IFAH-Europe
Impact Assessment
Data Package

Review of the European legislation governing veterinary medicinal products

2010

IFAH-Europe Impact Assessment Data Package

Preface

The purpose of this data package

The European Policy Evaluation Consortium (EPEC) has been commissioned by DG SANCO of the European Commission to assist with the preparation of an impact assessment on proposed revisions to EU legislation on veterinary pharmaceutical products[1]. EPEC is a consortium of 3 companies; the company managing this project is GHK[2] (www.ghkint.com).

In a first activity report to DG SANCO, GHK identified the data gaps that would need to be filled through consultations with stakeholders and experts. The data to be collected was identified in 12 data-sets.

To assist in this exercise, IFAH-Europe has assembled background data, explanations and its opinions on all sections of the data-sets that are relevant to the animal health industry. This data-package is structured in 12 chapters to match the 12 data-sets identified by GHK. An introduction has been included to provide essential background to the animal health industry and the objectives of IFAH-Europe.

The principal contribution of IFAH-Europe towards an assessment of the information obligations and administrative burden associated with the regulatory processes for veterinary medicinal products in Europe can be found in chapter 8.

The purpose of this data package is to provide GHK with supplementary background information and data felt relevant for the impact assessment. This is intended to be complementary to the work of GHK, who are consulting a selection of stakeholders, including individual animal health businesses, in order to measure the administrative burdens imposed by the legislation as it currently stands.

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[1] Directive 2001/82/EC, as amended by Directive 2004/28/EC, and Regulation (EC) No 726/2004

[2] GHK is an independent, international, employee owned private company with offices in UK, Belgium, North America, Hong Kong and Asia.

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Executive Summary

- The purpose of this data package is to assist with the preparation of an impact assessment that precedes the review of the EU legislation concerning veterinary pharmaceutical products. Case studies are provided to support the statements and conclusions made.
- The Animal Health Industry is a relatively small, high-tech sector, but it makes a disproportionately large socio-economic contribution to the EU and its citizens. People depend on animals as a major source of safe, affordable food and for companionship, support and assistance as well as many important leisure activities.
- The objectives of IFAH-Europe are to stimulate investment and innovation, to create a true single market for ALL veterinary medicines via an efficient and simplified regulatory system, and to reduce time and cost to market for new products.
- IFAH-Europe is seeking a regulatory framework that is more proportionate to the needs of animals and those responsible for their care. The veterinary sector is different from the human medicines sector, and requires separate legislation (while maintaining synergies with the human medicines legislation where appropriate).
- IFAH-Europe supports the statement *"The veterinary system needs its own specific organisation and regulation and no longer being a mirror legislation of the human legislation"* given in the Ernst & Young report on the evaluation of the European Medicines Agency (January 2010).
- The previous review of the legislation, culminating in 2004, created an improved regulatory environment for generic products, but decreased the overall data protection available for innovation. It also created an “un-level playing field”.
- The EU marketing authorisation procedures are complex and should be simplified, for example to a single procedure.
- The cost and time needed for new product development in Europe has significantly increased over recent decades. It is becoming increasingly difficult to obtain a reasonable return on ever-increasing-levels of investment in face of decreased data protection. Improved data protection is required to stimulate more investment in research and development in Europe, including significant investments into product maintenance.
- The number of animal health companies is contracting with an on-going series of company mergers. Global synergies are increasingly important.
- As a consequence of the latter three points, the number of new marketing authorisations for new products is declining, while the number of new marketing authorisations for “me-too” products has increased significantly. This means less new technology available for farmers, vets and companion animal owners.
- The right balance needs to be found between (a) providing sufficient incentive and return for originator companies to invest and develop new technologies for the veterinary market and (b) removing unnecessary hindrance to generic companies.
- The cost of product development inhibits the availability of a broad range of veterinary medicinal products (VMPs); a problematic situation exists already for some major species, such as sheep, horses, poultry, but is particularly evident for minor species, minor uses and in minor markets; off-label use is therefore common-place.
- The insufficient availability of VMPs presents risks to animal health and welfare from existing diseases (e.g. Blackhead disease in turkeys) and from emerging diseases, including those becoming established in Europe as a consequence of human

movement, animal and animal product movement and possibly climate change (e.g. Blue Tongue).

- The insufficient availability of VMPs presents risks to human health; the 'One World One Health' concept acknowledges the close link between animal disease and public health; many diseases are zoonotic; healthy food comes from healthy animals; healthy pets bring many benefits to human well-being.
- Consequently the use of VMPs can be highly effective in reducing disease in animals (increases agricultural efficiency) and in man (wildlife and dog vaccination programmes against rabies, poultry vaccination against salmonella have both been highly successful).
- The costs and administrative burden associated with the marketing authorisation (MA) procedures are presented, and the impact on reducing those costs through a (fully harmonised) single MA procedure is illustrated. Highly significant savings could be obtained (20 - 60%) for both the industry and the competent authorities.
- The costs associated with product packaging operations are examined in a series of case studies, and the significant reduction of those costs achievable with the use of multi-lingual packaging is shown.
- The costs and administrative burden associated with pharmacovigilance procedures are analysed in detail, and the positive impact of rationalisation is illustrated.
- The administrative burden created by additional national requirements, impacting business efficiencies and public and animal health, is illustrated with a case study.
- The final step in the marketing authorisation procedure is the administrative step to issue the marketing authorisation. Delays in this step at national level create a high cost to industry from delayed sales, missed 'seasons' and disrupted business plans. In 9 case studies it is shown that an average of 20% of annual sales was lost from potential revenue in year 1.
- A comparison is made between the EU position and third countries; the time and cost of product development has increased significantly more in Europe than in the USA. In particular a greater proportion of R&D funds are diverted into "defensive research" in the EU to maintain the products on the EU market.
- The European Medicines Regulatory Network is considering ways to address the compelling issue of resources; approaches to removing inefficiencies and duplication of work are being examined. A simplified regulatory environment would bring efficiencies and remove duplication. A single scientific assessment of a single European marketing authorisation dossier would remove disharmony and duplication of work. A single marketing authorisation across Europe would enhance the availability of VMPs in smaller markets and would promote innovation.

Introduction

The value of the animal health industry to society

A HEALTHY COMMUNITY DEPENDS ON HEALTHY ANIMALS

The citizens of the European Union depend on animals as a major source of supply for their food (eggs, milk products, meat and honey) and for companionship, support and assistance as well as many important leisure activities.

The animals in this relationship are dependent on human care. The provision of food, water, healthy living conditions and, when needed, medicines to both treat and prevent illness keeps them healthy, ensures their welfare and, in turn, contributes significantly to public health. The concept of One World One Health recognises this and signifies the convergence of human and animal health and their interdependency.

Over sixty percent of human diseases are zoonotic in nature (i.e. are acquired from animals), so that without animal medicines, Europeans would be at a far greater risk from such illnesses. These include serious zoonotic diseases including both food-borne diseases such as salmonella and campylobacter infections and also transmitted diseases such as rabies and avian influenza. Furthermore, because food products from sick animals cannot be sold for human consumption, without healthy livestock food products derived from animals would become scarcer and therefore more expensive, while farming would become less sustainable and would require far greater land areas to deliver the same quantity of food. These developments coupled with the prediction that the global demand for animal protein is expected to double by 2050, requires ever more effective control of animal diseases, underpinned by the need for a positive environment for investment and innovation in the development of new veterinary medicines and support for those already authorised.

The impact would be greater in developing countries, with a risk that EU and USA food safety standards could not be met and that many diseases could no longer be controlled.

The benefits of animal medicines to the companion animal and leisure sector are almost incalculable: the reduction in animal suffering being assured by the safety of close contact with pets and equidae, and the opening up of the cross-border travel of animals through health protection programmes are prime examples.

Just 3% of all global pharmaceutical sales are for animals, yet this tiny segment directly supports 50,000 jobs in Europe and contributes to the viability of Europe's 9 million farmers, the continued health, happiness and wellbeing of European citizens and their families and the development of extensive leisure industries. The development and authorisation of veterinary medicines is science-driven and are highly regulated like human medicines, which means animal medicines, including vaccines, deliver quality, safety and efficacy of the highest standards. However, unlike human medicines, the animal health industry does not benefit from the security of member state reimbursement schemes and yet invests €400 million annually in research and development to develop new products and retain and upgrade existing ones.

The animal health industry punches well above its weight in its importance to the health and welfare of Europe's people, their animals and its economy.

Global Vision

IFAH-Europe shares the same global vision as many of the regulatory opinion leaders in Europe, as expressed in the reflection paper published by the Heads of Veterinary Medicines Agencies in June 2009, namely to achieve a legislative system that:

- Will provide the greatest range of effective authorised veterinary medicinal products (VMPs) for use throughout the European Union in each Member State which are safe for the animals being treated, the environment and consumers;
- Will help the realisation of the single market of VMPs in the spirit of the European Single Act, of the Lisbon Agenda and contributing to the European Sustainability Strategy.
- Will fulfil the aims of the European Commission's Better Regulation initiative.

IFAH-Europe Objectives

- To stimulate investment and innovation, specifically via improved data protection.
- To create a true single market for ALL veterinary medicines via an efficient and simplified regulatory system.
- To reduce time and cost to market for new products, which are both seen as the major critical success factors for the industry in Europe.
- To achieve a level playing field – make the regulatory system fair to all applicants.
- To maintain the European Union at the forefront of research and development for innovative veterinary medicines.
- To maximise the availability throughout the EU of a broad range of veterinary medicines for all domestic animal species.

Obstacles to Success

The need to address the following six key factors has been identified as pivotal for achieving the key priorities for industry and for determining any strategy to develop and implement a better regulatory system:

- A lack of differentiation where appropriate between human and veterinary medicines in legislation.
- The complexity of the regulatory system with divergent competences and inconsistencies at national and European level, varying by procedure and leading to administrative burden and inefficiencies.
- Insufficient incentives to investment and innovation, particularly for product line extensions.
- The insufficient degree of member state alignment in implementing legislation and guidelines.
- Specific national requirements adding bureaucratic hurdles.
- The inconsistent alignment towards global harmonisation.

Special characteristics of the veterinary sector

The economic environment

There are four major reasons why the economics of the animal health industry drive it to take up some particular issues of its own:

- The 'patient' may have a defined economic value, which for farmed animals may be relatively low.
- Products derived from the 'patient' may be consumed, and therefore consumer protection is a key feature.
- The market is considerably smaller in size and value than the human medicines sector, and is very fragmented (e.g. by species).

- The entire cost of animal medicines has to be borne by the owner, with no state reimbursement scheme.

As a consequence, the cost implications and impact of legislation in this sector are a very real issue and require very careful reflection. In Europe in the last 15 years the length of the development time and costs for food animal products have increased by 6 years and 160% respectively. A failure in the past by regulators to fully appreciate this situation has contributed to the current problems concerning the availability of a full range of veterinary medicinal products, because of escalating requirements and regulatory costs arising from the European procedures. There is no disputing the legitimate needs of regulators to ensure the safety of such veterinary medicinal products. However zero risk is just not achievable and there is equally risk from not having adequate veterinary medicines available. The correct balance in benefit:risk must be attained. The current situation suggests that for many potential products that balance is far from being achieved.

To meet this goal IFAH-Europe is seeking a regulatory framework that is more proportionate to the needs of animals and those responsible for their care (i.e. with an *appropriate* level of regulatory demands firmly rooted in scientifically based risk assessment principles that will permit a sufficient range of essential and affordable veterinary medicinal products to be maintained on the market). The special characteristics of the animal health sector which justify this urgent need to review the regulatory framework are presented in the following section.

Profiling veterinary medicines (versus human medicines)

The heart of the problem lies in the tendency to impose rules developed for human pharmaceuticals on veterinary medicines, without proper consideration of:

- The very different requirements of human and animal medicines and the conditions under which they are used;
- The contrast between the resources available to the two industries, and the financial implications of regulatory requirements on individual sectors.
- The regulatory burden on VMPs is at its most extreme where products for food animals are concerned. Tests on these medicines must not only confirm their safety, quality and efficacy, but must also rule out the possibility that residues from their use will present risks to the environment or consumer of foods derived from the treated animals. The regulatory environment for antibiotics for veterinary use is particularly severe. Antibiotics developed for veterinary use must undergo additional testing to ensure that their use will not contribute to resistance development in man.

No matter how the two sectors are measured, comparisons between the human and veterinary pharmaceutical industries illustrate disparities on a huge scale (see box 1).

Box 1: Contrasting resources (data from 2007)

- While global sales of a leading cholesterol reducer for man total almost US$13 billion a year, annual revenues generated by one of the largest selling parasite control products for dogs are equivalent to less than one-tenth of that figure.
- The global market for human medicines is worth 40-times more than the veterinary market;
- Sales generated by the world's leading human pharmaceutical company are 20-times higher than those of the biggest veterinary products business;
- There is a 30-fold difference between the research spending capacity of the market leaders in the two sectors;
- The top-ranked human pharmaceutical company employs more research scientists than the world's 20 leading animal health businesses put together.

Figure 1: Global market value - 2007

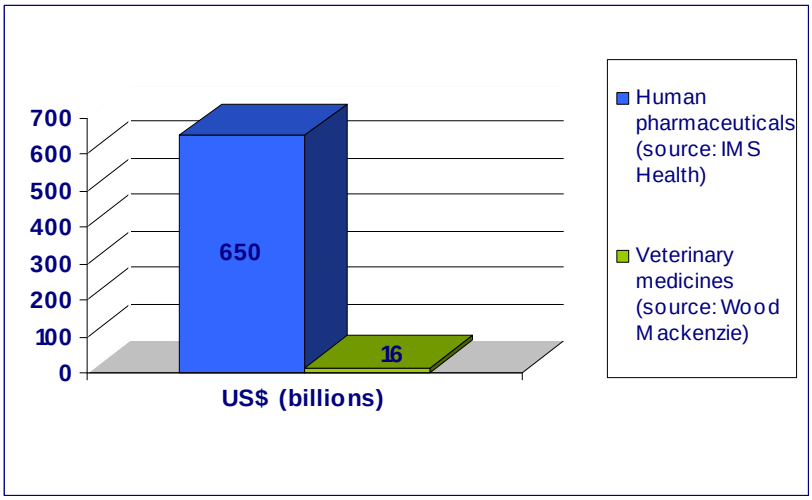
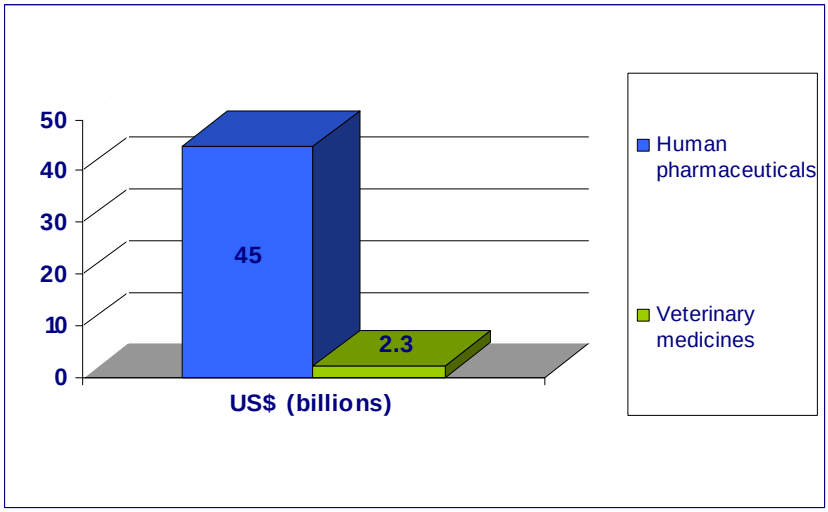


Figure 2: Global sales of leading company - 2007

(Source: Pfizer)



IFAH-Europe welcomes therefore the acknowledgement by the authorities that a radical re-assessment of the legislation for authorising veterinary medicines in the EU is urgently needed to facilitate the improved provision of these products to improve animal health and welfare.

Special Characteristics - The financial impact of over-regulation…

The failure in the past to acknowledge the major differences between human and veterinary medicines has driven up both the costs involved in the development of new animal health products and the time it takes to bring them to market. The disadvantage this places on the European industry in comparison to that in the USA is illustrated in Figures 3 and 4 overleaf.

Figure 3: Impact of regulatory factors on the average cost of developing a new product

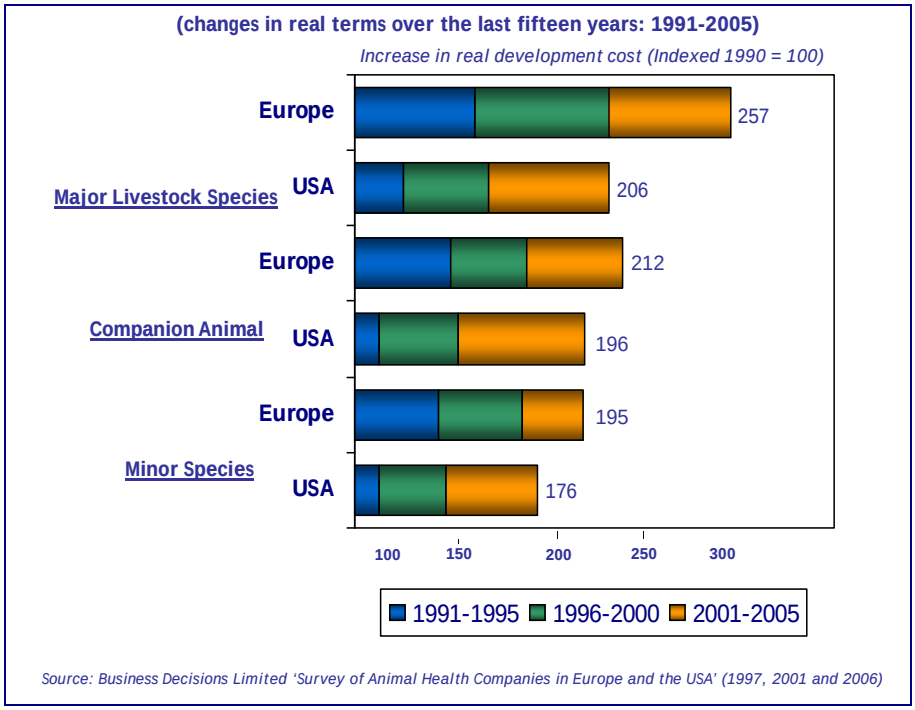
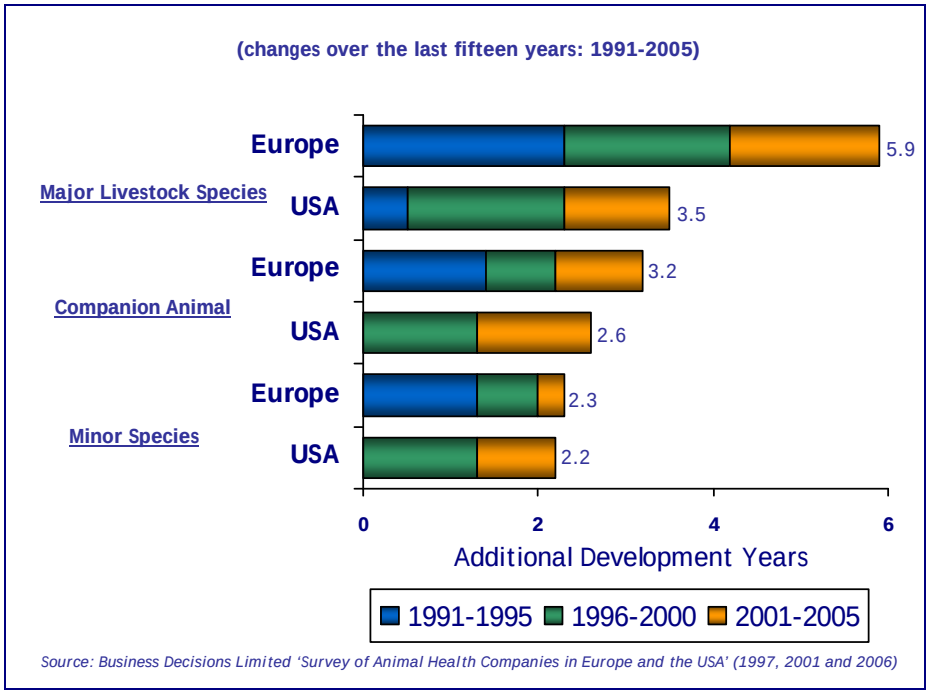


Figure 4: Impact of regulatory factors on the length of time to develop a new product



In conclusion therefore adapting legislation drawn up for human pharmaceuticals to obtain a 'best fit' for the veterinary sector is not a suitable option. Instead, those charged with drafting new regulations must consider from scratch exactly what measures are needed for the control of veterinary products, and how these measures can be tailored to the unique benefit:risk profiles of the veterinary sector.

In doing so, they must take account not only of the resources available to the animal health industry, but also the needs of animals, their owners and the veterinary profession. Scientifically sound, risk-based safety assessments should provide the platform on which regulatory requirements are based.

Chapter 1:

Total number of products with Marketing Authorisations on national markets

1.1 Timing Intervals for Analysis of Numbers of Products

IFAH-Europe notes the proposal in table 3.2 of the EPEC First Activity report to record how the number of products with authorisations on national markets changes annually and wishes to reiterate its concern previously expressed to GHK that such an analysis on an annual basis would be inappropriate, misleading and will fail to provide the relevant information to enable a successful impact analysis on the matters under review. Trends in the numbers of veterinary medicinal products available in member states will not become evident when evaluated over a short timescale as proposed on an annual basis. The greatest impact on the number of products is linked to major changes in the regulatory environment, such as:

- Major changes in the legislation which have inevitably led to increased regulatory standards and testing requirements resulting in many existing products being removed from the market as it is often not economically feasible to upgrade their registration dossiers (1981 Approximation of the laws, 1990 MRL legislation, 1993 EMEA and Centralised Procedure, 2004 new registration procedures).
- Such changes are also proving a disincentive to new product development because of the significant increase in financial resources needed to satisfy the new regulatory requirements.
- National reviews of all product licences in member states to comply with harmonised requirements in the 1981 legislation, took over 3 decades on an almost continuous basis as the members states undertook these reviews in different years. As each subsequent review often required studies done to the latest guidelines, which are continually evolving, data often had to be generated for each national review. Thus products have almost had to be continually redeveloped in Europe since the introduction of the first European legislation in 1981.

1.2 Importance of Product Classification

IFAH-Europe also wishes to point to an important omission in the proposed data sets in the EPEC Activity Report that needs to be addressed. Failure to analyse the data according to the therapeutic class of medicinal products will result in misleading conclusions. All the evidence suggests that the availability gap in the supply of medicines is more acute for certain therapeutic classes of products (e.g. antibiotics or anthelmintics) for certain diseases and for certain classes in certain species (e.g. coccidiostats in turkeys); but not all classes and species. For any impact analysis on possible changes required to the legislative framework to be meaningful the data on number of products must be analysed according to the types of product and the indications in the various target species for which they are approved.

