact on the agricultural sector. Examples are beef cattle liver abscesses, certain toxigenic bacterial diseases in poultry and swine, or dysentery in swine. In some circumstances, antibiotic-resistant animal pathogens which are multi-drug-resistant are emerging and there may be only one effective product remaining.

Consequence 6: Increased use of some antibiotics. In the case of non-development of new antibiotics, the possible lack of authorised and effective drugs for treatment of diseases in animals will lead to over-reliance on the use of specific groups of antibiotics, which can cause increased pressure on the emergence of resistant bacteria strains to those antibiotics.

Solutions: What Political Leaders Should Do

Action 1: Predictable regulatory processes. First and most important is that leaders state their support

for a stable, predictable regulatory process to allow investment in innovation to proceed without concerns about the "goalposts" being shifted. Examples of shifts are: listings of restricted antibiotic classes which have expanded over time, and narrow label indications which may unnecessarily limit use of new products and feed antibiotic constraints that are not practical. Leaders should encourage regulatory agencies to be innovative when it comes to new molecules that may not fit current guidelines.

Action 2: Support new veterinary antibiotics. Leaders need to signal their support for the commercialisation of new veterinary antibiotics (which minimise impact on human health) by indicating that they would very likely be considered a first-line treatment – thus encouraging veterinarians to preferentially use these antibiotics rather than older, cheaper antibiotics with a greater impact on human health.

Action 3: Encourage new antibiotics R&D. Leaders need to encourage the development of new antibiotics to prevent and treat diseases, as well as diagnostic tools to guide their appropriate use. There are creative approaches being undertaken or being considered to do this: public investment, public-private partnerships, de-linkage (disconnecting the costs of development from product sales), financial prizes for successful development of new medicines, and different incentive structures. The difference between the human and animal health markets is important to consider. A recent report suggested that a US$ 1 billion prize would be sufficient for a human health company to develop a new antibiotic. In reality, this would need to be closer to US$ 3-5 billion to have a motivational effect. But in the animal health market, a US$ 50 million prize would likely stimulate investment. Whichever approach is used, none will be successful unless it addresses the basic need for predictability in the regulatory process.

Action 4: Extend protection. Leaders need to consider extending the period of intellectual property (data) protection for new products developed to allow a longer duration of sales to recoup and reinvest revenue in R&D.

Action 5: Support antibiotic action plans. Leaders can emphasise the contribution to food security and food safety objectives achieved by responsible use all along the food chain. For example, they should show support and fund national or regional antibiotic action plans, particularly responsible antibiotic use programmes on farms to ensure that product are used appropriately. This includes also resistance monitoring programmes based on harmonised testing methodology to identify first-preference antibiotics for treatment purposes.

Action 6: Strengthen food hygiene practices. Leaders need to provide support to improve and strengthen abattoir food hygiene practices to minimise all food-borne bacteria, not just the resistant subset; as well as consumer education campaigns about correct storage and cooking. The food chain has multiple stages, each of which can have appropriate interventions that cumulatively contribute to food safety and public health.

Conclusions

Despite the growing and pressing need for new veterinary-use antibiotics, there is a decreasing trend of new products entering the market. The reasons include the increasingly complex requirements for regulatory approval, increasing internal competition for R&D funds from non-antibiotic animal health products, and political activities that create uncertainty and make investment less attractive.

The result is a gap between the growing demand for novel antibiotics and their likely future supply. As a consequence, the external environment needs to change to help companies support a re-focus of R&D towards veterinary antibiotics. Without this change in direction, important animal diseases may become resurgent because they can no longer be adequately treated, leading to animal welfare issues with a negative impact on sustainability of animal agriculture and food production.

Solutions require stronger political leadership to support predictable regulatory processes so that private investment in antibiotic innovations is not stopped or slowed, as it is now. Leaders need to encourage the development of new antibiotics using an array of different incentives. Relatively small investments in the animal health market could produce significant results, when compared to the finances required in the human health market to incentivise R&D companies.

There are great opportunities in the animal health world to address the need for an increased and sustainable food supply, the public health and food production challenges posed by old and new animal diseases, and emerging antibiotic resistance. Solutions require strategic and coordinated government and private sector action.

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