Chapter 2:

Prices of veterinary medicinal products

This is a very complex issue and a great deal of care will be needed in interpreting any data.

Chapter 3:

New marketing authorisations granted - as a measure of innovation

3.1 Introduction

In the animal health sector the most important driver of long term competitiveness and business success is innovation, specifically the development of new medicinal products and it appears that companies believe the regulatory framework can be the biggest obstacle to effective innovation in Europe. In this chapter IFAH-Europe justifies the need for regulatory reform by providing data from the main regulatory systems operating in the European Union which confirm that the numbers of new innovative medicines coming to the market are few in number. In addition the new data protection provisions of the current legal framework have proven to be a disincentive to the research based companies. The impact this has on innovation and investment is explained in detail (and is further elaborated in chapter 4 box 2).

3.2 The Impact in the field

The very real concerns about the lack of innovation in the industry in Europe is best illustrated in the following quote by a senior executive of a global animal health company which is an IFAH-Europe member.

"Most animal health research based companies see real opportunities for innovation - either with regards to new indications, new species, or new chemical entities. Often however it is difficult to make the business case for the investment and to secure the funds for many reasons: the very tight margins farmers are living with have an impact on the pricing of medicines; the lack of data protection for the innovative new medicines; the scale of the investment required to get through the regulatory process and the scale of investment relative to the market opportunity often does not fit."

New Market Authorisations: - How Many?

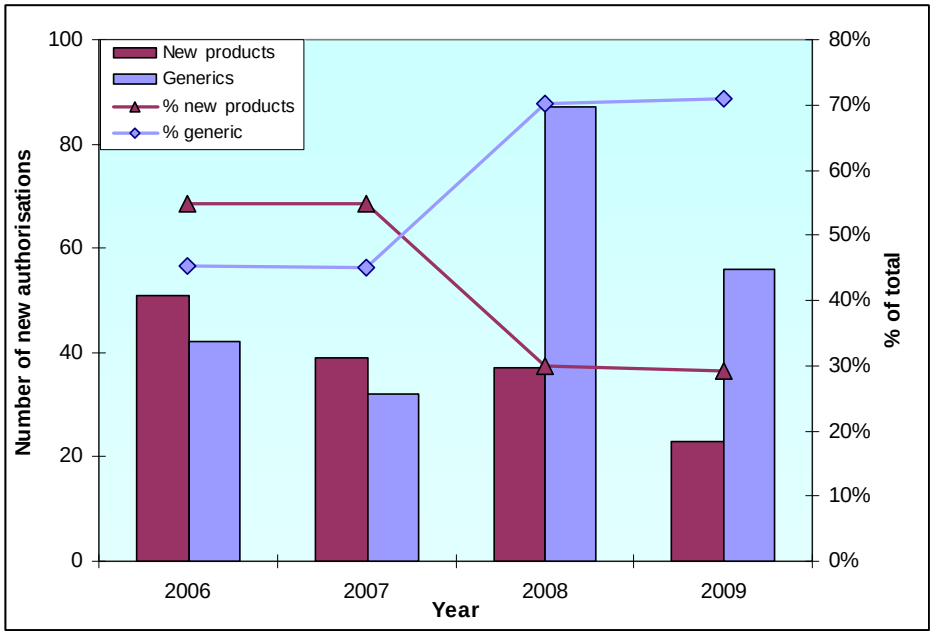
The number of applications submitted through the two main regulatory channels in the EU (the decentralised and the centralised procedures) provides a detailed insight into the numbers of new authorisations being granted, and is an indicator of the level of innovation in Europe.

Firstly the information presented in the surveys published by HMA(v)[3] provide valuable information on the trends in the numbers of products being licensed by the member states through Mutual Recognition (MRP) and the Decentralised Procedures (DCP[4]).

The recent surveys illustrate well the decline in the numbers of new products being licensed and the simultaneous large growth in generic products. In the MRP and DCP (combined) the number of applications for new products (article 12, "full" dossiers) fell from 51 in 2006 to 23 in 2009. However the picture was very different for generic applications (article 13, "generic" dossiers); the number submitted to the MRP and DCP increased from 45% of full+generic applications in 2006 to 71% in 2009 (see Figure 5).

[3] http://www.hma.eu/169.html
[4] The DCP was introduced in 2006 following changes to the legislation adopted in 2004.

Figure 5: Product profiles in the MRP and DCP



New Market Authorisations: - How Innovative?

When introduced in 1995 the centralised procedure for authorisation of medicines was intended to encourage the development of new and innovative medicines with the reward that an authorisation by this route would provide a pan-European marketing authorisation in one step. Conditions were imposed to restrict applications for this procedure to new actives, innovative products or those derived from biotechnology. Therefore statistics from the centralised procedure at the European Medicines Agency (EMA) provide a useful indication of the level of innovation in Europe.

The annual number of applications for new products through the centralised procedure has been steady but there are no signs of any significant growth over the past 5 years where reports are available. The 2008 EMA Annual Report states that whilst there were 13 applications, 3 of these were for generic products and the others included a “surge of applications for Bluetongue vaccines” in light of the spread of this disease in Europe.

These data should also be considered alongside those from the Annual Reports of the EMA for new applications to establish Maximum Residue Limits (MRLs) for medicinal products intended for food animals. Between 2005 and 2008 the number of applications to set new MRLs has been disappointingly low (2005:3, 2006:3, 2007:2, 2008:1), and also reflects the lack of investment in food animal product development.

Conclusions

The data above would strongly suggest that the current regulatory environment for veterinary medicines in the EU favours generic medicines but does not provide sufficient incentives for innovative research and development and the licensing of new medicines.

The European legislative and regulatory framework has continually evolved in the last 20 to 30 years; the most recent changes in 2004 have provided a more positive environment for the authorisation of generic medicines, but has effectively reduced the overall levels of data protection for the reference products. This is particularly the case for line extensions for additional species, for which the additional period of data

protection is now only one year (except for medicines for bees and fish which have a separate data protection period).

3.3 Why are there so few new and innovative medicinal products?

The key driver for private sector investment in veterinary medicinal product development is return on investment (ROI). The vast majority of the R&D spending is from private organisations, with limited public support for the development of new products. Therefore the R&D costs have to be earned back through sales.

This paper cannot go into the detail of the ROI decision of companies, but we will outline here the key elements where the current regulatory environment has an impact on the decision whether or not to develop new products.

Many elements influence this decision, including among others:

1. High cost of data versus the small market size (see chapter 8)
2. Lack of incentive to invest with insufficient data protection (see chapter 3)
3. Lack of private-public partnerships (see ETPGAH[5])
4. Packaging costs for the European market (see chapter 8).

The structure of these chapters follows the list of data-sets proposed by GHK. As there is not a specific chapter on innovation in the series of data-sets we will present our views on data protection in more detail here, as it is closely linked to the topic of new marketing authorisations.

3.4 Impact of current data protection provisions on innovation

The present veterinary legislation is linked to the human legislation – both pieces of legislation were considered together in the same legislative package when last reviewed in 2001-2004. Whilst the data protection (DP) provisions may be suitable for human medicine, they are unsuitable for veterinary medicine. There are two fundamental differences between the two sectors: firstly it is harder to obtain a return on investment within an acceptable period in the veterinary sector, making data protection even more critical. Secondly, in animal health there is more than 1 species, creating a fragmented market and necessitating major investments in line extensions to include other species. However the legislation was designed with just 1 species in mind – human beings.

Significantly there is no DP for extending the use of the product to companion animals, or for adding a new route of administration (i.e. a new pharmaceutical form).

(a) Current data protection provisions in the legislation

Data protection (DP) for veterinary medicinal products is defined by articles 5 and 13 of Directive 2004/28/EC.

The provisions are as follows:

[5] European Technology Platform for Global Animal Health; see http://www.ifaheurope.org/ then select 'ETPGAH'

- **10 years protection** is granted to the first use of a new veterinary medicine (this is the "first therapeutic indication" in the "first species").
  - This protection is in the form of 8 years data protection plus 2 years market protection (i.e. "8+2": a generic can refer to another company's data after 8 years, but cannot place their product on the market until year 10).
- **An additional data protection period of 1 year** may be granted for each additional *food producing species* added to the product up to a maximum of +3 years (i.e. 10+1+1+1 years) provided the additional licences are granted within the first 5 years of the life of the product.
  - Thus there is potential to obtain 13 years data protection from the date of the first product authorisation, provided the company has developed the product for 4 food producing species (with at least 3 *food producing* species within 5 years).
- **Other provisions**: 13 years data protection is granted for medicines for fish or bees; 3 years data protection is granted to new residue or clinical data generated by an applicant to obtain approval in a further food-producing species for an existing substance for which the data protection period has ended.

(b) Issues to be resolved

1. **8 years DP is insufficient** for the veterinary medicines market, which is characterised by high investment for small markets and long times to obtain return on investment.
   - The DP period was harmonised in 2004, but it was not increased, even though the cost of product development has doubled over the last decade. Overall DP was decreased, as DP was lost for additional species. For more detail see annex 1.
2. **There is only sufficient DP for the first species. The +1 year is insufficient** to warrant the large investment required to redevelop the product for another food-producing species. Special provisions are needed to for 'minor species'.
   - The investment decision is based on business parameters such a "time to obtain a [defined] return on investment (ROI)". Normally species 1 represents the major investment and the major market. Redeveloping the product for species 2 may be a smaller investment, but species 2 will normally also represent a smaller market. Consequently the time to obtain ROI will be similar, and the data protection period required to allow an appropriate time to ROI will be similar for both species. This is illustrated in Figures 6 and 7 overleaf.
3. There is a **5-year window** within which a company can qualify for the extra +3 years data protection; however this is insufficient to allow the R&D programme to add 3 food-producing species to the product label. In practice, the additional 3 years of DP is very difficult to achieve. The licensing process itself can take 1 to 2 years. For more detail see annex 1.
4. There is no DP for adding a **companion animal** to the product label, nor can the applicant profit from the +3 years for three additional food-producing animals if the molecule has first been developed for companion animals.
5. There is no data protection for data packages (except for environmental risk assessment data) requested by the regulatory authorities post-authorisation (see legal opinion in Annex 2).
6. There is no data protection for new excipients. For more detail see annex 1.

3.5 Conclusion

For research based companies the main factor causing a major disincentive to investment in new product development is the lack of data protection for any innovation (new pharmaceutical dosage forms, additional species) beyond the first product. However the multitude of increased regulatory requirements which have been imposed on the industry in the past 20 years are also a cause of fewer registrations and include additional testing, labeling in an increasing number of languages and pharmacovigilance reporting, all of which will be addressed in more detail later in subsequent chapters.

Figure 6: The similar relationship between investment size and market size for the first and the second species

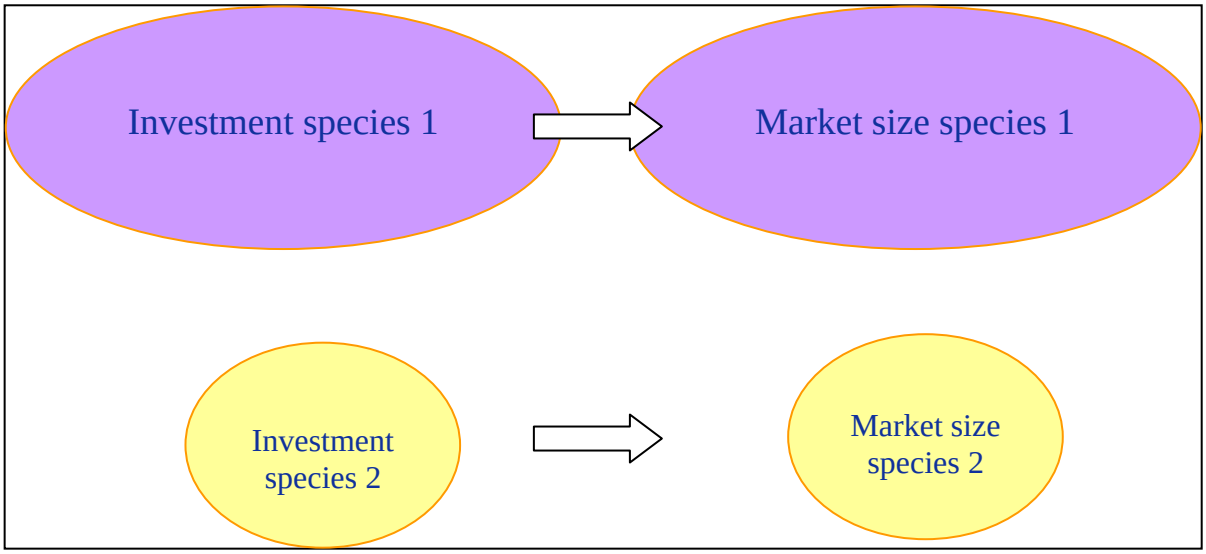
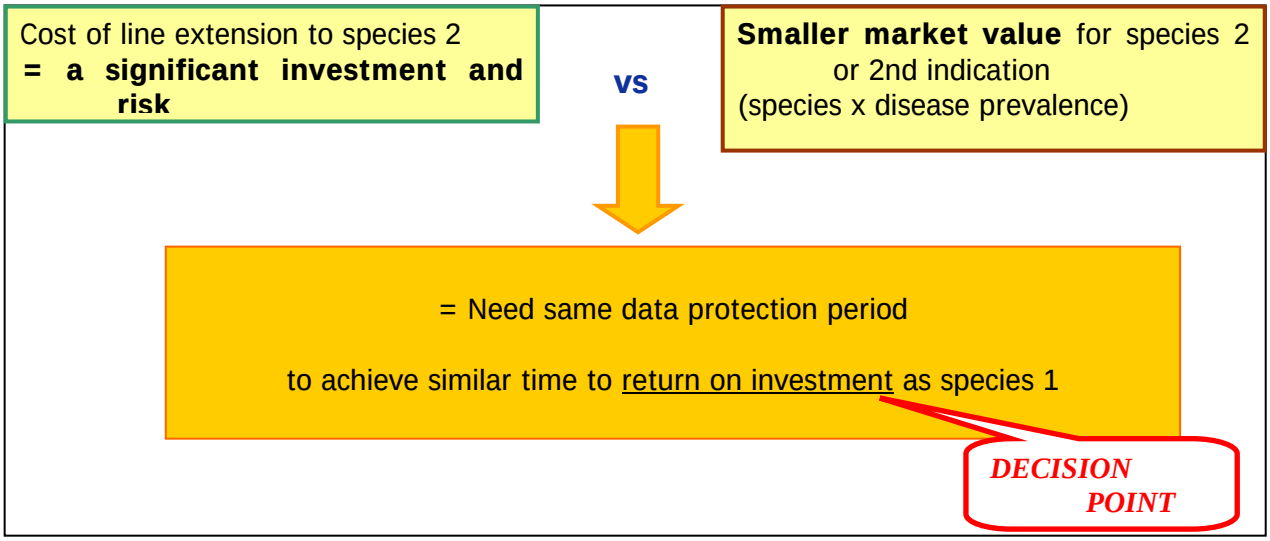


Figure 7: The relationship between investment size and market size and the time to obtain an appropriate return on investment for the second species



Chapter 4:

Profile of the veterinary industry

4.1 Introduction

The Animal Health Industry is a relatively small, high-tech sector, but it makes a disproportionately large socio-economic contribution to the EU and its citizens.

The Animal Health Industry meets the needs of farmers and pet owners for medicinal products that improve the health, welfare, and productivity of animals, whilst at the same time ensuring food safety, supporting viable farming, and helping to preserve the environment and providing for the well being of owners of companion animals. It does this by supplying a comprehensive range of pharmaceuticals, vaccines, and diagnostics developed and produced using traditional technologies and modern biotechnology.

This sector has a substantial socio-economic impact in Europe because:

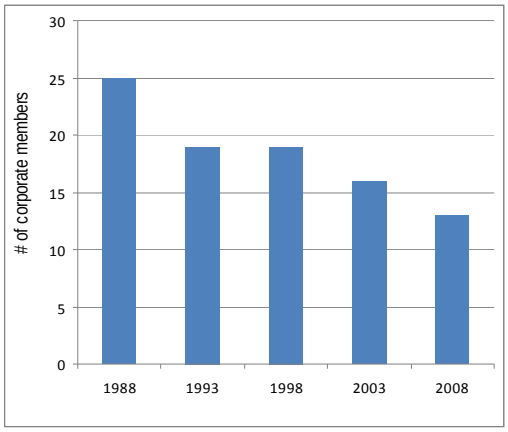
- It helps to protect and improve human health and wellbeing;
- It makes an essential contribution to the provision of safe, high quality food;
- It improves animal health and welfare;
- It contributes to a sustainable and competitive agricultural sector;
- It contributes to overall levels of global trade and plays a part in the economic development of poorer countries;
- It supports high quality jobs; and,
- It contributes to the development of a dynamic European economy based on innovation and knowledge.

4.2 The contraction of the animal health industry

The first 'approximation of the rules' to harmonise the European legislation governing veterinary medicinal products was introduced in 1981. In 1986 the European animal health industry established a separate European industry association. Up to that point it had been a sub-section of the human pharmaceutical industry association.

In 1988 there were 25 member companies; two decades later in 2008 this number had halved to 13 (Figure 8), and the trend towards mergers continues with no end in sight.

Figure 8: FEDESA / IFAH-Europe membership over two decades



The relentless contraction of the animal health industry due to mergers and acquisitions is partly a result of the majority of these companies being owned by larger parent human pharmaceutical enterprises, which are not seeing the return on investment that compels them to continue their interest in maintaining their animal health subsidiaries.

4.3 Generics in the veterinary sector: what are the issues

The provisions to streamline the registration of generic versions of medicines were introduced into the human medicines legislation to reflect the specific drivers inherent in the human medicines market. This is characterised by the need to contain and restrict the growth in the re-imbursement cost for national health schemes.

The Directive governing veterinary medicines was modelled on the human medicines Directive. Consequently the provisions for generics were 'carried over' into the veterinary legislation despite the absence of the primary drivers for this policy. In the veterinary sector there are no national re-imbursement schemes (except in unique circumstances in response to serious animal disease threats). The veterinary market is a 'free' market with open competition and no subsidies (except in specific public health situations), and a large part of the market (the agricultural side – livestock production) is very 'cost-sensitive'.

Farmers operate in a very tight business environment and will not purchase products, nor would veterinarians prescribe them, unless the cost:benefit case is clear. Product pricing in the livestock sector reflects this, extending the potential return-on-investment period and making it very difficult to make the business case for new investments in product development. This must be taken into account when presenting the policy drivers behind regulations aimed at creating a generic veterinary medicines industry.

- A regulatory system that supports innovation and creates competition between different innovative products with the same therapeutic indications is to be encouraged.
- The system should strike a correct balance between the research sector and the generic sector of the animal health industry; however a level playing field for all marketing authorisation holders is critical with the regulatory requirements equally applied to all.
- Price competition may lead to improved availability (increased access), but will also translate into lower revenues for reinvestment into research, and will have an impact on availability of new products long-term.

4.4 High Quality Jobs

Europe, alongside the USA, is one of the world's leading centres for the Animal Health Industry. Half of the leading multinational companies are based in Europe and many US-based companies have established important operations (including research and development - R&D - centres) in Europe. Europe therefore gains significant economic benefits from investments by animal health companies in innovation and in production.

An analysis[6] of the sector reveals that around 50,000 full-time jobs in Europe depend on the Animal Health Industry. This reflects the success of European companies in global terms, and their historic tendency to carry out R&D activities in Europe. Many of the jobs are highly skilled and highly paid, and involve the accumulation and exploitation of knowledge to create globally competitive products.

[6] Benchmarking the competitiveness of the European animal health industry, Business Decisions Limited, December 2006

The industry employs around 15,000 people directly in production, marketing, sales, administration and R&D. A further 19,000 people are employed indirectly as a consequence of the industry's purchases of goods and services, including contract R&D, logistics, capital equipment, and raw materials. Moreover, the industry creates a further 16,000 jobs through its "multiplier effects" (each Euro of expenditure on goods and services by the direct and indirect employees of the industry creates additional employment in other sectors, especially services). Our estimates of employment dependent on the animal health industry exclude the distribution of veterinary medicinal products and livestock farming.

Box 2: Key Characteristics and Facts of the research-based Animal Health Industry

Investment – the research-based animal health companies invest on average 10% of turnover in R&D; a high proportion of this money is spent re-registering existing products ("defensive" research) to meet new requirements and to prevent them from being removed from the market.

Time – development cycles are long, reflecting the nature of the technologies involved, the cost of development and the need for rigorous regulatory approval to protect public health and ensure animal welfare. Major new products take between 8 and 12 years to develop and obtain regulatory approval in the EU. 10-15 years of sales are then needed to recover the investment. Companies place a very high value on minimising time-to-market and on reducing risks of delay or market closure.

Cost[7] – after taking into account project failures, capital costs and the time needed to complete the development cycle, major new products cost between USD 80 million and USD 300 million[8], depending on the target sector and technology used. This sum must be recovered from sales. In view of this, companies seek to minimise time and cost of development.

Intellectual Property – in view of the scale and nature of these investments, they will only take place if protected legally through patents or data protection.

Funding – global multi-national animal health companies are either stand alone, self-funding subsidiaries of pharmaceutical groups or independent specialists. Investment resources for future innovation are provided principally from sales of existing products.

Risk - – by their nature, investments in science are risky. A high proportion of product development projects fail, for a mix of technical, market, and regulatory reasons. Successful projects must recover the costs of those that fail. Companies take active measures to manage all types of risk, including regulatory unpredictability.

Competition – the Animal Health Industry is mature and there is intense competition from major companies in most segments. Technological leadership is, therefore, difficult to achieve and, because of the technical expertise of competitors, is likely to be short-lived. Minimising time-to-market is, in this environment, critical.

Market Fragmentation and Scale – most animal health market segments are small, hence development costs must be minimised and recovered by gaining access to markets globally. Product development economics are, therefore sensitive to unexpected increases in cost and to the closure of major, regional or national markets.

[7] Estimates are based on five archetype product development projects covering major market sectors and technologies.

[8] Figures for the "full resource cost" of product development programmes are given in US dollars (USD), the functional currency of the global animal health industry.

Chapter 5:

Off-label use

5.1 Introduction

The lack of availability of veterinary medicinal products (VMPs) for some minor uses in major species such as cattle and pigs and for minor species such as goats and some species of poultry represents the inability of the current European regulatory framework for veterinary medicines to adequately provide safe authorized veterinary medicinal products for domestic animals throughout the Community.

5.2 The scale of the problem

Despite the repeated endeavours of interested parties to resolve the situation for over 15 years, veterinary professionals do not have the necessary tools to carry out their professional duties to ensure the health and welfare of certain animals in their care.

Veterinarians are forced to routinely use medicines off-label which in some food animals that occupy a major part of the livestock sector in certain countries presents a health risk to consumers. For example in Southern Europe, where goats and rabbits are farmed intensively, medicines are used off-label with the risk of violative residues being present in food derived from such animals.

5.3 Is the Cascade working?

Regulators have introduced the cascade system as a safeguard to protect animal welfare in the absence of a licensed VMP. Under the cascade provisions veterinarians may use products available for other species or for humans if no product is licensed for the animals being treated. However many of the member states apply the provisions of the cascade differently and inconsistently so that the application of the system proves difficult and often impractical; some authorities even discourage its use. So the fact remains that in the European Union the health of large numbers of animals is put at risk because of a shortage of veterinary medicines.

This difficult scenario is compounded by the fact that the use of cheaper human generics provides a disincentive to make the investment needed to develop new VMPs.

- IFAH-Europe supports the implementation of a fully harmonised Cascade across all MSs, but notes that the cascade was originally intended only for exceptional use – yet it has become necessary for vets to revert to the cascade almost routinely.
- The Cascade should not be an alternative to creating a simplified regulatory environment that encourages the development of a full range of needed innovative medicines, appropriately authorised for veterinary uses.
- The 1-1-1 Concept (1 dossier, 1 scientific evaluation, 1 pan-European marketing authorisation for all products – see Annex 3) would allow existing products to be placed on the market throughout the EU, thus improving availability of the range of existing products across MSs and reducing the need for recourse to the Cascade.
- Rules allowing a flexible approach to setting standard withdrawal periods for products used off-label under the cascade should be developed. Such rules should be established at the EU level and be based on scientific considerations.

Chapter 6:

Examples of risks to animal health from insufficient availability of veterinary medicinal products

6.1 Introduction

In this chapter several examples are provided of risks to animal health from insufficient availability of veterinary medicinal products (VMP). However first it is important to review what serious risks to animal health have already been successfully removed through the activities of the animal health industry. It is also important to review the indirect risks to VMP availability caused by negative public perceptions to new science and to livestock farming as a whole.

The message behind these examples is a reminder that a failure to provide a positive and predictable regulatory environment in Europe will mean that in future such innovative veterinary medicines will not easily become available to tackle the diseases that present such challenges to the animal health sector.

Examples of risks averted

Animal health products have, over the years been used to eradicate some of the most serious, debilitating diseases in livestock, such as Aujezkys disease in pigs and infectious bovine rhinotracheitis in cattle, resulting in huge economic benefits to the agricultural economies in many countries.

In dogs and cats enormous advances have been made in the prevention of serious diseases such as canine distemper and feline leukaemia through vaccination and the control of a host of parasitic diseases which can be devastating and distressing to owners of affected animals.

Importance of veterinary medicines to the agricultural economy and the environment

As one of the world's leading producers of meat and dairy products, overall output of livestock and related products accounts for around 2% of GDP in Europe[9]. However agricultural production can have major environmental impacts in terms of the nature of land use, and levels of waste and emissions. Proper and responsible use of animal health products by farmers reduces the number of animals needed to sustain existing levels of output of meat and dairy products. In the absence of animal health products, it is estimated that the EU would require 89% more cattle, 54% more pigs, 25% more poultry, and 28% more sheep[10]. Research by the animal health industry also advances understanding amongst farmers and vets of the causes of disease and helps them lessen its impact on the effective use of agricultural resources.

Veterinary medicines represent only a very small proportion of agricultural input costs (on average less than 2%), but they are crucial to the ability of European farmers to produce high quality meat and dairy products on an efficient and sustainable basis, to compete internationally, and to minimise environmental impact. The environmental

[9] OECD *'OECD in Figures'* (2005)
[10] Viaene J. and De Craene 'How do Animal Health Products Contribute to Economic and Environmentally-friendly Livestock Farming' (University of Ghent report for FEDESA, 1995)

impact of farming is reduced by increasing efficiency (lower inputs and higher outputs), reducing waste, minimising the excretion of micro-organisms by sick animals, and indirectly by increasing the technical knowledge of vets and farmers.

Animal health products improve animal nutrition and prevent, diagnose, and treat disease at low cost. As a consequence there are fewer premature animal deaths, improved output from production processes and improved productivity. Higher agricultural productivity improves international competitiveness for livestock products and enhances the long-term earnings of farmers. Over time, it contributes to greater economic viability and sustainability for livestock farming.

6.2 Examples of risks to animal health from insufficient availability

New and Emerging Science

Availability into the future must also be considered. The work of the ETPGAH[11] & DISCONTOOLS[12] coupled with the Animal Health Strategy reminds us of the concerns relating to the arrival of new diseases into the EU. At present, the EU legislation cannot respond at a pan-European level. For example, in the recent case of Bluetongue, Member States had to issue national temporary-use authorisations as the EU legislation could not accommodate the pan-European licensing of a vaccine in response to this very real emergency situation. The legislation needs to be amended to provide the necessary flexibility to respond.

The legislation needs to be designed to provide a real benefit:risk assessment. In the case of an emergency, the regulator must be satisfied that the vaccine will produce sufficient benefit for an acceptable level of risk under realistic scenarios. If the choice is between animals dying and the availability of a vaccine, the only criterion that matters is freedom from extraneous agents in the vaccine. If this criterion is met, it should be possible to issue a conditional licence with conditions attached concerning timelines to supply the normal set of data, which, on approval, will allow the issuance of a normal licence.

Reduced research into veterinary antimicrobials

Much of the debate surrounding antimicrobial resistance today highlights the concern about a lack of new antimicrobials for human use but often ignores the problems that will be caused if no new products are developed for animals. It is inconceivable that a discussion on antimicrobial policy cannot include the need for new antimicrobials in veterinary practice as well.

The ongoing criticisms by leading authorities in the human sector and some members of veterinary scientific committees and working/advisory groups about the use of antimicrobials in animals leading to increased resistance in man, often without sound scientific rational or proper assessment of the perceived risk, has led to a very antagonistic environment for antimicrobial use in the EU for animals. Such developments have proved to be a major disincentive to the animal health industry to develop new products, and the situation is likely to get worse.

Foot and Mouth Disease (FMD)

In the UK FMD outbreak in 2001 the disease cost the UK economy over £8 billion with millions of animals slaughtered, resulting in a public outcry. Whilst the fast spread of the

[11] The European Technology Platform for Global Animal Health see http://www.ifaheurope.org/ then select 'ETPGAH'
[12] *www.discontools.eu/*

disease meant that a vaccination regime alone could not have been used to bring the outbreak under control, a reduction in such costs might have been achieved if the UK government at the time could have used vaccination in selected areas. At the time there was no satisfactory vaccine available which enabled the distinction to be made between vaccinated and infected animals. New vaccines are now becoming available called DIVA vaccines where the ability exists to Differentiate Infected from Vaccinated Animals and in any future outbreak a member state government may choose to use these.

It might be argued that with a more positive regulatory environment for animal health companies to work in, the advent of such vaccines may well have been advanced with significant and positive consequences so that the controversial slaughter policy that caused such a public outcry can be replaced by an effective and economically advantageous vaccination policy. This would also have a positive impact on the farmers themselves by removing the psychological stress of having their herds slaughtered (including pedigree animals).

Blue Tongue case study

Blue Tongue is a debilitating viral disease of cattle and sheep leading to severe production losses and in extreme cases death of the animals concerned. It is a perfect example of how climate change is leading to the emergence of vector borne diseases in parts of the EU where the disease has not previously occurred. It also illustrates the need for the urgent development of vaccines and their expedited authorisation is of critical importance for animal health in the Community.

The industry responded rapidly to the Blue Tongue crisis in 2006 by developing new vaccines in record time, but the regulatory framework was regrettably not adequate to play its part. The fastest way to get vaccines licensed was for companies to apply to member states individually for exceptional authorisation with limited data. There is currently no legal basis under Community law that would allow a company to obtain a national marketing authorisation under exceptional circumstances which would be valid automatically in more than one Member State, in other words a pan-European “opinion for exceptional use”. In accordance with the international principle of respect for State sovereignty, each Member State is entitled to issue purely national authorisations, in accordance with its national laws, which will however be valid only within its own territory.

Whilst it might be assumed that the centralized procedure should offer an efficient and rapid way of obtaining an exceptional authorisation which would be automatically valid in all member states the experience with Blue Tongue vaccine highlighted that the exceptional circumstances provision used by EMA/CVMP did not allow the CVMP to take fast decisions reflecting the emergency situation. The legal framework made the Committee insist on an almost complete dossier, which of course significantly extends the timelines to approval and decision.

Histomoniasis (Blackhead in Turkeys)

Histomoniasis, also known as Blackhead disease, is primarily a disease of young turkeys. Chickens are more resistant to the effects of the infection but may act as carriers of the disease-causing organism. Histomoniasis is caused by a microscopic protozoan called *Histomonas meleagridis*. Histomoniasis can cause considerable losses in farm turkey flocks and most infected birds will die if untreated.

The standard treatment to control outbreaks of histomoniasis was with Dimetridazole used in the drinking water or feed. Other medicines are used occasionally for treatment but these are more suitable as preventatives. The European Committee for Veterinary Medicinal Products (CVMP) was unable to establish a Maximum Residue Limit for this

product when it assessed the available data in the late 1990s; consequently it became illegal to use this medicine in food-producing animals. Since then there has been no satisfactory treatment available for Blackhead disease, with dire consequences for the European turkey industry (some farms had to cull entire flocks).

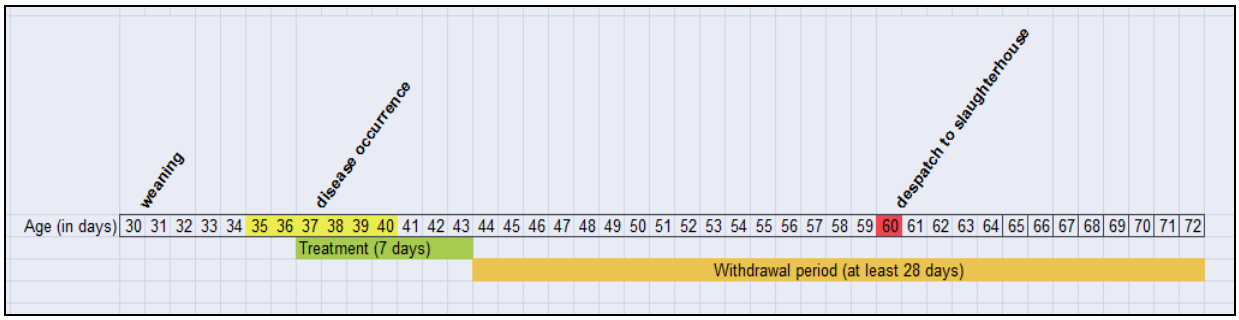
Bacterial and Parasitic Diseases in Rabbits

In Spain there are approximately 4000 rabbit farms rearing over 7 million animals for meat consumption. Rabbit meat is popular in Spain and many other Mediterranean countries with average consumption estimated at 1,5 Kg/year per person.

Although specific animal health programs are in place at farm level, disease occurs and animals must be treated for animal health, welfare and economic reasons. According to the rabbit producers' association (Intercún), all farms and near to 70% of groups have to be treated due to a diversity of diseases (respiratory, enteric, parasitic or fungal infections).

In some cases, particularly for respiratory and parasitic disorders, the lack of availability of VMPs for rabbits (see Annex 4) forces vets to make use of the cascade, prescribing VMPs registered for other food producing animal species. This "off-label" use implies a significant handicap for rabbit farming, as the administrative withdrawal period for meat as prescribed in the cascade rules (at least 28 days) is not consistent with the animal life cycle of 60 days (see Figure 9).

Figure 9: production life cycle for rabbits



When animals are treated under the cascade, they are dispatched from the farm late in time so reducing their commercial value and reducing farmers' revenue and competitiveness. As a consequence, farmers have to choose between treating animals to control the disease and avoid suffering or not treating in order to dispatch unaffected animals in due time. Under this last hypothesis, diseases become enzootic and impact seriously on animal health and welfare.

Bees

It is generally acknowledged that the situation regarding availability of medicines in bees is becoming critical with resistance developing to current treatments for some of the more common diseases (e.g. the varoa mite) and no medicines available for others. The value of bees to the environment and society at large is immeasurable and a solution must be found. This is also a public health issue as the illegal use of unlicensed products for this species leads to violative residues in honey and the consequent risks to the consumer.

Chapter 7:

Example of risks to human health from insufficient availability of veterinary medicines

7.1 Introduction

In this chapter several examples of risks to human health from insufficient availability of veterinary medicines are summarised. However the importance of this aspect of the impact assessment merits more detail, to foster a full understanding of the issues, and this is provided in Annex 5.

Animal health is synonymous with human health

The link between animal diseases and human health is captured in the concept of 'One World One Health[13]', which emphasizes the convergence of human and animal health and the measures necessary to optimize both in an integrated approach. Over 60% of known human diseases are sourced from animals as are 75% of emerging human diseases. World production of food is reported to be reduced by more than 20% due to animal diseases with subsequent consequences for human health.

Human health and well-being

Zoonotic[14] diseases, such as Avian Flu, pose a direct threat to human health. Animal health products help control these diseases and in some cases have eradicated them (e.g. rabies and bovine brucellosis). The emergence of new zoonotic diseases also presents a challenge and is difficult to predict; therefore preparedness is essential. Our ability to respond depends on the efficient development of new vaccines and treatment regimes in animals as well as man.

Vector-borne zoonoses (e.g. West Nile virus and tick-borne encephalitis) already present or endemic in Europe and with potential for more widespread occurrence present a direct risk to human health. Climatic changes and more interplay between humans and nature are enhancing the possible spread of these zoonoses. The treatment of the diseases in animals can reduce the threat they pose to man.

Pet ownership can contribute to higher levels of well-being amongst their owners. It is suggested that levels of stress are reduced and the degree of happiness is increased.

Safe, high quality food

Safe food comes from healthy animals. Sick animals cost more to feed and the food they produce can often not be sold or can even pose a health risk to humans. Animal health products have, for example, reduced the incidence of Salmonella in humans, since the introduction of vaccines for chickens and cattle. Data show that the incidence of human salmonellosis in the UK has fallen from over 30,000 cases per year in the period 1990-97 to less than 13,000 since 1997 after the introduction of the salmonella vaccination into the "Lion Code" for egg production[15].

[13] Initiated by the Wildlife Conservation Society http://www.oneworldonehealth.org/
[14] Animal disease that are transmissible to man are known as zoonotic diseases
[15] Advisory Committee on the Microbiological Safety of Food (ACMSF) UK (2001)

Veterinary medicines also help to improve the standards of diet and the accessibility of essential and affordable food for all citizens through their impact on the price and availability of safe food. The ability to treat and control the diseases in animals has a large beneficial impact on human health in the Community.

The spread of infections such as avian influenza[16] has highlighted both the crucial role played by veterinary medicines and the need for continued development of new and improved products. Unfortunately the availability of these vital tools is sometimes being compromised by current regulatory approaches (see 'Avian influenza' below for details). Failure to address this issue risks undermining the ability of the animal health industry to provide solutions to problems that threaten both human and animal health.

7.2 Veterinary medicines in the control of human infection

Avian influenza

Highly pathogenic avian influenza (HPAI) is a serious disease due to the very high mortality rate in affected birds. The current variant of HPAI is now present in many poultry species in Europe. Between 2003 and 2010, 116 people have died from the disease following close, direct contact with infected birds.

From the viewpoint of human health, it is imperative to have vaccines available for use in poultry when it is not possible to control the disease only by culling infected birds. This greatly reduces the possibility of humans becoming infected.

However, emergency marketing authorisation provisions in the EU legislation require companies to go through a full development programme within a set period of time if they wish to retain the right to place a product on the market in the interim period. But where culling has been shown to be effective in the EU, no market exists for avian influenza vaccines. Some companies had to withdraw their products from the market as there is no financial incentive to continue the development process. If the disease proves to be more difficult to control in the future, these valuable vaccines will not be available.

The current regulatory framework places very onerous demands on companies developing VMPs. There is a clear need for a true benefit:risk assessment where the emergency vaccines are allowed to remain potentially available with further development only being required if the disease proves to be an ongoing problem where vaccines are actually routinely used in the field.

Food Borne Infections[17]

Campylobacteriosis

In 2008, *campylobacteriosis* continued to be the most commonly reported gastrointestinal bacterial pathogen in humans in the European Union with 190,566 confirmed cases[18] (see Figure 17 in Annex 5). *Campylobacter* is commonly detected in

[16] More information on avian influenza is available at
http://www.ifaheurope.org/CommonTP.aspx?SubMenuId=44&MenuId=14
http://ec.europa.eu/health/ph_threats/com/Influenza/influhome/avian_influenza_en.htm

[17] The Community Summary Report on trends and sources of zoonoses, zoonotic agents and foodborne outbreaks in the European Union in 2008

[18] Analysis of the baseline survey on the prevalence of *Campylobacter* in broiler batches and of *Campylobacter* and *Salmonella* on broiler carcasses in the EU, 2008

poultry meat and from live poultry, pigs and cattle. The average rate of contamination from those countries producing the majority of chickens is 71.2%.

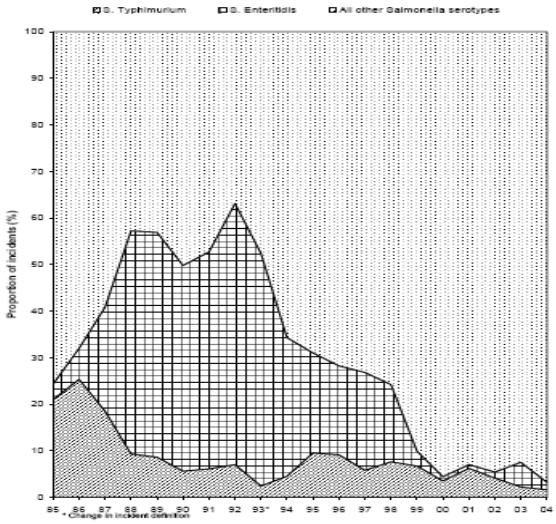
The deployment of vaccines against Salmonella proved to be a very effective method of control coupled with a range of other initiatives (see below). Public health would benefit if such vaccination occurred for *Campylobacter* by reducing the high rate of illness it causes.

Salmonellosis

Salmonellosis remains one of the most common foodborne diseases, causing a major public health burden and cost in many countries. Millions of cases are reported worldwide every year resulting in thousands of deaths. In 2008 in Europe, salmonellosis was the second most common zoonotic disease in humans with 131,468 confirmed cases (see Figure 17 in Annex 5). Chicken eggs are an important source for these infections. An important decline in the prevalence of Salmonella in laying hens was observed when Member States implemented new control programmes; in the UK the Veterinary Laboratories Agency reported "vaccines undoubtedly contributed to the control of salmonella in poultry flocks" (see Figure 10 below).

There is a real need for the development of a range of effective medicines, including vaccines, for its control in all species of animal livestock.

Figure 10: Effect of vaccination against *S. enteritidis* and *S. typhimurium* in poultry



"Vaccines against *S.Enteritidis and S.Typhimurium are now very widely used in the commercial layer sector and are also used in parent broiler breeders. Their use will have undoubtedly contributed to the control of Salmonella in poultry flocks."*

Ref: VLA's 2004 report in Salmonella in livestock.

Rabies – a vaccination success story

Rabies is now one of the least reported zoonotic diseases in the EU (see data and Figure 17 in Annex 5). This illustrates how a well executed vaccination policy (oral vaccination programmes in the wildlife with Community co-financing) can have a dramatic impact on public health. This is supported by investment into research (e.g. development of stable oral vaccines that can be used in 'bait').

Zoonoses in the European Union and item-specific summaries

The importance of a zoonosis as a human infection is not dependent on incidence in the population alone. The severity of the disease and fatality rate are also important factors affecting the relevance of the disease (e.g. rabies versus salmonella food-poisoning).

Bovine Tuberculosis

This is a major intractable disease in cattle in Ireland and the UK with significant risks to consumers of unpasteurized dairy products. It has a high impact on the finances of affected farms through reductions in sales of milk or beef caused by the loss of culled animals, the inability to market store cattle, and extra costs (extra feed and bedding for impounded stock and even putting up new buildings to house them).

In the UK a report by the Farm Crisis Network[19] illustrates the toll that TB in cattle can have on farmers' health. Many farmers affected by TB in their herds show clear signs of psychological distress as well as physical illness. They worry about the impact on their families and are concerned about their children's distress. Some indicated a desire to abandon farming or even end their lives because under the current control regime they could 'see no light at the end of the tunnel'.

There are still no TB vaccines available and they are urgently needed.

Foot and Mouth Disease (FMD)

Whilst this disease is not classically a zoonosis, it can have a dramatic impact on human health in the farming sector. The psychological impact of FMD on farmers is mentioned in the Anderson enquiry[20] (government enquiry) into the 2001 FMD outbreak as well as in numerous other enquiries. Many of these reports mention the stress on people involved in culling operations, and the impact on children (e.g. unable to attend school). Vaccination can replace the traditional culling policies employed for many such diseases and remove the stress and anxiety that such policies cause to all concerned.

The importance of antimicrobial use in animals to human health

The veterinary profession and the farming community throughout the EU strive to provide the best healthcare and welfare for their animals, which contributes to the production of safe, affordable and abundant food, critical to European food security. Maintaining the health of European herds and flocks requires veterinarians and farmers to have all authorised animal health products including antimicrobials available to them.

The responsible, professional use of these products is important for animal welfare, but also can bring potential benefits to human health by reducing pathogens in and on foods; these benefits can exceed the relatively low increased human health risks associated with antibiotic resistance[21].

The primacy of preventing food borne illness in man is well appreciated and a major strategy to achieve this is the further reduction of pathogens on meat, poultry and eggs from levels already present. The availability of all the classes of antimicrobials for treatment of animals is therefore fundamental to the control of these food borne diseases in human medicine.

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[19] http://www.farmcrisisnetwork.co.uk/latestnews/stress-and-loss-a-report-on-the-impact-of-bovine-tb-on-farming-families

[20] The Anderson Inquiry into the 2001 FMD outbreak- http://archive.cabinetoffice.gov.uk/fmd/fmd_report/report/index.htm
Pages 134, 136 and 137 detail psychological impact and also describe how children's education suffered- http://archive.cabinetoffice.gov.uk/fmd/fmd_report/report/SECT_14.PDF

[21] A 2004 study done by scientists at the University of Minnesota College of Veterinary Medicine in which the potential risks associated with increased levels of antibiotic-resistant bacteria in meat were compared with the potential benefits associated with decreased risk of food-borne illness found potential benefits to human health associated with the use of antibiotics in chicken far exceeded the relatively low increased human health risks associated with antibiotic resistance.

Chapter 8:

Costs associated with each major Information Obligation

8.1 Introduction and objectives of this chapter

One primary objective of the European Commission's impact assessment report will be to examine the regulation-driven time for research and development, costs and risks to develop veterinary medicinal products (VMPs). The objective of this chapter is to provide information and data to support this aspect of the impact assessment.

Due to the current complexity of (a) the multiple procedures for the registration of veterinary medicinal products and (b) their transposition, implementation, management and interpretation by 27 member states, the significant administrative costs of fulfilling Information Obligations (IOs) have been identified as a key problem for the animal health sector with resulting negative impacts for animal health, innovation and competitiveness.

The costs of all major Information Obligations are a key component of an impact assessment and are a necessary part of the Standard Cost Model (SCM) used to calculate the administrative costs/ burdens of legislation.

The costs associated with each of the major Information Obligations (IOs) imposed by the current legislative framework for VMPs have been differentiated according to:

- Market authorisation (MA) process (new application, repeat-application (MRP only), MA renewal, and post-authorisation/pharmacovigilance);
- Market authorisation route (centralised procedure, mutual recognition procedure (MRP), decentralised procedure (DCP));
- Packaging information obligations and impact on product distribution; impact on costs if individual language packs can be combined to multiple language packs to avoid inefficient small manufacturing/labeling operations.

In addition to the data provided on IOs for the existing procedures, a second important aspect of the impact of administrative costs is the impact on competitiveness in the marketplace. If the administrative costs fall disproportionately to one segment of the market then the market competitiveness becomes distorted. This can be described as the impact of "an un-level playing field". Therefore a series of case studies are presented to illustrate where the legislation inadvertently creates disproportionate costs to one group of companies. These case studies reflect the complex nature of the regulations, and are therefore complex themselves by necessity.

The final section of this chapter refers to the results of a survey of the functioning of the centralised procedure, part of which investigated the reasons why companies chose a particular registration route. The objective of this information is to illustrate that companies choose, and desire, simplified predictable and centralised systems as these are more efficient (provided they do not become too bureaucratic and inflexible).

However, while centralised systems are preferred by international companies, SMEs require equally efficient systems but without the extra cost that comes with an expensive centralised system (e.g. high regulatory agency fees and the cost of translating labelling and packaging into all official languages of the EU). Furthermore,

the EU has already committed itself to reduce regulatory burdens for SMEs as it accepts that regulatory and administrative costs (measured, for instance, per employee and compared to turnover) for smaller businesses can be up to ten times higher than for large companies.

Consequently IFAH-Europe has elaborated proposals for a simplified regulatory system in Europe that takes into account the needs of both large and small companies (known as the "1-1-1 Concept", and described in Annex 3). In this chapter data is presented to illustrate the potential administrative savings from this simplified procedure.

8.2 Administrative costs for the different procedures

8.2.1 Methodology

A summary of the methodology used is presented in the box below. The basic principles described in the European Commission guidance[22] were followed where possible for the quantification of the administrative costs of the different regulatory procedures and other information obligations.

Data collection method:

The estimates and working assumptions were produced by a focus group of experts in regulatory procedures representing 14 companies[23]. This group of experts met 4 times during the project period, and also worked via written exchange of views and by teleconferences. The steps followed were:

Step 1: a full mapping of the existing information obligations (IO) for each procedure, marketing authorisation process and marketing authorisation route (including differentiation between recurring administrative costs and one-off administrative costs).

Step 2: agreement on a standard tariff across this business sector, based on an average labour cost per day (gross salary at level of qualification for regulatory staff required by the main actions), including pro-rated overheads. A standard labour cost of €1000 per day is used in all calculations.

Step 3: agreement on the typical time required for each action or IO. Sometimes numerous staff members across several departments may be involved in an action. This is presented as the number of working days utilised, and transcribed into the number of 'full-time-equivalents'.

Working assumptions:

- For each non-centralised procedure a typical number of involved concerned member states was assigned (taking the average number of concerned member states from the CMDv/IFAH-Europe survey reports on the functioning of the MRP and DCP); this is indicated in the data tables for each procedure.

- When transcribed into 'full-time-equivalents' (FTEs), it is assumed that a typical person in Europe will work 223 days per year (i.e. excluding weekends, public holidays and annual leave), and an 8 hour day.

[22] Part III: Annexes to Impact Assessment Guidelines, 15 January 2009, Chapter 10. Assessing administrative costs imposed by EU legislation

[23] Alpharma, Bayer, Boehringer Ingelheim Vetmedica GmbH, Ceva Santé Animale, Elanco, Fort Dodge, Huvepharma, Intervet/Schering-Plough, Janssen Animal Health, Merial, Novartis, Pfizer, Vetoquinol, Virbac

In the cited guidance (footnote 22) administrative costs are defined as the costs incurred by *inter alia* a company in meeting legal obligations to provide information on their activities or production, to *inter alia* public authorities. Information is to be construed in a broad sense, i.e. including labelling, reporting, registration, monitoring and assessment needed to provide the information. Recurring administrative costs and, where significant, one-off administrative costs have to be taken into account. The administrative costs consist of two different cost components: the business-as-usual costs and administrative burdens.

Administrative costs have been assessed on the basis of the average cost of the required administrative activity (price) multiplied by the total number of activities performed per year (quantity). The average cost per action has been estimated by multiplying a standard tariff (based on average labour cost per day including pro-rated overheads) and the time required per action. Where appropriate, other types of costs such as outsourcing, equipment or supplies' costs have been taken into account.

The estimates are based on working assumptions simplifying the complex reality of a wide range of possibilities. These assumptions are presented in the box above.

It is important to note that these estimates do not include testing and scientific costs (i.e. the costs of generating the data and information that must be submitted - testing costs are not considered as administrative costs in the EC guideline). The costs reported only include the administrative costs of compiling the data and information, submitting it to the regulatory authority, and following the process until a marketing authorisation is issued.

It should of course be recognised that irrespective of this administrative cost estimate, the enormous increase in testing requirements in the European Union over the last 15 years have increased product development costs by approximately 160%.

The main costs induced by the information obligations are labour costs (at the necessary level of qualification and skill).

As the suppression of a 'pure' obligation will provide greater cost relief than the suppression of an obligation that is to a large extent part of business as usual activities, the costs of renewals and repeat-use procedures have been included.

The information obligations for veterinary medicinal products are described in a European Directive[24] that requires transcribing into national law. The standard practice and interpretation of the rules or guidelines can vary between national competent authorities. If the transposing authority goes beyond what is needed to meet the obligation, the % increased costs resulting from 'gold plating'[25] by the transposing authority should be identified. This has not been done. However the impact of one option for simplification via a single procedure and thus avoiding national differences has been presented to illustrate the possible savings that could arise from simplification, avoidance of national gold-plating and removal of duplication.

The administrative burden for the main post-authorisation activity, pharmacovigilance reporting requirements, is presented separately (section 3 of this chapter).

[24] Directive 2001/82/EC as amended by Directive 2004/28/EC

[25] In the EC Impact Assessment guidance, 'gold plating' refers, in the case of administrative obligations, among other things, to increasing the reporting frequency, to add "data requirements" or to widen the target groups.

8.2.2 Administrative burden of marketing authorisation procedures

Tables providing the detailed information obligations for the different procedures, and the time needed for each, are annexed (Annex 9). This annexed data is summarised into the main phases for each procedure in table 1 below. The data is presented in terms of cost (Euros) and time (days); the time (days) is further presented in terms of "full-time-equivalents" (FTEs) per year (assuming 223 working days per year).

Table 1: Information Obligations and administrative costs for marketing authorisation procedures

PROCEDURE	steps of procedure	Administrative costs (Euros)	Administrative Workload (days)
CENTRALISED PROCEDURE 27 member States	Pre-submission	€ 7,000	7
	Dossier compilation	€ 25,000	25
	Submission and Validation	€ 10,000	10
	Evaluation procedure	€ 27,000	27
	Post Opinion	€ 50,000	50
	Total days or Euros	**€ 119,000**	**119**
	FTEs		**0.53**
MUTUAL RECOGNITION PROCEDURE **N.B. excluding the national procedure:** add 42 days for national procedure as in dossier compilation for DCP **Assumptions:** 13 member states involved	Pre-submission	€ 13,000	13
	Dossier compilation	€ 25,000	25
	Submission and Validation	€ 17,000	17
	Evaluation procedure	€ 22,000	22
	Post Opinion	€ 20,000	20
	Total days or Euros	**€ 97,000**	**97**
	FTEs		**0.43**
DECENTRALISED PROCEDURE **Assumptions:** 13 member states involved (RMS + 12 CMSs)	Pre-submission	€ 3,000	3
	Dossier compilation	€ 42,000	42
	Submission and Validation	€ 17,000	17
	Evaluation procedure	€ 49,000	49
	Post Opinion	€ 20,000	20
	Total days or Euros	**€ 131,000**	**131**
	FTEs		**0.59**
Repeat Use MRP/DCPs **Assumptions:** 15 member states for the original MRP/DCP 5 new CMS for repeat-use	Pre-submission	€ 13,000	13
	Submission and Validation	€ 7,000	7
	Evaluation procedure	€ 5,000	5
	Post Opinion	€ 38,000	38
	Total days or Euros	**€ 63,000**	**63**
	FTEs		**0.28**
Renewal **Assumptions:** 15 member states for the renewal	Pre-submission	€ 17,625	18
	Submission and Validation	€ 7,000	7
	Evaluation procedure	€ 7,000	7
	Post Opinion	€ 10,000	10
	Total days or Euros	**€ 41,625**	**42**
	FTEs		**0.19**

8.2.3 Commentary on the results

For the main marketing authorisation procedures the total administrative workload in terms of days was estimated to be:

1. Centralised Procedure 119 days
2. Mutual Recognition Procedure 139 days (97 + 42 days for the national phase)
3. Decentralised Procedure 131 days

As each product, each company's way of working and each marketing authorisation procedure are very different, it is important to remember that these are just estimates of the typical costs across the industry for providing these information obligations.

Never-the-less the results do serve to illustrate some underlying principles:

1. The least burdensome system is the centralised procedure.
2. Renewals and repeat-use MRP/DCPs represent in the region of 30% to 50% of the administrative burden of a full procedure.

There is a need for simplification of the procedures.

The administrative burden of the procedures can be significantly reduced if the differences in opinion between member states and additional national dossier requirements are removed from the system as these cause significant delays and additional workload. These differences in opinion occur at validation, and throughout the scientific assessment process. For example, in the decentralised procedure these validation and assessment phases accounted for 17 days and 49 days of the workload.

The administrative burden represented by renewals and repeat-use MRP/DCPs are particularly of major concern to industry, as there is no need for these procedures. Consequently the administrative costs incurred for these procedures are regarded as a very wasteful use of resources.

Pure obligations – renewals and repeat-use procedures

Renewals are regarded as redundant because the safety of products in the market place is continually monitored through the pharmacovigilance system. The 2004 amendments to the veterinary medicinal products Directive introduced changes designed to strengthen the pharmacovigilance systems. This brings higher administrative burden with it (see section 8.2.4 below). The animal health sector has finite resources. The increased focus on pharmacovigilance is supported, but only if it is balanced by a decrease in redundant administrative costs, most particularly renewals.

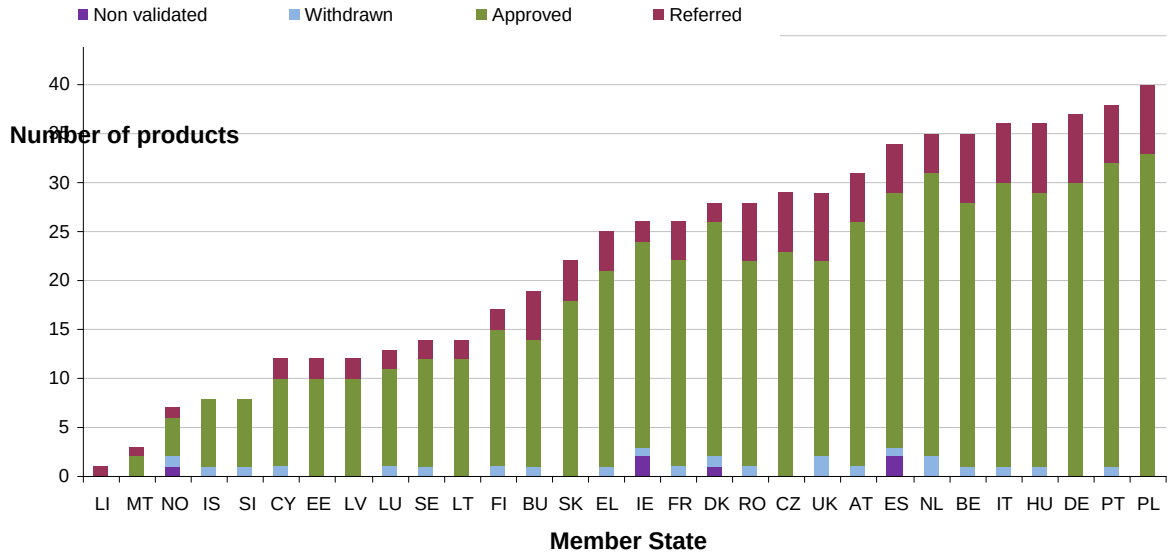
Repeat-use MRP/DCPs are also seen as redundant, as the scientific assessment has already been done during the first procedure. The first scientific assessment should be adopted by all member states and the repeat-use procedure replaced by automatic mutual recognition of the first marketing authorisation.

The removal of renewals and repeat-use procedures could result in a win-win situation for animal health companies and authorities through better use of resources by removal of duplication of controls.

Exclusion of small markets

Data from CMDv/IFAH-Europe surveys of the functioning of the MRP and DCP illustrate that small markets, such a Slovenia, Estonia, Latvia and Luxembourg, are routinely excluded as the administrative costs of the procedures outweigh the potential returns from these markets (see Figure 11 below where the 2009 data is presented showing how many times a member state is involved in a MRP/DCP). A significant part of these administrative costs is the cost of packaging and labelling in individual language packs for these small markets.

Figure 11: Decentralised Procedures 2009



8.2.4 Potential savings from 1-1-1 Concept proposals

One of the proposed policy options favoured by industry is the introduction of a single marketing authorisation procedure that would bring simplification and a single EU market via the use of:
1. A single marketing authorisation application dossier (avoiding additional national requirements)
2. A single European scientific assessment and scientific opinion (avoiding differences in opinion between member states at validation and during the assessment phase).
3. A single pan-European decision for marketing authorisation (to ensure the product can be placed on the market throughout the European Union).

The single dossier/single scientific assessment/single decision is known as the 1-1-1 Concept. Under these proposals there would be greater alignment and work-sharing between National Competent Authorities, which could lead to significant improvement in the utilisation of resources for both competent authorities and applicants, including reduced labour costs, materials costs and real time. In addition, the need for national adaptation or translation of dossiers would be eliminated and the number of copies of the dossiers to be printed and dispatched would be greatly reduced.

Table 2 shows the estimated savings from introducing the 1-1-1 Concept in labour (FTE[26]) costs and time for applicants associated with new applications (including line extensions and generics) and Type I and Type II variations. It should be noted that the costs and time requirements of applications (particularly new applications) vary according to the size and complexity of the dossier, but IFAH-Europe has based its calculations on the following scenarios:

- "Small" new application dossier (ca 20 volumes) with FTE costs (related to the authorisation procedure only) of €16,000 (16 FTE days) over 15 weeks.
- "Large" new application dossier (ca 100 volumes) with FTE costs of €61,000 (61 FTE days) over 52 weeks.

[26] FTE (Full Time Equivalent) is a measure of the cost of the time spent by employees. IFAH Europe uses a nominal FTE value of €1000 per day in all calculations.

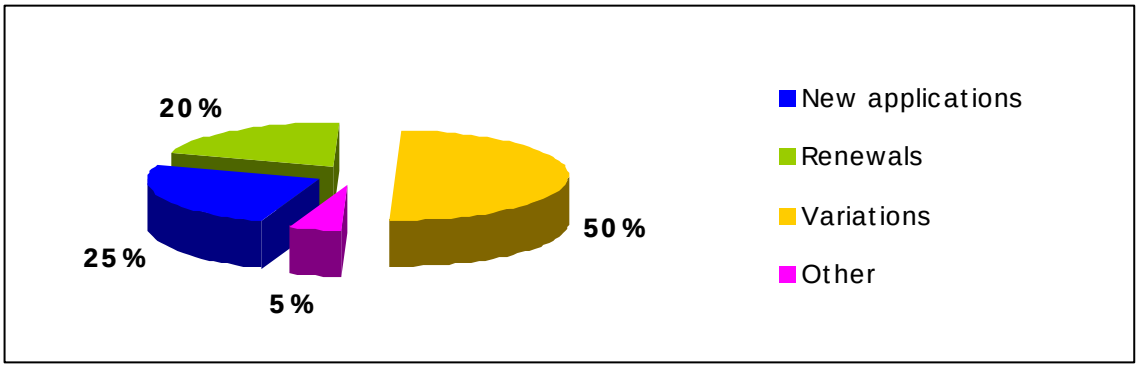
- Type I variation application dossier with FTE costs of €4,000 over 4 weeks.
- Type II variation application dossier with FTE costs of €15,000 over 14 weeks.

The potential savings from the 1-1-1 Concept proposals range from 15% to 61% for labour costs and from 12% to 61% for time. In real terms, the savings associated with a large new application could be €22,500 in labour costs and 6 months in time.

Variations

Even a Type I variation could have savings in the region of €2,000 and 2 weeks, which is highly significant considering a typical company may need to submit hundreds of variations per year. A company may also have to submit numerous Type II variations per year, and for a vaccine manufacturer the large majority of variations are typically Type II by default, creating a very significant cost. Typically, variations can account for 50% of the workload of regulatory staff (see Figure 12). The European Commission has estimated[27] that in 2006 the veterinary industry submitted 9077 variations to the competent authorities.

Figure 12: Share of workload by major Information Obligations (IFAH-Europe 2005)



Repeat Use Mutual Recognition Procedures

Table 3 shows the costs associated with Repeat Use Mutual Recognition Procedures, by describing three case studies. The total cost of each case study (labour and material costs) ranges from €24,000 to €65,300 reflecting different product types and different numbers of Concerned Member States, but the savings in each case under the 1-1-1 Concept Proposals would be 100% as Repeat Use MRP would no longer be required.

Conclusion

In conclusion, although there is wide variation in the costs and time associated with individual marketing authorisation applications, the 1-1-1 Concept proposals are expected to result in significant savings for applicants in all cases. The proposals will also reduce the workload for competent authorities as duplication would be removed.

[27] IMPACT ASSESSMENT COM(2008)123 final SEC(2008)274 (Brussels, 4.3.2008) - proposal for a Directive - as regards variations to the terms of marketing authorisations for medicinal products

Table 2: Estimated Savings Resulting from Adoption of the 1-1-1 Concept Proposals

Activity		New MA Application, Line Extension or Generic				Type I Variation		Type II Variation	
		FTE[28] Cost (Euro) Minimum	Real time[29] (weeks) Minimum	FTE Cost (Euro) Maximum	Real time (weeks) Maximum	FTE Cost (Euro)	Real time (weeks)	FTE Cost (Euro)	Real time (weeks)
Dossier compilation		€ 1,000	1	€ 20,000	6	€ 1,000	1	€ 2,000	3
% Saving from 1-1-1 Concept		0%				0%		0%	
Dossier printing and shipping		€ 1,000	1	€ 5,000	2	€ 1,000	1	€ 2,000	1
% Saving from 1-1-1 Concept		50 - 95%				50 - 95%		50 - 95%	
National adaptation/translation in local country office & submission to the Competent Authority		€ 1,000	1	€ 3,000	2	€ 1,000	1	€ 1,000	1
% Saving from 1-1-1 Concept		100%				100%		100%	
Response to validation issues		€ 1,000	2	€ 2,000	2	€ 1,000	1	€ 1,000	1
% Saving from 1-1-1 Concept		20 - 50%				20 - 50%		20 - 50%	
Preparation of Response to CLOQ[30]-1		€ 4,000	3	€ 15,000	24	N/A		€ 3,000	3
% Saving from 1-1-1 Concept		0 - 50%						0 - 50%	
Printing and shipping of Response to CLOQ-1		€ 1,000	1	€ 3,000	2	N/A		€ 1,000	1
% Saving from 1-1-1 Concept		50 - 95%						50 - 95%	
Preparation of Response to CLOQ-2		€ 1,000	1	€ 2,000	1	N/A		N/A	
% Saving from 1-1-1 Concept		0 - 50%							
Printing and shipping of Response to CLOQ-2		€ 1,000	1	€ 1,000	1	N/A		N/A	
% Saving from 1-1-1 Concept		50 - 95%							
National phase : approval of mock-ups and PIL		€ 5,000	4	€ 10,000	12	N/A[31]		€ 5,000	4
% Saving from 1-1-1 Concept		10 - 15%	10 - 50%	10 - 15%	10 - 50%			10 - 15%	10 - 50%
Total Cost (Euro) or Time (weeks)		**€ 16,000**	**15**	**€ 61,000**	**52**	**€ 4,000**	**4**	**€ 15,000**	**14**
Total Savings from 1-1-1 Concept (Euro or Weeks)	Min	**€ 3,200**	**3.3**	**€ 8,900**	**6.1**	**€ 1,700**	**1.7**	**€ 2,700**	**2.2**
	Max	**€ 7,600**	**8.85**	**€ 22,550**	**26.25**	**€ 2,450**	**2.45**	**€ 5,850**	**4.9**
Total % Savings from 1-1-1	Min	**20%**	**22%**	**15%**	**12%**	**43%**	**43%**	**18%**	**16%**
	Max	**48%**	**59%**	**37%**	**50%**	**61%**	**61%**	**39%**	**35%**

[28] Full Time Equivalent is a measure of the cost of the time spent by employees. A nominal FTE value of €1000 per day is used in all calculations.
[29] Real time refers to the amount of time that elapses during the course of a procedure, as distinct from the number of days actually spent on a task.
[30] CLOQ = Consolidated list of questions
[31] Assumes no changes to the product literature. If changes are required costs will be incurred in the National Phase. Savings from 1:1:1 will be similar to a Type II variation.

Table 3: Cost of Repeat Use Mutual Recognition Procedures

	Case Study A	Case Study B	Case Study C
Parameters			
Number of volumes in dossier	9	11	156
Number of CMS in repeat use MRP	10	1	1
Submission and validation			
Cost of paper dossiers and CDs, including printing/copying and despatch	€ 1,031	€ 1,511	€ 4248
FTE[32] cost	€ 5,000	€ 5,000	€ 13,000
Fees			
Regulatory Fees - total CMS	€ 34,278	€ 1,000	€ 3,350
Regulatory Fees - RMS	€ 25,000	€ 28,000	€ 3,400
Total Cost	**€ 65,309**	**€ 35,511**	**€ 23,998**

These case studies were provided by 3 IFAH-Europe companies in 2009-2010.

[32] FTE (Full Time Equivalent) is a measure of the cost of the time spent by employees. IFAH-Europe uses a nominal FTE value of €1000 per day in all calculations.

8.3 Administrative burden of pharmacovigilance

While administrative processes represent an important part of the general workload in Pharmacovigilance a distinction must be made between the general tasks involving the set-up and maintenance of the system and the reporting of the actual cases.

In the following tables workload is in days per year unless otherwise stated. One "full time equivalent" employee (FTE) is assumed to work 223 days per year (i.e. excluding weekends, public holidays and annual leave). Across a company many different individuals are involved in the pharmacovigilance tasks, including: Pharmacovigilance managers (head office), local office manager and field reps, technical services, marketing, IT manager, finance department (payment of fees). This assessment uses a standard labour cost of €1000 per day in all calculations.

8.3.1 General Task - Develop and maintain a pharmacovigilance system

The set up and maintenance of the pharmacovigilance system requires a significant amount of administrative work (see table 4 tasks 1 to 3), but is in general not considered as the major contributor to the workload. The major task is the submission of variations to those new or renewed marketing authorisations (MAs) that contain a "detailed description of the pharmacovigilance system" (DDPS), which has been required since 2005 (see table 4 task 4). An industry average for the number of MAs involved has been estimated at 25 per company.

In exploring potential solutions that reduce the administrative burden, significant benefits could be expected through the adoption of a pharmacovigilance master file system for all the products marketed by the company. The improvements would be realised because the DDPS would have to be submitted just once, and updated via a single variation procedure instead of multiple variation procedures, one per product. Considering the number of products involved the beneficial impact would be tremendous (e.g. the estimates in table 4 would generate savings of **24** days per year, as illustrated in the second part of the table).

Table 4: Develop and maintain a detailed description of the pharmacovigilance system (DDPS)

Subtasks	**Workload (days)**			**Comment**	**Average frequency per year**	**Total average days per year**
	Average	*Min*	*Max*			
1. Produce DDPS	10	5	15	Single event	Year 1 only	Year 1 10 (5 - 15)
2. Register DDPS	5	1	10	Per license application (range 1-20)	4	20 (1 - 200)
3. Update DDPS	3	0.5	5	Per change (range 0 to 3)	1	3 (0.5 - 15)
4. Amend DDPS in the MAs for recently registered products	1	0.5	5	Per change (0 to 1) and *per new MA*	1 x 25 products (range 10–100)	25 (for 25 products) 10 (10 products) 100 (100 products)
Total days year 1	**43** (for 10 products) **58** (for 25 products) **133** (for100 products)					
Total days year 1+	**33** (for 10 products) **48** (for 25 products) **123** (for100 products)					

Table 4: part 2

Reducing the administrative burden (if subtask 4 is no longer per product licence):						
Subtasks	**Workload (days)** Average, min and max			**Comment**	**Average frequency per year**	**Total average days per year**
Tasks 2 to 3 remain unchanged						20 + 3
4. Amend DDPS	1	0.5	5	Per change	1 (0 – 1)	1
Total days per year (after year 1)						**24**

8.3.2 Main task - Database management

The maintenance of the electronic system, which is meant to simplify and standardize the pharmacovigilance work appears to be more important, due to the need to maintain the database up-to-date (see table 5).

While some companies provided actual estimations, which are summarized in table 5, at least one other company just described it as "a major task". The wide range in workload is explained by the fact that some companies work with in-house built systems, leading to a major workload, while others work with commercially available systems, leading to less workload but involving a substantial financial cost. It may be difficult to reduce the workload involved in these tasks, and considering the importance of it, reducing administrative burden should focus on reduction of the other administrative tasks involved in pharmacovigilance.

Table 5: Database management

Subtasks	**Workload (days)**			**Frequency per year**	**Total average days per year**
	Average	*Min*	*Max*		
Validation (Data elements GL, VEDDRA, VICH)	20	1	40	Year 1 only	20 (1 – 40)
Maintenance	110	50	600	1	110 (50 – 600)
Exchange with competent authorities' database	10	1	60	1	10 (1 – 60)
				Total year 1	**140 (52 – 700)**
				Total year 1+	**120 (51 – 660)**

8.3.3 Inspections

Another increasingly important task concerns the work associated with inspections, which is estimated in table 6 to require 30 days work per year. Especially now that several MS are inspecting, and in some cases more than once per year, this may become a major task. It should be noted that inspections themselves may lead to further burden on the maintenance and updating of the systems involved as it may involve substantial preparative work. It is hoped that the workload currently caused by this task is artificially inflated by a "first wave" effect and that in the future inspections will become more routine and less workload-intensive by being limited to a "have to" approach, avoiding unnecessary work for both the licence holder and the inspecting authority.

Table 6: Main task - Inspections

Subtasks	Workload (days)			Frequency per year	Total average days per year
	Average	*Min*	*Max*		
1. Internal audits	6	2	10	1	6 (2 – 10)
2. EU and National inspections	8	4	15	3 (1 to 5)	24 (8 – 40)
				Total days p.a.	**30 (10 – 50)**

8.3.4 Case related tasks

The work involved in the handling of a single case (adverse drug reaction reports from the field) is limited but in view of the number of cases (as all 'suspected' cases are reported) should not be underestimated. The actual portfolio (companion animals, innovative products, therapeutics, vaccines,…) may have an important impact on the number of cases. Therefore the number of cases per licence holder can range from around ten cases per year to hundreds to thousands of cases depending whether the company is small, medium or large (for example, seven large and medium sized companies reported the following number of cases per year; 20000, 230, 550, 6000, 8500, 1300, 3100, giving an average of 5667 cases per annum). This is reflected in table 7 below, with an industry average estimated at 250 days per year spent handling individual pharmacovigilance case reports.

To accommodate this very wide range, a [low] industry average of 500 has been used for the impact assessment. A web based reporting system exists already for smaller operations and it has gone some way to improving their ability to compete.

Table 7: Main task - Case handling

Workload (days)			Repeat	Frequency per year	Total average days per year
Average	*Min*	*Max*			
0.5	0.1	3	Per case	500 (10 - 20,000)	250 (5 – 10,000)

8.3.5 PSUR handling

Although there are clearly efforts to reduce the work load (e.g. HMA synchronisation and work-sharing initiative), Periodic Safety Update Report (PSUR) handling remains a major burden. The frequency will vary in relation to the age of the licence from 2 per year to once per 3 years (a PSUR is required every 6 months for the first year of a product's life, then every year for the next 2 years, and then every 3 years thereafter). However taking into account the large number of products currently marketed, it is clear the time spent in the EU on these tasks over the different licence holders is enormous.

For example, a typical small company may have up to 100 licences; a typical large company may have 1000 licences; the largest animal health company may have 5000 product licences.

Seven large and medium sized companies reported an average of 158 PSURs prepared per year (data: 35, 50, 70, 100, 250, 250, 350 PSURs p.a.). It is assumed a small company may prepare 10 PSURs per year. Therefore a typical range can be taken as 10 to 350 PSURs p.a. with an industry average of 50 PSURs p.a. (see table 8). This may require around 500 workdays involving many people across the company, from the pharmacovigilance manager in head office to the national office manager.

Therefore the further removal of duplication of work and rationalization of the PSUR schedule can only be supported and encouraged.

Table 8: Main task - Prepare PSURs

Subtasks	Workload (days)		
	Average	*Min*	*Max*
1. Gather and review published data	2	0.2	4
2. Gather 3rd country reports	1	0.1	2
3. Gather use volumes / patterns	1	0.2	4
4. Compile report	4	0.5	10
5. Submit report, pay fees, answer validation questions	1	0.1	2
6. Handle assessment report, comments, requests for clarification	1	0.1	3
Total days per PSUR	**10**	**1.2**	**25**
1. Total days per annum small company (10 PSURs)	**100**	**12**	**250**
2. Total days per annum average company (50 PSURs)	**500**	**60**	**2,500**
3. Total days per annum large company (350 PSURs)	**3500**	**420**	**8,750**

8.3.6 Summary

A summary of the estimated time spent on the 5 main pharmacovigilance tasks is presented in table 9. It shows that an industry average would be in the region of the equivalent of 4.3 full time staff working solely on pharmacovigilance per annum. This would represent the summation of a range of personnel across the organisation contributing to the tasks, with the bulk of the work being handled by pharmacovigilance managers. It also illustrates that the greatest impact on the workload comes from individual case report handling and the preparation of PSURs.

The minimum and maximum figures have also been summarised for some of the tasks. The minimum figures could be representative of a small company with a range of products that do not generate serious cases. However the maximum figures cannot be summated to give an overall maximum figure because they would be based on the assumption that all cases were 'worst cases' (i.e. required a significant amount of time to 'follow-up' and report). As no company would have a product range where all the products were generating serious cases, this scenario would be completely unrealistic. Therefore the maximum figures for the cases studies and PSURs are not reported in the summary table.

Table 9: Summary of days per annum (& FTEs) attributed to pharmacovigilance tasks

Main task	Estimated total days per year	Minimum days per year	Maximum days per year
1. Detailed description of the pharmaco-vigilance system	**48** (for 25 new or renewed products)	**33** (for 10 new or renewed products)	**123** (for 100 new or renewed products)
2. DB management	**120**	**51**	**660**
3. Inspections	**30**	**10**	**50**
4. Case handling	**250**	**5**	
5. Prepare PSURs	**500** (50 PSURs)	**100** (10 PSURs)	
Total days p.a. (FTEs)	**948 (4.3)**	**199 (0.9)**	

8.4 Packaging costs – monolingual vs multilingual packaging case studies

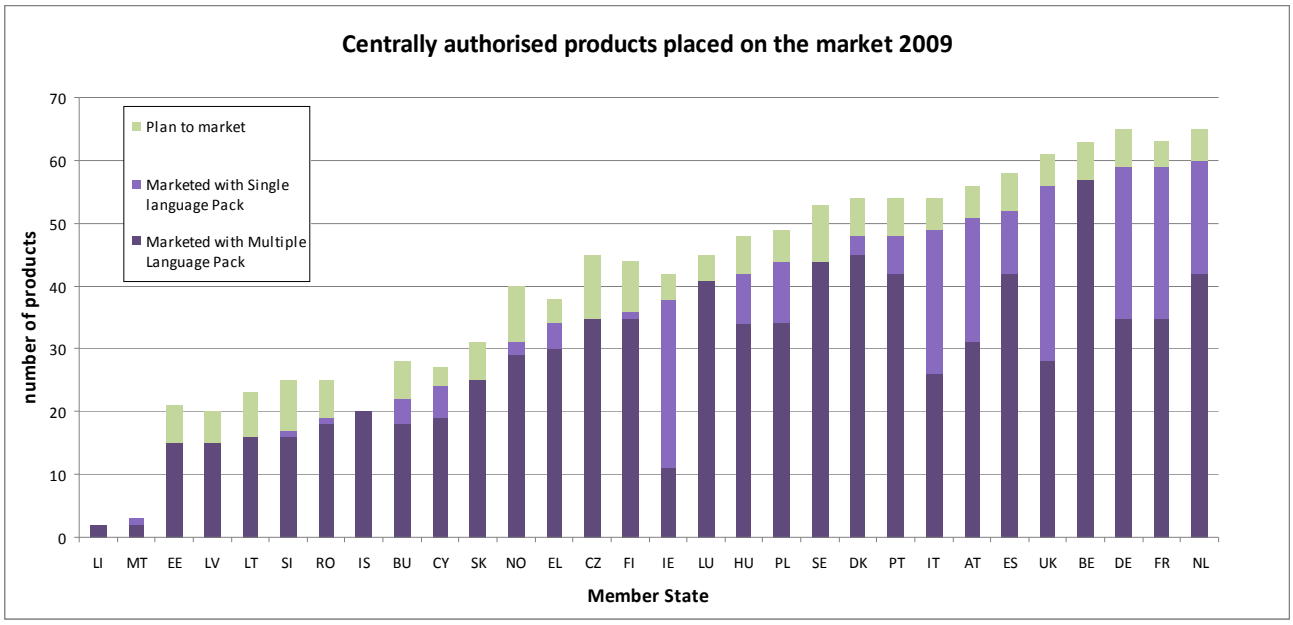
8.4.1 Impact on availability of veterinary medicinal products in small markets

The unit cost of manufacture is dependent upon the batch size. In Europe each market must be supplied with product labeled and packaged in the local language. For small markets the batch sizes needed are small. The cost of the packaging operation for small batches can mean that it is not financially viable to supply product to some small markets as the units costs are too high. The use of multi-lingual packaging can overcome this issue by allowing larger batch sizes for the packaging operation. Unfortunately the current legislation requires a large quantity of text to appear on pack labels, making the use of multi-lingual labels difficult.

The potential cost savings from the use of multi-lingual packaging have been investigated in a series of case studies (see section 8.4.2).

To provide an illustration of the problem, the results from a survey of the distribution of veterinary medicinal products authorised via the centralised procedure are shown in Figure 13 below. Even though the centralised procedure provides companies with a pan-European marketing authorisation, the product may not be placed on the market in the smaller markets. This is largely due to the packaging costs. It is interesting to note that some countries that represent relatively small markets, such as Luxembourg, Belgium and Austria, never-the-less have a high proportion of products on their markets. This may be partly due to the packaging batch sizes being increased by combining these markets with larger markets with the same language, such as France and Germany.

Figure 13: Graph on availability of centrally authorised products across EU 2009



8.4.2 Summary of the case studies

Four case studies are presented to illustrate the potential savings from the use of multi-lingual packaging. These case studies are summarised below, and the details can be found in Annex 6.

Case study 1 – blister packs with a leaflet in a carton

	13 individual presentations	1 single presentation with 13 languages	Cost saving	% saving
TOTAL Packaging costs	253,775€	121,667	132,108	**52 %**
QA/QC	13 batches	1 batch	12/13	**92 %**

Case study 2 – product packed with a leaflet in a carton

Activity	3 individual presentations	Single 3 language presentation	% Cost saving
Preparation of artwork	1 FTE	0.6 FTE	**40 %**
Costs of printing materials	3 x 10,000 units 3 x 500 units	30,000 units 1,500 units	**3 %** **12 %**
Packing operation – setup (and line clearance)	3 batches	1 combined batch	**67 %**

Case study 3 – 3 examples of vaccines packed with leaflet in an outer box

	monolingual pack 6 batches of 100 units	3-lingual pack 2 batches of 300 units	6-lingual pack 1 batch of 600 units
Product 1: Total Cost	3498 €	2034 €	1050 €
reduction of costs compared to monolingual pack		**-42%**	**-70%**
Product 2: Total Cost	4420 €	2964 €	1656 €
reduction of costs compared to monolingual pack		**-33%**	**-62.5%**
Product 3: Total Cost	4732 €	2330 €	720 €
reduction of costs compared to monolingual pack		**-51%**	**-85%**

Case study 4 – small vial and 500ml vial packed with leaflet in a carton

	1 language on 6 different packs (6 Lots of 10,000 units/lot)		3 languages on 2 different packs (3 lots of 20,000 units/lot)		6 languages on 1 pack (1 lot of 60,000 units)	
Small vial sterile liquid						
Total Cost including FTE	$28,200.00		$24,300.00		$16,800.00	
Savings vs 6 Lots			**-14%**	-$3,900.00	**-40%**	-$11,400.00
Non- Sterile Liquid 500 ml full label						
Total Cost including FTE	$16,440.00		$12,000.00		$7,200.00	
Savings vs 6 Lots			**-27%**	-$4,440.00	**-56%**	-$9,240.00

8.4.3 Conclusions from the case studies

The use of multi-lingual packs can significantly reduce the cost of producing individual language packs for each market, and will enable the product to be manufactured for small markets. The savings occur with the artwork, printing and packing operations; the warehousing and distribution costs are not significantly affected.

8.5 Disproportionate costs to pioneer companies due to legislation (impact on 'level playing field')

The introduction of the 'European Reference Product'[33] concept to facilitate the marketing authorisation process for generic products was intended to remove regulatory hurdles for generic procedures caused by disharmonisation in Europe. However it has had some unintended consequences, with a direct and serious impact on the 'level playing field' within the marketplace for veterinary medicinal products.

Typically if the originator (owner of the European Reference Product) wishes to remain competitive, he must now follow more difficult and costly procedures in order simply to obtain harmonized SPCs that are on a parity with those obtained by the generic. The steps to be followed by the originator to recover parity with the SPC of the generic depend in part on the circumstances and route of the initial registrations and are complex; the difficulties are demonstrated using a number of examples.

The following 7 case studies, which are described in detail in Annex 7, show how the generic procedure benefits from use of a European Reference Product (ERP), but the originator (i.e. the owner of the ERP) cannot compete without incurring significant additional costs. These case studies illustrate the additional costs that are incurred by the owner of the ERP in the following situations:

1. update the original marketing authorisation dossier;
2. running a repeat-use MRP;
3. the 'treatment withdrawal period' must be harmonised with the generic product;
4. applying for a 'line extension';
5. market distortion caused by national law;
6. loss of sales when the ERP was denied access to a MS market;
7. an article 34 referral.

Case 1: the owner of the ERP must incur significant costs to update the original marketing authorisation dossier.

Assume the Pioneer product is registered nationally in Members States (MS) A, B & C. The generic product, using a mutual recognition procedure (MRP) based on a European Reference Product (ERP), can apply for a marketing authorisation in MS 'D'. If the pioneer company wants to do the same, the level and cost of the data dossier required for a type II variation by the regulatory authorities is significantly higher, particularly since the originator has already borne the cost of the original data dossier.

Updating the dossier would take two to three years at a significant cost (> € 1 million).

Examples of typical costs would be:

Updating dossier part II, III & IV:	500,000€
Environmental safety package:	300,000€
Clinical update (if any):	250,000€
Fees for the type II variation:	100,000€
Total:	1,150,000€

Case 2: the owner of the ERP must incur significant costs running a repeat-use MRP.

Assume the Pioneer product is registered via MRP in Member States (MS) 1 to 12. The Generic product based on an ERP can apply for a MA in MS '13'. If the pioneer company wants to do the same, a repeat-use procedure is necessary. First it may be necessary to updating the dossier, which would take two to three years at a significant

[33] Article 13 of Directive 2001/82/EC as amended by Directive 2004/28/EC.

cost (> € 1 million) (see case study 1). In addition to this cost, and the cost of the repeat-use procedure in the new MS(s), two further costs will be incurred:

- pay repeat-use fees to some of the MSs (those who request it) involved in the original procedure; estimate 6 x 15,000€ = 90,000€;
- if the SPC is changed during the repeat-use procedure then variations will have to be submitted to the majority of MSs involved in the original procedure; assume 10 x 1500€ = 15,000€ plus significant human resources. In addition significant costs will incurred replacing pack leaflets to reflect the new SPC (estimate 50,000€).

Total costs = 1 million + 90,000 + 15,000 + 50,000 = 1,155,000€

Case 3: the owner of the ERP will incur costs because the 'treatment withdrawal period' must be harmonised with the generic product.

Assume the Pioneer ERP product is registered nationally in MSs A, B & C with different SPCs and withdrawal periods (WP) based on the same original dossier (i.e. the same dossier resulted in different national decisions in the national authorisation procedures). For example, MS 'B' and 'C' may have added a longer safety span to the results of the tissue residue studies leading to disharmony in the length of the WP.

The Generic product starts a MRP based on the national reference product in these 3 MSs with MS 'A' as Reference Member State (RMS). The generic will obtain an SPC with the WP used in MS 'A'. This gives a significant advantage to the generic product in MSs 'B' and 'C'. To get the same WP in MSs 'B' and 'C', the owner of the pioneer product is required to submit a type II variation. This will trigger requests from the competent authorities for new studies in line with the latest guidelines.

In total, this typically results in more than two years of delay and 500,000€ regulatory costs before it is possible for the pioneer product to compete with the generic on equal terms. The regulatory costs have been estimated but, as the length of the WP can be a critical issue in livestock production, this may also cause significant sales losses as the pioneer product may loose significant market share.

Case 4: the owner of the ERP must incur significant costs applying for a 'line extension' for the original product in some member states.

During the original registration of the pioneer product via national procedures, it is commonplace that different national competent authorities reach different decisions, resulting in different national SPCs for the product. Typical differences might be the refusal of an additional form of administration (i.e. a different method of giving the medicine to the animal) or the refusal of an additional species (i.e. the medicine can be used to treat a broader range of animals). Therefore in some MSs the use of the pioneer product is more restricted.

The generic can apply via the MRP using the 'best' SPC of the pioneer product as its ERP. The result is that the generic obtains the broader use of the product in all MSs, placing the generic at a competitive advantage over the pioneer in those MSs that restricted the use of the pioneer product.

To get an equivalent product the pioneer must ask for a line extension of its product; the cost and the timeline are higher than for a type II variation. For example:

Total Costs to update of the dossier: 460,000 to 800,000€
Total time of competitive disadvantage for the pioneer: more than two years.

This delay may result in the pioneer never recovering its market share.

Case 5: Shows the cost of market distortion caused by national law.

This case follows the same scenario as in case 3 (differences in the withdrawal period in the SPCs of the ERP). Based on national law (e.g. Germany), the shortening of a WP is only possible if there has been an official change to the maximum residue limit (adopted as an amendment to MRL Regulation 2377/90) for the particular Active Pharmaceutical Ingredient (API). If this is not the case a full new marketing authorisation application will be necessary.

This will require investment of several million Euros to redevelop the product as Germany – like all EU MSs – will only accept efficacy and safety studies according to today's standards. The time needed for completion of the task is around 4 years (conducting state of the art studies, registration process, re-launch).

This delay may result in the pioneer never recovering its market share.

Case 6: Cost of lost opportunity when the owner of the ERP is denied access to a MS market, then a generic obtains access via the European Reference Product system.

Prior to the introduction of the DCP a pioneer company would typically submit a marketing authorisation application to 15 to 20 Member States. It would not have been uncommon for about 15 of these applications to be successful and the remaining 5 to have suffered rejection or have been withdrawn by the Applicant because of the potential high cost to respond to questions from the assessor. Furthermore, it would not have been uncommon for some MSs to come to different opinions about the wording in the Summary of Product Characteristics (SPC) of the national marketing authorisation.

A generic applicant can now select the MS which possessed the best SPC/label of the pioneer product to use as the European Reference Product (ERP).

This process discriminates against the pioneer company, which was denied access to certain EU markets while the generic can obtain access free of competition. The revenues lost by the pioneer could be very considerable.

This market size could range from €1- 5 million.
The pioneer is therefore losing revenues of €1-5 million p.a.
The cumulative loss in denied sales for the first ten years (i.e. the period of data protection) is 10-50 M€.

It should be noted that the generic received its authorisation based on the safety and efficacy data of the pioneer ERP. **Therefore one has the extraordinary situation whereby the pioneer is excluded from some markets because those MS deem the data to be deficient while a generic enjoys full access in those markets based on the identical data set of the pioneer.**

Case 7: the cost of an article 34 referral to harmonise the conditions of use of the product (as defined in the 'Summary of Product Characteristics' of the marketing authorisation).

During the scientific assessment of a generic application via a Decentralised Procedure (DCP), it is possible that one MS may take a divergent opinion to the other MSs and call an Article 34 Referral to arbitrate on the matter. This involves the CVMP conducting a review of the data generated by the pioneer. The outcome of the CVMP review leads to a harmonisation of the pioneer and generic Summary of Product Characteristics (SPC).

This process involves the pioneer in retrieving all the relevant data requested by CVMP and defending it during oral hearings.

This involves expending considerable resources in terms of deployment of experienced personnel and cash resources. For example

Overall cost: 445,000€ (including labour costs and out-of-pocket costs)
Overall timeline: 18 - 24 months

8.6 Preference for centralised (efficient) procedures

IFAH-Europe has conducted several surveys of the functioning of the Centralised Procedure (CP). These surveys were conducted jointly with the European Medicines Agency, although each party produced their own report.

The most recent survey covered centralised procedures where the Commission Decision for MA fell between 01.01.2005 and 31.08.2007. The data obtained in the survey represented 25 of the 28 centralised procedures that occurred in this time period, and is based on data from 9 questionnaires, each referring to between 1 and 7 procedures from 9 IFAH-Europe corporate members (i.e. international/multi-national companies); it includes 3 avian influenza vaccines registered under exceptional circumstances (Article 39(8)).
The main reasons given for choosing the CP were:

- Avoidance of divergent national views; the scientific assessment is agreed via a majority voting at the Committee for Veterinary Medicinal Products at the EMA (2 replies);
- The CP has well defined, transparent timelines, allowing business planning (2 replies), expressed as "shorter timeline for approval and delivery of the marketing authorisation".
- Less national requirements (1 reply);
- It is the most efficient way for companies to obtain a pan-European marketing authorisation (4 replies)
- For two procedures the CP was compulsory (see Annex to Regulation 726/2004).

It is important to note that of the 25 procedures, only 2 were obliged to use the CP; the other 23 chose to do so. From this it may be concluded that companies prefer a centralised procedure if given the choice. However it is also recognised that SMEs are reluctant or unable to use a centralised procedure due to the high cost of the fees and the high cost of having to provide translations for all the packaging elements, even if the SME does not intend, or is unable, to market the product in every member state.

Chapter 9:

Variations in national requirements to marketing authorisations

9.1 Introduction and objectives

The objective of this chapter is to present the administrative burden arising from divergent national requirements (e.g. national differences in the Summary of Product Characteristics (SPC) for a product), resulting in potential fragmentation of the single market and the impact on business, on society and on animal health and welfare.

The impact can be assessed at three levels:

1. the additional administrative burden arising from the extra work created for companies during the regulatory procedures.
2. the impact on the efficient business operations of companies from the lack of a single market in veterinary medicinal products in Europe.
3. the impact on public and animal health from the lack of a single market in veterinary medicinal products in Europe.

9.2 Problem statement

The European Directive governing the authorisation and control of veterinary medicines is transposed into national law, or the implementation guidelines are interpreted differently, in a way that is fragmenting the single market resulting in high costs for companies. This damages competitiveness and innovation and ultimately the availability of animal health products. There appear to be cases where certain member states have either conflicting national law, or where translation differences create a disharmonised interpretation of the requirements. This can result in national requests for additional information/data over and above that laid down in the directives and guidance notes leading to excessive bureaucracy and work burdens for applicants wishing to license their products. An example is annexed (Annex 8: Poland case study).

Such divergent national requirements are identified as a major cause of the deficiency in the European single market for veterinary medicinal products. As there is a true single market for food in Europe, any divergent national requirements for veterinary medicinal products do not result in improved consumer safety.

In order to successfully tackle existing regulatory burdens, a number of challenges must be confronted.

It is important that there is a better understanding of Information Obligations (IOs), and resource cost to originators, for each divergent national requirement in order to assess the national administrative burden created by the subsequent need for harmonisation of national Summary of Product Characteristics (SPC) of products. This is important so that policy options can be assessed according to the extent to which they harmonise market authorisation requirements across the EU.

Information obligations (IOs) either above and beyond EU requirements or above and beyond those deemed necessary by other member states could be assessed via systematic comparison of additional national requirements.

9.3 The additional administrative burden arising from the extra work created for companies during the regulatory procedures.

Harmonisation of national SPCs case study

During assessment of a generic application via a decentralised procedure (DCP) it is possible that one member state (MS) may take a divergent opinion to the other MSs and call an Article 34[34] Referral to arbitrate on the matter. This involves the CVMP conducting a review of the data generated by the pioneer. The outcome of the CVMP review leads to a harmonisation of the pioneer and generic SPCs.

In case study 7 in chapter 8, an overall additional cost of €445,000 was incurred by the pioneer company, with an overall timeline of 18-24 months as the pioneer has to divert cash and personnel to retrieve all the relevant data requested by CVMP and defend it during oral hearings. All these costs are basically incurred because of divergent decisions by the national competent authorities during the original national registration procedures.

9.4 The impact on the efficient business operations of companies

Such divergent decisions in the European regulatory system significantly increase the time needed and the costs of authorising veterinary medicines in the EU and undermines the willingness and ability of the animal health industry to meet the social objectives of citizens (see 'Introduction – The value of the animal health industry to society'). Furthermore they undermine the confidence of companies in their attempts to succeed in their business endeavours in those member states taking such divergent opinions. Where such problems arise companies are choosing not to license their products in those markets with the loss of revenue that results and the decline in return on investment which ensues.

9.5 The impact on public and animal health

If such divergent approaches by some member states continue and new medicines are not licensed in their territories, the availability of new and innovative medicines will be impaired with citizens facing the possibility of increased risks to human and animal health and animal welfare, agricultural competitiveness and sustainability, and European trade.

[34] Article 34 of Directive 2001/82//EC, as amended by Directive 2004/28/EC

Chapters 10 and 11 (combined):

Time taken (and costs) for marketing authorisations to be approved; comparison of the EU with third countries

10.1 Introduction and objectives

The overall objective of this chapter is to illustrate that excessive bureaucracy and an overly risk averse approach to the regulatory framework is damaging competitiveness and innovation.

The animal health industry recognises the importance that the European authorities play in shaping the business environment. The primary objective of the authorities is to protect public and animal health, preferably by means that do not place any unnecessary burdens on business.

Companies fully recognise the need for government action and fully accept that high quality regulation is an essential pre-condition for competitiveness. However, risks must be managed proportionately to ensure the benefits of animal health products are accessible for consumers and animals. Otherwise an imbalance develops which adversely impacts the critical success factors for the industry; the two most important of these being time and cost to market.

10.2 The phases in obtaining a marketing authorisation

There are 3 main phases to be completed in bringing a new product to market:

1. Research and development phase
2. Application for a marketing authorisation and the scientific assessment phase
3. The administrative phase for the granting/issuing of the marketing authorisation.

Research and development phase - the situation in Europe

Since 1990 the industry has benchmarked the regulatory systems for veterinary medicines in the EU with those in other regions of the world. This has provided an invaluable archive of information on the cost and development times for comparative purposes, and it has identified several areas of serious concern with the regulatory environment in Europe. In particular both the time and cost of product development has increased significantly over the periods of the benchmarking surveys, and much more than in other regions. The key results of the most recent benchmarking survey, published in 2007, are highlighted later in this chapter.

Although the data requirements are not within the scope of this review of the veterinary legislation, the draft EMA Roadmap to 2015, page 19, presents an approach that could spread the impact of increased data requirements for veterinary medicines:

"In the field of veterinary medicines, the European Commission's impact assessment of the veterinary legislation will provide an opportunity to explore the possibility of developing a post-authorisation framework that is particularly suited to the needs and resources of the animal health sector. The Agency will consult with all involved stakeholders on how best to develop an appropriate risk management framework and to what extent it is possible to licence medicines for veterinary use at an earlier stage of development based on the requirement to provide the necessary post-authorisation data. "

Approval Times for Marketing Authorisations

For the scientific assessment phase, the timelines are well defined and considered acceptable for the purposes of obtaining a sound scientific assessment as the basis for a risk benefit assessment, particularly in the centralised procedure.

However delays can be incurred, particularly in the Mutual Recognition Procedure (MRP) or Decentralised Procedure (DCP), due to lack of a harmonised interpretation of the data requirements among member states, differences in scientific opinion or the benefit:risk assessment, and additional national requirements. These issues cause delays in the marketing authorisation application validation period, and the scientific assessment period (3 to 6 months clock-stop delays to allow time for the applicant to answer questions, which can be extensive and require the generation of additional data).

This aspect is not further explored within this chapter as removing the disharmonised interpretation of the requirements and additional national requirements has been discussed in chapters 8 and 9.

Granting of the marketing authorisation

The marketing authorisation granting phase for the centralised procedure results in a community decision on marketing authorisation, and is well defined (comitology procedures) and reasonably predictable. However the MRP and DCP require each concerned member state to issue a national marketing authorisation and this administrative step can be highly variable and create severe delays. This has a significant negative impact on businesses, as business planning, cash flow and competitiveness can all be adversely affected. Data showing the 'opportunity lost' cost arising from these delays is illustrated in the next section of this chapter using real data in 9 product case studies.

10.3 The impact of time to market on sales revenue

Case studies: the cost of sales opportunity lost through delays in obtaining the MA

In the MRP and DCP, following the end of the scientific assessment phase, the member states are then required to turn the scientific decision into a national marketing authorisation. The concerned member states are required to issue the authorisations within 30 days of final translations being approved, as recommended in the CMD(v) Best Practice Guide and article 32.5 of Directive 2001/82 as amended. This target is routinely exceeded, and can cause significant problems to the business plans of companies.

IFAH-Europe has collected 9 case studies (see tables 1 and 2) from recent decentralised procedures to illustrate the delays experienced in issuing the national marketing authorisations and the economical impact of this.

Method

The case studies are from 9 new or recently authorised products from four animal health companies and involve on average 19 member states each. The duration of any delay from the close of the procedure to the receipt of the licence is counted after the first 30 days (1 month) post-opinion have elapsed, as the member states are allowed 30 days to issue the licence (as referred to above).

The commercial impact of delaying the possibility to launch the veterinary medicinal products into the marketplace has been estimated using the annual sales (or forecast sales for new products) for each product for each member state; the monthly sales figure (or forecast) has been multiplied by the corresponding number of months of delay in each member state, to give the total value of the sales that have been 'delayed'.

The total annual sales for each product are known (or a forecast is known for new products). Thus the amount of 'lost/delayed' sales can be expressed as a percentage of the total annual sales for each product. The total lost/delayed sales were summated and expressed as a percentage of the total annual sales of all of the 9 products.

Results

Only 21% of the involved member states in these case studies issued the marketing authorisations within the stipulated 30 days from the end of the procedure (table 14).

The average delay in obtaining the MA across these case studies was 3.1 months. The longest delays in each case study ranged from 5.7 months to 21.8 months. This has a direct commercial impact, in terms of estimated "sales opportunity lost" of an average of about €566 000 for each of these case studies, corresponding to 20% of the annual sales of the products (table 15).

Table 14: Number of member states issuing the marketing authorisation within 30 days

Case Study number	Number of involved member states	Number of CMSs issuing the licence within 30 days	% of total CMSs in the procedure
1	23	2	9%
2	25	4	16%
3	21	7	33%
4	21	7	33%
5	8	1	13%
6	21	4	19%
7	21	4	19%
8	20	5	25%
9	12	2	17%
Average	**19**	**4**	**21%**
Total	**172**	**36**	**21%**

Discussion and explanations

The registration of veterinary medicinal products (VMPs) in the EU Member States proceeds mainly through the Decentralised Procedure. The process and the timing of the scientific assessment phase, which are strictly defined in legislation and best practice guides, are carefully applied by the Reference Member State and all the Concerned Member States.

However the final "National Phase" of the procedure where the national marketing authorisation is issued is less well regulated or not regulated. In some member states protracted administrative processes cause significant delays; in a few MSs these delays can be caused by national administration legislation.

For example, with the submission and the acceptance of the final product information translations, including packaging mock-ups for some concerned member states, with the delivery of the national marketing authorisation document and its compulsory registration number, the timing to place the "approved" veterinary medicinal product on the market for all concerned Member States (MSs) is not predictable, not transparent and can be extended to several months. This makes business planning very difficult.

Table 15: sales opportunity lost in year 1 due to delays in issuing a marketing authorisation following submission of the final product information translations

Case Study number	Number of involved member states	Average delay (months)*	Maximum delay (months)	Sales opportunity lost in year 1**	Percent of total annual sales
1	23	3.0	7.0	€ 2,971,973	19%
2	25	3.8	10.8	€ 137,380	9%
3	21	3.0	10.8	€ 379,507	19%
4	21	2.4	6.0	€ 511,253	19%
5	8	3.2	5.7	€ 22,300	4%
6	21	2.2	6.0	€ 409,000	21%
7	21	2.2	6.0	€ 268,000	17%
8	20	5.1	21.8	€ 374,100	25%
9	12	3.2	10.0	€ 23,280	46%
Average	**19**	**3.1**	**9.3**	**€ 566,310**	**20%**

* allowing 1 month before the delay is counted
** monthly sales for each CMS multiplied by number of months delay for that CMS

Delays often arise due to the need for mock-ups to be provided for some MSs, or for the product name to be approved – even though typically the name is not questioned during the actual procedure (one example reported that in the end the product was not launched in 2 MSs as it is not possible to force a MS to accept a common name with the 20 other MSs).

More and more applicants are submitting multilingual packaging, but the discussion with just one MS on the mock-up delays all the concerned MSs involved in this pack. It can also happen that a MS finalises the national MA in good time, but then a 'variation procedure' must be applied to this MA to accommodate a change asked by another MS before it will agree to issue the MA. All of those exchanges between national authorities and companies are a huge work load and are very time consuming for no good reason.

Loss of a season, loss of peak sales and loss of exports

It is important to note that these commercial figures should be considered a minimum loss, as they do not take into account two important compounding factors. Firstly, they do not take into account the seasonality of the use of the veterinary medicinal products. In some cases, it is possible that 2 or 3 months delay will impact the market of a full year if the product use is seasonal (i.e. it is only used at a specific time of the year).

Secondly, they do not take into account the potential impact of delayed market entry in terms of competition with other companies. The business plan will assume a sales growth curve that at some point will reach a peak representing maximum sales; at some point a competitor may enter the market, and from that point the sales of the first product will decline. However, if there is a delay in launching the first product, the effect of a competitor entering the market sooner after launch may mean that potential peak sales are never achieved. This can have a compound effect upon the life-time sales of the product.

In the case of products manufactured in the EU which are also exported, an additional "sales opportunity lost" may be factored in when a delay in the issuance of the MA in the Member State of manufacture also has a knock-on effect of delaying the availability of a Certificate of Free Sale needed for registration in the export market.

10.4 Data from the IFAH Benchmarking survey on the increase in time and cost of product development

Issue summary

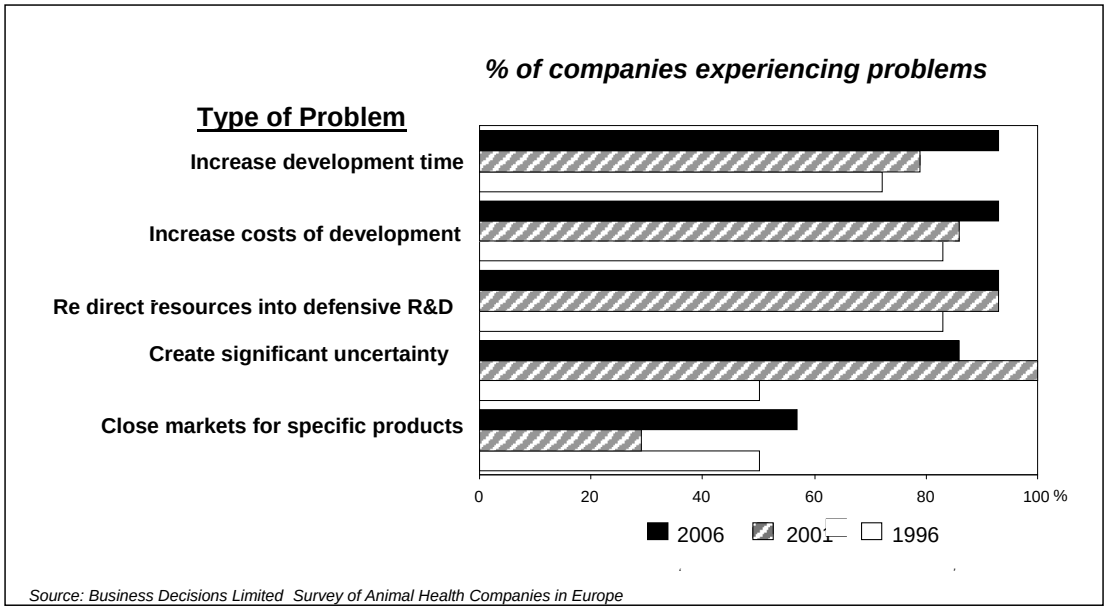
The time & cost of product development have significantly increased; since 1990 -

- product development time has increased by 2-4 years;
- cost of product development has more than doubled;
- meanwhile the data protection period has not been increased.

Excessive regulations create problems for companies because of their negative impact on the critical success factors for new product development (Figure 14). Over time, this negatively affects the number and type of product development investments undertaken by animal health companies, leading to a reduction in product numbers and a more limited range of indications.

The industry welcomes good regulation, and is all too aware of the impact of poor regulation, which European companies believe has increased development time (93% of companies), increased development cost (93%), re-directed resources into defensive R&D (93%), and created significant uncertainty (86%). This is illustrated in Figure 14.

Figure 14: Major Problems Created by Regulations for New Product Development in Europe: 2006 Compared to 2001 and 1996



Source: Business Decisions Limited Survey of Animal Health Companies in Europe

One step forward, one step back

There have been reforms over recent years to both the legislation (e.g. introduction of the decentralised procedure and fixed timelines in the European decision making process (comitology)) and detailed operating procedures that have improved the scientific assessment timeline and made it more predictable. However, set against this, there have been other changes in regulatory requirements that have expanded the research and development phase of the product cycle (see box 3).

Taken together, the regulatory-induced increases in product development time have offset the improvements in risk assessment times made by the competent authorities. Based on qualitative evidence from the IFAH Benchmarking surveys, possible explanations for the increases in time since 2001 include increased quality and safety requirements, but also inflexible [implementation of] guidelines and continued differences in approval requirements between countries appear to be an ongoing and persistent burden.

Box 3: Examples of increase in regulatory requirements since 1990

- Increase in safety requirements for food-producing animals; additional toxicity studies; and more complex studies, including additional Maximum Residue Limits, user safety, and environmental safety information
- Expansion of overall efficacy requirements in areas such as vaccines, antibiotics, limitation of therapeutic claims, long duration products, and specific doses;
- Increase in the use of comparative efficacy requirements, despite the presence of well-functioning product markets characterised by expert buyers and high levels of competitive intensity[35];
- Overall increase in safety, quality, and efficacy (SQE) requirements for companion animals, including target animal safety and efficacy; non-selective reviews of test data obtained from other sectors and species; and, increases in user safety studies;
- Increase in requirements based on human pharmaceutical requirements;
- Increase in manufacturing requirements, including the time needed to obtain GMP approval;,
- Continued use of some inflexible quality guidelines;
- New guidelines for testing requirements that impose new tests on products under development or awaiting approval on a retrospective basis;
- Lack of binding pre-development testing protocols to limit unforeseen changes in regulatory requirements; and,
- Continuing differences in approval requirements between countries.

Impact on time and cost of product development; comparison of EU position with that of third countries

Over the 15 year period between 1991 and 2006 companies in Europe believe that regulations have increased the average time needed to develop a major product by nearly 6 years for food producing animals and by over 3 years for pets. In the same period companies believe that the average time needed to develop a new product for minor species in Europe has increased by nearly 2.5 years because of increased regulatory burdens (see Figure 15). Nearly all of this increase has taken place in the last ten years.

In comparison regulations in the USA have had less impact on the time needed to develop new products. Over the same 15 year period regulations increased the time needed to develop a major new product for the livestock sector by 3.5 year (or less than 60% of the increase in Europe for the same period).

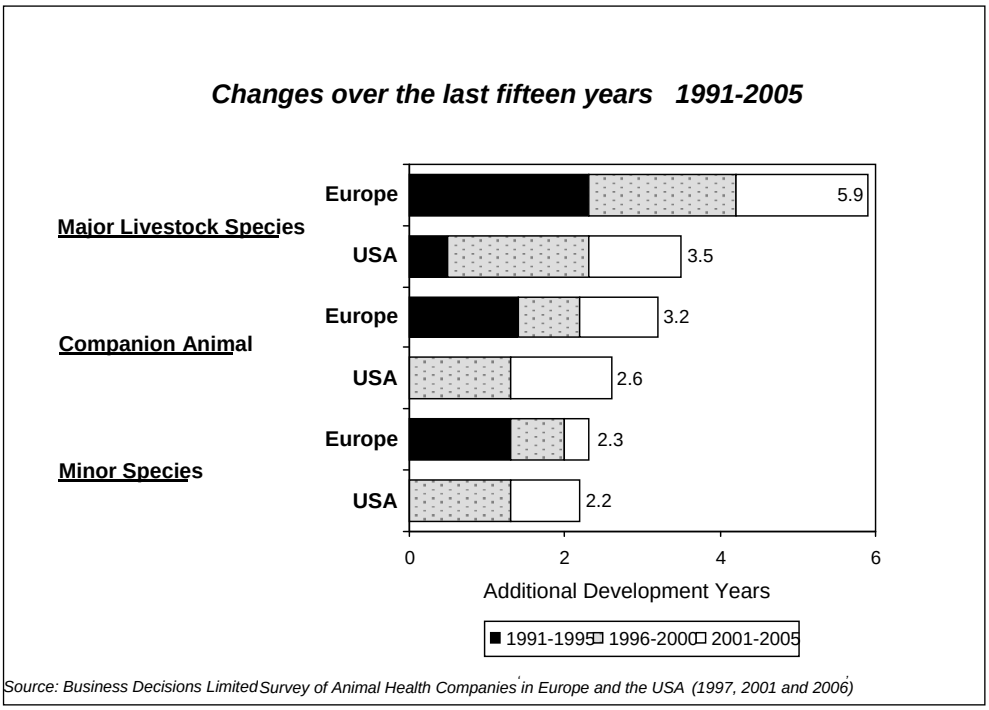
[35] Use of comparative efficacy requirements is justified on the basis of market failure that is the result of the presence of asymmetries of information. This is, companies believe, unlikely to be the case in the animal health industry because of expert buyers (vets) and high levels of competitive intensity. Moreover, the use of comparative efficacy by regulators erodes the functioning of markets; creates monopoly-type rents for existing competitors; fails to recognise the wide range in which products create value for customers; and leaves older, less efficacious products on markets whilst discriminating against newer ones.

Moreover, regulatory factors have caused the average cost of developing a major new product for the livestock sector in Europe to increase by 157% in real terms over the last fifteen years. The comparative number for the USA is 106% - or two-thirds the rate of increase in Europe.

There is a link between strategic business decisions (such as relocation of R&D facilities) and regulatory factors. Increased development time means increased costs. Consequently the situation in Europe means there is less economic attractiveness in developing new products in comparison to the USA and this of course results directly in a loss of innovation.

The EU 2020 strategy calls for 3% of EU GDP to be invested in R&D. However, poor Regulations reduce the "bang for your buck" of R&D budgets by impacting not only on the cost of development of new products but also by diverting scarce funds away from innovation and into the defence of existing products ("Defensive R&D"), especially in Europe.

Figure 15: Impact of regulatory factors on the average length of time taken to develop a new product in Europe and the USA



Source: Business Decisions Limited Survey of Animal Health Companies' in Europe and the USA (1997, 2001 and 2006)

Impact on Innovation

Current Situation

In the animal health industry, a significant proportion of research and development expenditure is used to maintain existing products on the market. Known as "Defensive R&D", this activity takes place because of the impact of scientific progress, market experience, and the need to remain competitive.

However, regulatory requirements, especially in Europe, create additional, mandatory defensive requirements, further reducing the availability of resources for the development of new products.

A continued high level of mandatory Defensive R&D in the EU has three significant negative impacts on the competitiveness of the European animal health industry:

- First, the level of financial resources available for investment in innovation of all kinds is reduced, leading to fewer new or improved products;
- Second, further strategic product rationalisation may be triggered, as companies become reluctant to continue to commit financial and human resources to the defence of 'old' products. Over time, this may create a "medicines availability" crisis;
- Third, it may reduce the relative attractiveness of the EU market for product development and exploitation.

Defensive R&D is high in Europe compared to USA

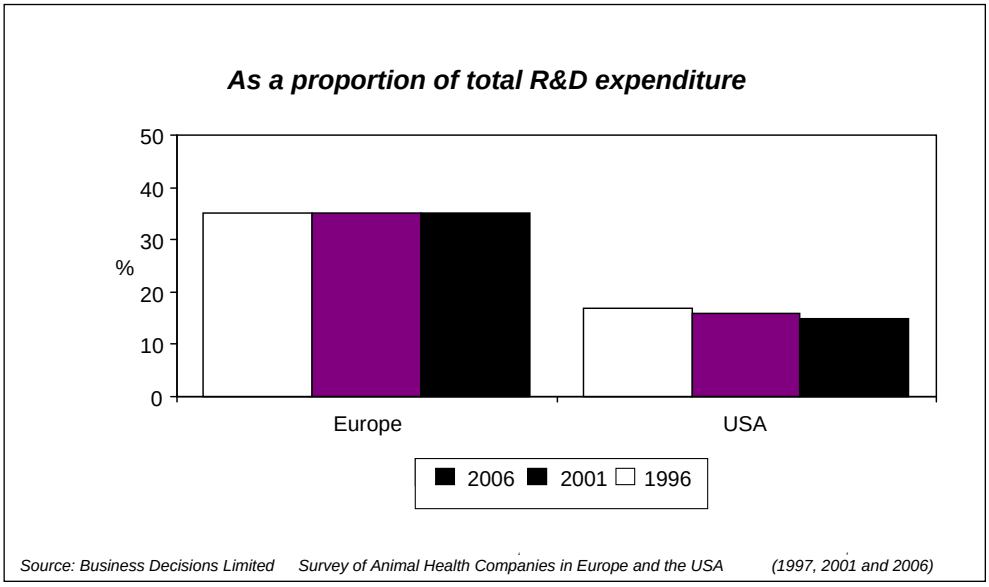
Evidence from the IFAH Benchmarking surveys carried out in 1996, 2001 and 2006, shows that companies in Europe spend circa 35% of their total R&D budgets on Defensive R&D (see Figure 16). This level has remained unchanged for the 15 year period of the surveys. It suggests that a high level of expenditure on defence of existing products has become a cost of doing business in the EU rather than, as was originally expected, a one-off cost of achieving a single market in veterinary medicinal products.

By comparison, companies in the USA spent about 16-18% in the same period, a slight decrease since 1996. In the opinion of technical, regulatory and scientific experts in companies, only 50% of the level of defensive R&D in Europe was justified by increased scientific knowledge, improved statistical methods and concerns about safety based on the best available science. The reasons given for why the remaining 50% is considered unjustified are listed in Box 4 overleaf.

In Europe there are many potential reasons why defensive R&D has remained high for over a decade, and these are listed in Box 5.

Overall, despite recent regulatory reforms at EU-level that have tried to alleviate these problems, for example, removing the need for existing products to be re-licensed on a five-yearly basis, and despite the launch of the EU 2020 strategy much improvement remains to be done to rectify the negative impact Europe's regulatory framework.

Figure 16: Level of defensive R&D, 2006 compared to 2001 and 1996



Box 4: "Unjustified" Defensive R&D

In-depth interviews with company experts suggest that 50% of the existing level of Defensive R&D is unjustifiable. This results from two factors: poor regulatory quality and decisions based on inappropriate or irrelevant science; and incomplete or inadequate assessment of risk. The specific problems include:

- **Application of legal requirements on a bureaucratic basis** – failure to use risk assessment appropriately or to consider the costs of administrative compliance when implementing manufacturing variations requirements;
- **Continued use of prescriptive test requirements that define both ends and means** ("command and control" regulation), including the requirements of the European Pharmacopoeia – this is a failure of regulatory quality;
- **Differences in the tests required by different national governments** – in most cases, licence renewals remain a national issue within the EU;
- **Introduction of new safety, quality, and efficacy requirements that are not based on relevant, high quality scientific evidence and a realistic assessment of risk** – in some cases, for example, there has been an expansion of tests based on *perceived* risks (and precaution) rather than robust scientific evidence of harm and realistic risk exposure scenarios;
- **Implementation of test requirements on a bureaucratic basis** - a failure to use realistic risk assessment and pharmacovigilance evidence to determine the scope of retrospective application of new tests to old, well-established products.

Box 5: Potential reasons why defensive R&D has remained high in Europe for over a decade

- **Continued mandatory renewal of the marketing authorisation of existing products on a five-yearly basis** – this provides regulators with a formal opportunity to seek new, additional test data (;
- **Dossier up-grading, improvement, and expansion programmes undertaken by a number of Member States** – national regulators and regulatory requirements remain important drivers of regulatory costs because of the large number of national product licences held by companies, especially for 'old' products;
- **Application to existing products of the test requirements for new products** ("retrospective application");
- **Continued use of inflexible guidelines to determine test requirements for new and existing products** – issued by the European Pharmacopoeia and regulatory authorities, especially the Committee for Veterinary Medicine Products at the EMEA, they prescribe the details of tests to be carried out and leave little room for flexible interpretation by companies;
- **Proliferation in the number of risk assessment and risk management bodies,** at EU and national level, involved in setting and implementing guidelines for animal health companies – new EU-level requirements have increased since 2001 without any significant corresponding decrease in national rules or involvement in overseeing existing products. This has led to an expansion in the number of tests required for new and existing products;
- **Continued differences in test requirements, and interpretation of legislation,** between Member States, leading to additional test requirements;
- **Proliferation of controls by national regulators over variations** in manufacturing activities (locations, processes, materials, suppliers) that might affect product quality, triggering substantial process, administrative compliance, and testing costs;
- **Expansion of national and EU-level safety test requirements for existing products** – additional tests have been required, for example, for environmental risks, antibiotics, and residues, including a progressive widening of the scope of MRLs;
- **Growth in scope and complexity of national and EU-level quality requirements for existing products** – major drivers of additional activity include widespread application of human pharmaceutical standards and of the requirements of the European Pharmacopoeia;
- **Increase in the safety and quality standards applied to existing products** used in the companion animal sector – progressively over the last decade, companies have been required by regulators to apply similar standards of safety and quality to all products regardless of the risks associated with different customer sectors;
- **Expansion in the efficacy requirements applied to new and existing products** – major examples include additional requirements for vaccines and antibiotics, as well as the expanded use of comparative efficacy requirements.

Chapter 12:

Resourcing and expertise

Major sources of information:

- EMA Roadmap to 2015
- HMA Strategy Document (2006)
- HMA BEMA reports (Benchmarking the European Medicines Agencies)
- HMA Proposed Training Strategy (2009 draft)

12.1 Resourcing

European Medicines Regulatory Network

The HMA Strategy Document (2006) recognises that the availability of resources within the European Medicines Regulatory Network (EMRN) is a compelling problem; a flexible and more efficient approach to the allocation of resource to European procedures and European projects is needed. Improved efficiency is needed by reducing duplicated work in different national competent authorities, e.g. sharing inspection reports, sharing information on lab testing, processing PSURs, and Pharmacovigilance signal detection and generation.

Some member states that are frequently used as the reference member state (RMS) in MRP and DCPs have had to introduce a queuing system due to the overload on requests to act as RMS. A better system to coordinate the allocation of work across the EMRN is needed. For example the animal health industry has proposed a single European procedure with a central coordination body that would oversee the appointment of a single scientific assessment team in Europe. Where appropriate the scientific assessment team could be multi-national.

A tremendous amount of resource is wasted for both companies and national competent authorities from the difficulties and inefficiencies caused by disharmonisation among the member states. This could be avoided with a single scientific assessment in Europe.

AFFSA Public Conference September 2008

The AFFSA Public Conference on improvements to the veterinary legislation concluded with the maxim “Do it well enough and do it ONCE”, in recognition of the resources wasted in repeating regulatory tasks such as scientific assessments.

To make effective use of resources, both systems and processes for the regulation and control of veterinary medicinal products should always be streamlined with efficient well-targeted approaches. Risk assessments should identify where the most relevant risks occur, and resources should be focused here; for example, resources should not be spent on PSURs for well-established products with no case-reports; resources would be better focussed on new products.

HMA Reflection Paper on the improvement of veterinary pharmaceutical legislation (draft, June 2009)

The HMA Reflection Paper recognises the pressure on resources within the EMRN, the need to avoid duplication of work and to simplify the regulatory procedures (line 684: “redundancies and waste of resources are identified in the marketing authorisation

process..”). In line 739 the reflection paper states: “Any consideration of how to change the authorisation processes should include the “1-1-1 Concept” of 1 dossier, 1 assessment and 1 authorisation…” as this proposal would remove duplication of work.

12.2 Expertise and training

The need for a 21st century regulatory environment for 21st century technology is paramount. The rate of scientific progress will require regulators to keep up to date with new technologies and to learn from research and experience in other industry sectors.

Both at the European Medicines Agency (EMA) and in the member state authorities attention must be given to the adequate recruitment of scientific staff appropriately trained in the relevant disciplines and continuing development of existing staff to be reasonably competent with such emerging science and technology. For the actual scientific assessment, the European Medicines Regulatory Network must have access to appropriately qualified experts to be part of the [multi-national] scientific assessment teams.

Historically at EMA and in member states having joint human and veterinary regulatory agencies, the smaller veterinary department has always struggled to get approval for additional staff when competing with the priorities of the human units and other responsibilities. This limitation on resources can be overcome by pooling expertise at a European level, appointing a [multi-national] single scientific assessment team to conduct a single scientific assessment for Europe.

Common Training

The outcomes of regulatory decision making must be robust and effective and have validity at EU level (to be accepted by all MSs). Enhanced training of assessors is identified as one way of reinforcing confidence in the Network, e.g. by the creation of an assessor’s academy, the organisation of common training on key regulatory or scientific issues and better links with large international training providers such as DIA, TOPRA, ISPE, etc. The current system does not provide systematic training or any of the advantages of shared training resources.

In addition the EMRN needs a system of audits or inspections of national competent authorities to demonstrate a required level of competence. Stronger investment in people with staff motivation/job satisfaction surveys would help to retain qualified staff.

EMA Roadmap to 2015

In the veterinary sector the state of art in terms of the benefit/risk methodology is not as advanced as in the field of medicines for human use; it needs the development and documentation of a systematic methodology for benefit/risk assessment, as well as training; the methodology can bring benefits in terms of availability when applied to medicines for emergency diseases and limited markets.

Annexes

Annex 1: More detail on the issues relating to data protection

[return]

1. Problem Statement: new species, line extension, new indication or dosage form

Directive 2004/28/EC strengthened the position of generic companies, but did this at the expense of research-based companies, and now presents a disincentive for innovation:

1. The link between data protection (article 13) and the global marketing authorisation (Article 5), which previously existed for centrally authorised products and is now extended to all European procedures, does not take into account the significant innovation required for developing a data package for a product line extension for an additional species, new indication or new dosage form.
2. Where a substance is developed first for companion animals the principle of the global marketing authorisation in Europe removes all data protection provisions for a subsequent development of corresponding livestock products, which will usually take longer because of the extra requirements to safeguard consumers of animal produce. This is a special, very unfortunate situation for the Animal Health industry.

In addition (a) there is no data protection for additional data requested and generated during the lifetime of a product, and (b) the product composition is published as a full list of excipients in the Summary of product Characteristics (SmPC), which potentially discloses trade secrets and proprietary information.

2. The 5-year window

In reality, the additional 3 years of data protection which can theoretically be gained from adding 3 species is almost impossible to obtain because the 5 year deadline is far too short. It would require an enormous R&D budget to run several R&D programmes in parallel on the same molecule in order to meet this deadline. In order to expand the use of the veterinary medicine to another food producing animals, a maximum residue limit must be assigned to the substance by the European Commission for the new species; for this an updated MRL dossier must be generated containing consumer safety studies on the new species, and then this dossier must be submitted to the European Medicines Agency for a scientific evaluation – this all takes several years. It may be possible to get 1 additional species licensed within the first 5 years but very difficult to get more than 1 - the licensing process itself can take 1 to 2 years.

The data protection periods for each species need not be cumulative, but should run separately for each species. In addition, they should be granted to the company that generates the data - this may or may not be the company that launched the original product on the market for the ‘first species’. Such an approach will remove major data protection obstacles to innovation. Innovation will be stimulated and more products will become available for more species. The concept is consistent with the approach in the existing legislation but recognises the reality of more than 1 species existing in the veterinary field.

3. Problem Statement regarding list of excipients in the Summary of Product Characteristics (SmPC)

Following the adoption of the amended directive, new SmPC guidelines were issued[36]. Section 6.1 of the guideline states a "full list of excipients" should appear on the SmPC. This wording has been transferred to the veterinary SPC guidelines from the *human* guidelines.
The requirement to list the full composition on the SmPC immediately discloses valuable information to competitors. We believe this is unjustified, is contrary to the rights of a marketing authorisation holder to keep certain licence information confidential, does not take into account the characteristics of the veterinary sector, does not meet the purpose of the Directive (to safeguard animal and public health, without hindering industry) and that this interpretation goes beyond the meaning of Article 14.

Background

Directive 2001/82/EC as amended by 2004/28/EC, clarified the content and order of the information to appear in the SmPC for veterinary medicinal products. According to Article 14, point 2 of the SmPC should contain the qualitative and quantitative composition in terms of the active substance and also any excipients where knowledge of them is essential for proper administration of the product. Article 14.6, simply states a requirement for a "list of excipients".

The current interpretation of article 14.6 requiring a "full list of excipients" is having a detrimental effect on innovation in the veterinary medicines industry.

The disclosure of this information is not sufficiently justified as it will not make a corresponding contribution to the protection of animal or public health.

The purpose of a SmPC is to provide veterinarians with the technical information necessary for safe and effective use of the product. Due to the incidence of allergic reactions, a human patient may well need to know which excipients are contained within a certain medicinal product. However, in the veterinary field, reports of allergic reactions as such are extremely rare, and because of this the need for a full disclosure of the composition of a veterinary product cannot be justified in this way. We believe that the current requirement is a clear example of the veterinary industry being disadvantaged by the application of a rule designed for products for human use.

Our interpretation of the intentions of the legislation is that excipients should be mentioned on the SPC where knowledge of them is essential for the safe administration of the product, but that there is no justification for disclosure of the full list of excipients.

[36] Guideline on preparation of Summary of Product Characteristics SPC - Pharmaceuticals for veterinary medicinal products (revision 2 - 07/2006).
Guideline on preparation of Summary of Product Characteristics SPC - Immunologicals for veterinary medicinal products (revision 2 - 07/2006).

Annex 2: Legal opinion: Additional data submitted post-authorisation

[return]

Under the current regime of the Veterinary Directive (Article 13), applicants for a marketing authorisation of a generic veterinary medicinal product[37], are not required to provide certain types of data that so-called "*reference applicants*" are obliged to submit as part of their full dossier[38]. Article 12(3) of the Veterinary Directive lists all data that should accompany the application for a reference marketing authorisation.

Indeed, Article 13 of the Veterinary Directive – which governs the authorisation procedure and information requirements for generic products – provides that "*by way of derogation from point (j) of the first subparagraph of Article 12 (3)*" a generic applicant is allowed to refer to the data contained in the complete dossier of the reference product only to the extent that these concern the results of the safety and residue tests or the pre-clinical and clinical trials and provided that the data protection period of 8 years has expired.

Article 13 does however not exempt generic MAHs from the obligation to submit additional data which were not already part of the authorisation dossier of the reference product at the time when the application for the initial marketing authorisation of the generic product was made.[39]

Indeed, pursuant to Article 13, generic producers wanting to introduce their generic product on the market for the first time and applying to that effect for a marketing authorisation, are exempted only from submitting the safety and residue tests or of the pre-clinical and clinical trials which are - at that point in time - already contained in the reference product dossier. This means *a contrario* that generic producers are required to submit (i) data other than the safety and residue tests or of the pre-clinical and clinical trials (even if contained in the reference product dossier, such as for instance, ERA tests); and (ii) once the generic producer has obtained its marketing authorisation, any additional data which, by definition, were not contained in the reference dossier at the time when the generic producer applied for his initial marketing authorisation.

The rationale for the limited exemption contained in Article 13 is to facilitate the entry of generic products into the market. Once the generic product is on the market, i.e. once the generic producer has obtained his initial marketing authorisation, this rationale obviously disappears. Therefore, once both generic and reference producers are present on the market and compete, there is no longer any justification for allowing a generic MAH to continue (without any limit in time) to "*free ride*" on the data submitted by the reference MAH. On the contrary, we consider that such "*free riding*" would be at odds with the principle of non-discrimination and reduce competition on the market between the generic and reference producers. In order to prevent a duplication of data, generic and reference MAHs should share the cost for additional data (e.g. via consortia).

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37 A "*generic medicinal product*" is defined by Article 13(2)(b) of the Directive to mean "*a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product [i.e. product that has been granted an authorisation within the meaning of Article 5 of the Directive] has been demonstrated by appropriate bioavailability studies*". A generic medicinal product is therefore essentially similar to the reference medicinal product and should in principle not have any characteristics which would require a re-evaluation of the product's potential negative impact on public health and environment.

38 See Article 5 *juncto* Article 12(3)(j) of the Directive.

39 In case of doubt, it should be recalled that Article 13 is an exception to the general rule and must therefore be interpreted strictly.

Annex 3: The 1-1-1 Concept

[return p.32]

The 1-1-1 concept is a vision for a single European procedure for all products (i.e. not just those that qualify for the centralised procedure) with 1 dossier, 1 European scientific assessment and 1 decision for marketing authorisation.

Organised through **a central coordination body**, with **national agencies as the backbone,** and would apply to all new and existing EU products, generics, classical and hi-tech products.

1 single dossier in English submitted to the central coordination committee which assigns the assessment team.

1 single European scientific assessment, with an assessment team using the best expertise within the EMRN, and with a single fee paid to the central coordination body.

1 single decision and a single European marketing authorisation valid in all member states, with the payment of a national fee for placing on the market of a member state (pay and do).

Why do we need a single system?
The current licensing system is complex, leading to a high administrative burden and inefficiencies. A lack of sufficient alignment between member states implementing the legislation and guidelines which creates additional bureaucratic hurdles.

The 1-1-1 Concept is a preferred solution, as it would maintain existing safety standards, while:

- Improve veterinary medicines availability
- Reduce administrative burden, thereby improving competitiveness
- Ensure a harmonized and practical implementation of the legislation leading to predictable, efficient and proportionate regulatory procedures
- Achieve a better regulation and simplification, creating a regulatory environment proportionate to the needs of the animal health industry
- Efficient utilization of resources within national competent authorities.

A more efficient regulatory system would benefit all stakeholders through:

- Efficient use of the European Medicines Regulatory Network's (EMRN) resources: reducing bureaucracy, removing duplication, attracting/retaining high quality staff.
- Workload reduction for the national authorities
- Fair and equitable regulatory environment for all applicants
- Harmonized implementation leading for efficient and proportionate system
- Better regulation, giving increased public confidence
- Increased access to EU markets creating business opportunities for SMEs
- Improved product availability benefiting animal health and welfare through improved access to veterinary medicines for pet owners, vets and farmers
- Enhanced food safety, food security, and protection of public health from zoonotic diseases
- Resources freed to provide market control and surveillance which will increase public confidence in the EMRN.

Annex 4: status of availability of veterinary medicinal product for rabbits in Spain

[return]

Table 16: Wish list of active pharmaceutical ingredients and registration status for rabbits in Spain (Source: Intercún)

		Availability		
	Molecule and administration route	**No**	**Application ongoing**	**Yes**
Respiratory disorders:				
	Chlortetracycline oral	**x**		
	Doxycycline oral		**x**	
	Enrofloxacin oral			**x**
	Erythromycin oral or subcutaneous	**x**		
	Spiramycin oral or subcutaneous	**x**		
	Streptomycin intramuscular		**x**	
	Oxytetracyclin oral			
	Tylmicosin oral or subcutaneous		**x**	
	Trimethoprim-sulfonamides oral	**x**		
Enteric disorders:				
As above	*Chlortetracycline oral*	***x***		
As above	*Doxycycline oral*		***x***	
As above	*Enrofloxacin oral*			***x***
As above	*Spiramycin oral*	***x***		
As above	*Oxytetracyclin oral*		***x***	
	Apramycin oral			**x**
	Avilamycin oral	**x**		**(x Italy)**
	Bacitracin de zinc oral			**x**
	Colistin oral			**x**
	Gentamicin oral	**x**		
	Neomycin oral		**x**	
	Tiamulin oral			**x**
	Tylosin oral			**x**
Parasiticides:				
	Benzymidazols oral	**x**		
	Ivermectin oral or subcutaneous	**x**		
	Levamisol oral	**x**		
	Robenidine oral	**x**		
	Salinomycin oral	**x**		
Antifungals:				
	Enilconazole spray	**x**		
	Griseofulvin oral	**x**		

Annex 5: Risks to human health from insufficient availability of veterinary medicines – examples in more detail

[return]

Introduction

Animal health is synonymous with human health

The link between animal diseases and human health has always been known, but its importance is lately underpinned by the attention that is being given to the new concept of 'One World One Health[40]', which emphasizes the convergence of human and animal health and the measures necessary to optimize both in an integrated approach. Over 60% of known human diseases are sourced from animals as are 75% of emerging human diseases. Authoritative sources suggest that world production of food is reduced by more than 20% due to animal diseases so that even those not transmissible to man may lead to shortages of food with consequences for human health.

Human health and well-being

The animal diseases which are transmissible to humans are known as zoonotic diseases and these pose a direct threat to human health. Animal health products help control these diseases and in some cases have eradicated them. Examples include the success of products to control brucellosis in cattle; the eradication of rabies in most of Western Europe, and the current potential threats posed by Avian Flu. Recent research also suggests that the ownership of pets can contribute to higher levels of well-being amongst their owners. It is suggested that levels of stress are reduced and the degree of happiness are increased.

The emergence of new zoonotic diseases also presents a challenge and it is virtually impossible to tell in advance when the next new disease from animal reservoirs will occur; preparedness is essential because predicting such developments is so difficult. Knowledge about zoonoses must be improved and the means to respond depends on the efficient development of new vaccines and treatment regimes in animals as well as man.

Vector-borne zoonoses already present or endemic in Europe and with potential for emergence include West Nile virus (WNV), sandfly-borne diseases, CCHF, tick-borne encephalitis (TBE), ehrlichiosis, bartonellosis, rickettsiosis, Lyme borreliosis, babesiosis, and leishmaniasis. Factors enhancing the possible spread of these zoonoses are climatic changes, increased animal reservoir densities, and more interplay between humans and nature (recreational activities). Different management of growing wildlife populations may lead to larger and possibly new tick populations. The relevance of these endemic and potentially emerging zoonoses for Europe must be considered in the context of availability of medicines for animals so that treatment of the diseases in animals can reduce the threat they pose to man.

Safe, high quality food

Veterinary Medicines make an essential contribution to protecting the health of Europeans. Safe food comes from healthy animals. Sick animals not only cost more to feed but the food they produce can often not be sold or poses a health risk to humans. Animal health products have, for example, reduced the incidence of Salmonella in humans, since the introduction of vaccines for chickens and cattle. Data show that the incidence of human salmonellosis in the UK has fallen from over 30,000 cases per year

[40] Initiated by the Wildlife Conservation Society http://www.oneworldonehealth.org/

in the period 1990-97 to less than 13,000 since 1997 after the introduction of salmonella vaccination into the "Lion Code" for egg production[41].

Veterinary Medicines also help to improve the standards of diet and the accessibility of essential and affordable nutrition for all citizens, particularly the less affluent, hence improving lifestyles, health and living standards. They achieve this through their impact on the price and availability of safe food.

Since the end of the Second World War, there has been a sustained fall in the real price of food. In 1950, for example, the average consumer spent nearly 40% of disposable income on food. Today, that figure has declined to less than 20%. The impact of the effective use of animal health products on production costs in the meat and dairy industries has contributed to this and consumers have the reassurance that products are extensively tested and heavily regulated to ensure that they are safe, and that residues do not pose a risk to the human food supply.

The control of zoonoses in production animals is therefore paramount. In Europe the list is an extensive one and includes tuberculosis, brucellosis, salmonellosis, campylobacteriosis, verocytotoxin-producing Escherichia coli (VTEC), trichinellosis, toxoplasmosis, hepatitis E, cryptosporidiosis, and cysticercosis, so the ability to treat and control these diseases in animals would have a huge and beneficial impact on human health in the Community.

Veterinary medicines in the control of human infection

Avian influenza

The spread of infections such as avian influenza[42] has highlighted both the crucial role played by veterinary medicines and the need for continued development of new and improved products. And yet, as this document explains, the availability of these vital tools is sometimes being compromised by current regulatory approaches. Failure to address this issue risks undermining the ability of our industry to provide solutions to problems that threaten both human and animal health.

Highly pathogenic versions of avian influenza (HPAI) is a serious disease due to the very high mortality rate in affected birds. The current variant of HPAI is now present in Asia, the Middle East and parts of Africa and Europe. It is most common in wild waterfowl species, but has also been reported in many common species of poultry, including chickens, ducks, turkeys, geese, pheasants and quail.

It is important to note that all reported human cases of H5N1 avian influenza (in Southeast Asia and Turkey) have occurred in people who have had close, direct contact with infected birds. So far there is no evidence of any human to human transmission of the H5N1 virus. Between 2003 & 2010, 116 people have been reported to have died from the disease. The reported symptoms of avian influenza in humans range from typical influenza-like symptoms (e.g., fever, cough, sore throat, and muscle aches) to eye infections (conjunctivitis), pneumonia, acute respiratory distress, viral pneumonia, and other severe and life-threatening complications.

From the viewpoint of human health, it is imperative to have vaccines available for use in poultry when it is not possible to control the disease only by culling infected birds. This greatly reduces the possibility of humans becoming infected.

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[41] Advisory Committee on the Microbiological Safety of Food (ACMSF) UK (2001)

[42] More information on avian influenza is available at
http://www.ifaheurope.org/CommonTP.aspx?SubMenuId=44&MenuId=14
http://ec.europa.eu/health/ph_threats/com/Influenza/influhome/avian_influenza_en.htm

However, the EU legislation requires companies to go through a full development programme within a set period of time if they wish to retain the right to place a product on the market. In the context where culling has been shown to be effective in the EU, no market exists for avian influenza vaccines. Some companies have responded by withdrawing their products from the market as there is no financial incentive to continue the development process. If the disease proves to be more difficult to control in the future, these valuable vaccines will not be available.

This points to the clear need for a true benefit/risk assessment where the vaccines are allowed to remain potentially available with further development only being required if the disease proves to be an ongoing problem where vaccines are actually used in the field. Where vaccination is used as a measure for control of this disease companies are at a big disadvantage because the regulatory framework requires that any time there is a change to the serotype of the virus a whole new dossier has to be compiled with new quality, safety and efficacy sections, which places very onerous demands on the applicants.

Food Borne Infections[43]

Campylobacteriosis

In 2008, campylobacteriosis continued to be the most commonly reported gastrointestinal bacterial pathogen in humans in the European Union with 190,566 confirmed cases[44] (see Figure 17). In foodstuffs, the highest proportion of *Campylobacter* positive samples was in fresh poultry meat where on average 30.1% of samples were positive. *Campylobacter* was also commonly detected from live poultry, pigs and cattle. Whilst the rate of Campylobacter in chickens across the EU varies from enormously, the average rate of contamination from those countries producing the majority of chickens is 71.2%.

The deployment of vaccines against Salmonella proved to be a very effective method of control coupled with a range of other initiatives. The lack of availability of a vaccine against Campylobacter in chickens represents a risk to human health. As Campylobacter is not detrimental to the chicken, there is no reason to vaccinate a chicken to protect its health. However, public health could benefit if such vaccination occurred as this, possibly coupled with other measures, would help to reduce the high rate of illness caused by Campylobacter.

Salmonellosis

According to the World Health Organization salmonellosis remains one of the most common and widely distributed food borne diseases which constitutes a major public health burden representing a significant cost in many countries. Millions of cases are reported worldwide every year resulting in thousands of deaths.

In 2008 in Europe, salmonellosis was again the second most often reported zoonotic disease in humans accounting for 131,468 confirmed human cases (see Figure 17). An important decline in the prevalence in laying hens was observed in 2008 which was the first year when Member States implemented new control programmes in this animal population. The improved situation in laying hen flocks may have been reflected in the decrease of *S. Enteritidis* cases reported in humans, since eggs are an important source

[43] The Community Summary Report on trends and sources of zoonoses, zoonotic agents and food borne outbreaks in the European Union in 2008

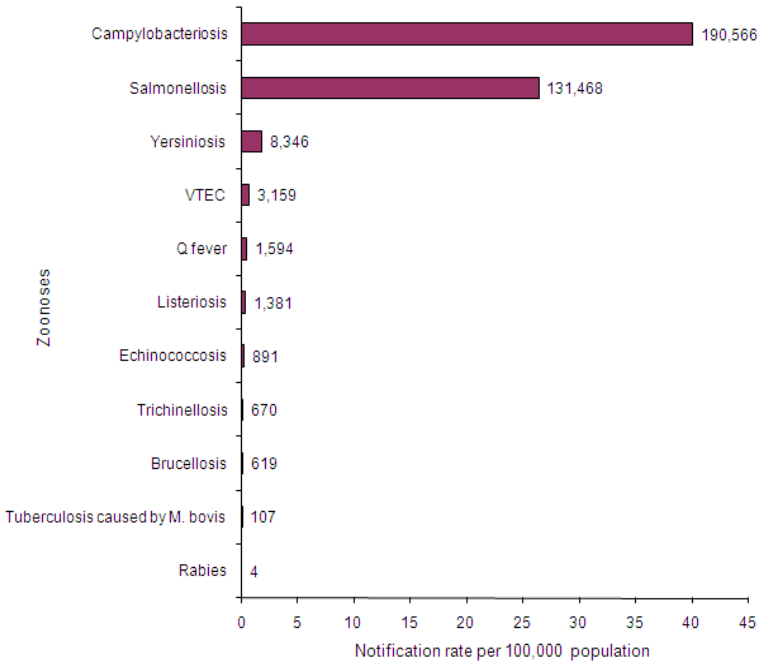
[44] Analysis of the baseline survey on the prevalence of *Campylobacter* in broiler batches and of *Campylobacter* and *Salmonella* on broiler carcasses in the EU, 2008

for these infections. This is the fifth consecutive year that a decreasing trend in the notification rate of the salmonellosis cases has been reported in the European Union.

In foodstuffs, *Salmonella* was most often detected in fresh broiler, turkey and pig meat, on average at levels of 5.1%, 5.6% and 0.7%, respectively.

Whilst antimicrobials play an important role in the control of this disease in animals there is a real need for the development of a range of effective vaccines for its control in all species of animal livestock.

Figure 17: Reported zoonoses rates in confirmed human cases in the EU, 2008[45]



Note: Total number of confirmed cases is indicated at the end each column

Rabies – a vaccination success story

Rabies is now one of the least reported zoonotic diseases in the EU (see Figure 17). This illustrates how a well executed vaccination policy can have a dramatic impact on public health.

Four cases of rabies were reported in humans in 2008 with one of them being acquired in mainland Europe and one in a French overseas department. In animals, most MSs have reported no or very few cases of classical rabies for a number of years. The Baltic and some south-eastern European MSs are an exception where sylvatic rabies is still endemic in wildlife and where rabies cases also occurred in farm and pet animals.

In wildlife, the majority of rabies cases were reported in foxes and raccoon dogs. The higher total number of rabies positive animals in the EU observed in 2008, compared to 2007, is mainly due to two MSs that did not provide any data in 2007. When results from 2008 are compared with results reported for 2006, the total number of rabies cases has decreased by 53.5%.

[45] The Community Summary Report on trends and sources of zoonoses, zoonotic agents and food borne outbreaks in the European Union in 2008

It is also important to note that Estonia, Latvia, Lithuania and Poland have reported a considerable decrease in the number of rabies positive animals during the past years, especially in foxes and raccoon dogs. These four MSs have implemented oral vaccination programmes in the wildlife with Community co- financing, and the results achieved by the programmes are monitored in the wildlife population.

Zoonoses in the European Union and item-specific summaries

The importance of a zoonosis as a human infection is not dependent on incidence in the population alone. The severity of the disease and case fatality are also important factors affecting the relevance of the disease. For instance, despite the relatively low number of cases caused by VTEC, *Listeria, Echinococcus, Trichinella* and *Lyssavirus* (rabies), compared to the number of human campylobacteriosis and salmonellosis cases, these infections are considered important due to the severity of the illness and higher case fatality rate.

Bovine Tuberculosis

This is a major intractable disease in cattle in Ireland and the UK with significant risks to consumers of unpasteurized dairy products. In addition the impact on the finances of the farm was the most frequently mentioned factor when farmers were asked about how the outbreak had affected the running of their farm business. Reductions in sales of milk or beef caused by the loss of culled animals and the inability to market store cattle were frequently cited. There were many comments about extra costs including having to buy extra feed and bedding for stock which had to be 'finished' instead of being sold as 'stores', putting up new buildings for them and employing extra labour.

In the case of farms with pedigree cattle there were losses from being unable to gain a premium price for pedigree sales whilst the herd was under movement restrictions and the cost of losing valued lines which had been bred on the farm by generations of the farming family. These losses were increased because the compensation given did not cover the premium value of pedigree cattle.

Whilst a culling policy is in place for infected cattle and the culling of badgers, which are the alternative host and are assumed to be a reservoir of infection, is under consideration there are still no vaccines available and they are urgently needed

The costs in terms of human health can also be significant. In the UK a report by the Farm Crisis Network illustrates well the toll that TB in cattle can have on farmers. TB in cattle is not seen by many as being a real zoonotic threat anymore as a result of the success of milk pasteurisation, but many farmers show clear signs of psychological distress as well as physical illness and while some assume cool resignation about the situation for themselves it is clear that they worry about the impact on their families. Farmers are also highly conscious of and concerned about their children's distress. Some indicated a desire to come out of farming or even end their lives because under the current control regime they could 'see no light at the end of the tunnel'.

http://www.farmcrisisnetwork.co.uk/latestnews/stress-and-loss-a-report-on-the-impact-of-bovine-tb-on-farming-families

Foot and Mouth Disease (FMD)

Whilst this disease is not classically a zoonosis, it can have a dramatic impact on human health in the farming sector. The psychological impact of FMD on farmers is mentioned in the Anderson enquiry (government enquiry) into the 2001 FMD outbreak as well as in numerous other enquiries.

Many of these reports mention the stress on people involved in culling operations, children unable to attend school etc. It is of paramount importance therefore that the authorities recognise that over-burdensome regulation reduces the scope for companies to develop vaccines that veterinarians and farmers can use in disease eradication and control programmes. Vaccination can replace the traditional culling policies employed for many such diseases and remove the stress and anxiety that such policies cause to all concerned.

The Anderson Inquiry into the 2001 FMD outbreak- http://archive.cabinetoffice.gov.uk/fmd/fmd_report/report/index.htm
Pages 134, 136 and 137 detail psychological impact and also describe how children's education suffered- http://archive.cabinetoffice.gov.uk/fmd/fmd_report/report/SECT_14.PDF

The importance of antimicrobial use in animals to human health

The veterinary profession and the farming community throughout the EU strive to provide the best healthcare and welfare for their animals, which contributes to the production of safe, affordable and abundant food, critical to European food security. Maintaining the health of European herds and flocks requires veterinarians and farmers to have all approved safe and effective animal health products including antimicrobials available to them.

The responsible, professional use of these products is important for animal welfare, but can also bring potential benefits to human health by reducing pathogens in and on foods; these benefits can exceed the relatively low increased human health risks associated with antibiotic resistance [46].

The primacy of preventing food borne illness in man is well appreciated and a major strategy to achieve this is the further reduction of pathogens on meat, poultry and eggs from levels already present. The availability of all the classes of antimicrobials for treatment of animals is therefore fundamental to the control of these food borne diseases in human medicine.

[return**]**

[46] A 2004 study done by scientists at the University of Minnesota College of Veterinary Medicine in which the potential risks associated with increased levels of antibiotic-resistant bacteria in meat were compared with the potential benefits associated with decreased risk of food-borne illness found potential benefits to human health associated with the use of antibiotics in chicken far exceeded the relatively low increased human health risks associated with antibiotic resistance.

Annex 6. Packaging case studies

[return]

General points

When companies produce a pack for a small market or for a big market, the product is marketed with almost the same price regardless of whether it is an important market or a smaller market, despite the higher cost for producing or ordering a few packs for a small market.

Case study 1 – blister packs with a leaflet in a carton

This case study compares the costs for the following:

1. Multilingual pack: a carton box (containing blisters of tablets) on which texts in 13 different languages (17 countries) are labelled, versus
2. Monolingual pack: the same carton box (containing blisters of tablets) on which the text is labelled in only 1 language.

1) Artwork creation/preparation

This stage covers the following: from translation stage to colour pdf, and includes regulatory affairs/studio/contractors/design costs etc, including manpower costs and actual costs.

A third party is used to prepare artworks at the following costs:

- Multilingual pack: Cost: 1,772 € for 1 single presentation (i.e. 1 combined package leaflet + 1 combined blister foil + 1 combined folding box).
- Monolingual pack: Cost 23,000 € (13x 1,772 €) for 13 individual presentations (i.e. 13 package leaflets, 13 blister foils and13 folding boxes).

2) Costs of the printed materials (blister, folding box, package leaflet)

This stage covers the printing of the packaging elements, and is contracted out. The costs are included in the manufacturing costs (see summary table).

3) Costs of packaging operations

This stage covers the manufacturing operations, including labelling, boxing etc per line batch release by QA/QP, the line clearance costs (N.B. the line has to be cleared more frequently for individual country runs). Include Costs and FTEs, e.g. QA, QP, packaging personnel.

To obtain a realistic outcome different production run sizes are used to show how one print run can replace (say 3 print runs) for different orders sizes (order for supplying large quantities of folding boxes in case of a major market versus order for supplying small quantities of folding boxes in case of a small market).

Batch release

In case of many monolingual packs and if the packaging operations take place at different time periods (according to the supply order, for example every quarter), the tablets will be packed at different dates and testing and releasing will be repeated accordingly.

4) Costs of Inventory/warehousing/write-offs

In terms of warehousing we pay a fixed rate irrespective of the number of pallets for storage. In terms of outbound handling, this would be the same as with country specific labels since the countries would all order and need deliveries. Where we would save would be in inbound handling.

In the case of a pallet load of 1920 packs per pallet, the inbound handling fee is 6.21€ per pallet, or 0.0032€ per pack.

Write-offs in case of expired material or product soon expired is included.

Table 17: Summary of packaging costs for packaging case study 1

Activities	13 individual presentations	1 single presentation	Cost saving	% Cost saving
Artwork creation/preparation	23,000 € (13x1,772)	1,772€	21,228 €	92%
Costs of the printed materials (blister, folding box, package leaflet) and Costs of Packaging operations- labelling, boxing etc per line as well as line clearance, except batch release	• blister (2 foils): (96,990+ 9,650) = 106,640 € • folding box: 84,000 € • package leaflet: 18,800 € Total: 209,440 €	• blister (2 foils): (78,050+ 7,245) = 85,295 € • folding box: 22,520 € • package leaflet: 12,080 € Total 119,895 €	21,345 € 61,480 € 6,720 € 89,545 €	20% 73% 35% 43%
Warehousing: fixed rate irrespective of number of pallets for storage	• warehousing: fixed rate • outbound handling: similar costs in both cases • inbound handling: 0.0032€ per pack	• warehousing: fixed rate • outbound handling: similar costs in both cases • inbound handling: • 0.0032€ per pack	0	0%
TOTAL	**253,775€**	**121,667**	**132,108**	**52%**
Other costs				
Write-offs	21,335€	0 €	21,335€	100%
QA/QC	13 batches	1 batch	12/13	90%

Conclusion

The use of multi-lingual packs can significantly reduce the cost of producing individual language packs for each market, and will enable the product to be manufactured for small markets. The savings occur with the artwork, printing and packing operations; the warehousing and distribution costs are not affected.

Case study 2 – product packed with a leaflet in a carton

The case study has examined the costs of a typical product packed with a leaflet in a carton. The costs are split into the following phases:
1. Preparation of artwork (from final text to final pdf ready to be printed)
2. Costs of printing materials for outer and immediate package label and leaflet
3. Packing operation – cost savings related to line setup and line clearance.

1. Preparation of artwork
Assume the costs for individual mock-ups for countries A and B and C = 1 FTE
Then costs for combined mock-up preparation A+B+C = 0.6 FTE
i.e. a 40% cost savings when preparing a trilingual mock-up
Amendment of mock-up (further to regulatory request): cost savings for a trilingual version (compared to 3 individual country mock-ups): 134 € / amendment

2. Costs of printing materials
Case 1: order of 10 000 units per country for countries A, B and C.
Savings per unit by combining 3 countries (order of 30 000 units): 0.20 € = 3% from the total cost

Case 2: order of 500 units per country for countries A, B and C.
Savings per unit by combining 3 countries (order of 1500 units): 1.78 € = 12% from the total cost

3. Packing operation – setup (line clearance) savings
1 batch respectively for country A, B and C
1 batch for all 3 "combined" countries (A+B+C)
Savings 450 € per batch

Table 18: Summary of packaging costs for packaging case study 2

Activity	3 individual presentations	Single 3 language presentation	Cost saving
Preparation of artwork	1 FTE	0.6 FTE	40%
Costs of printing materials	3 x 10,000 units 3 x 500 units	30,000 units 1,500 units	3% 12%
Packing operation – setup (line clearance)	3 batches	1 combined batch	67%

Conclusion

The use of a 3 language pack can significantly reduce the cost of producing individual language packs. The largest impact is on the packing operation, which involves both setting up the packing line, and clearing the packing line at the end of the packing run.

Case study 3 – vaccines packed with leaflet in an outer box

- 3 different vaccines for which production batches are the same are compared to show the costs of mono- and multi-lingual packaging. The costs are summarised in the table below.
- For each product there are an outer box, a vial label and a leaflet. The figures include the printing and site costs.
- The artwork preparation/creation covers from word text to the colour pdf.
- The personnel FTE costs for each activity are not included – only direct costs in Euros are mentioned. The FTE costs for line clearance between packaging runs are not included.
- Warehousing costs are not significant (it does not show real financial saving) – these are not mentioned in the tables.
- Write off costs are calculated by kg of finished product - these are not mentioned in the tables.

Table 19: Summary of packaging costs for packaging case study 3

Activity	Mono-lingual pack 6 batches of 100 units COST (€)	Multi-lingual pack (3 lingual) 2 batches of 300 units COST (€)	Multi-lingual pack (6 lingual) 1 batch of 600 units COST (€)
PRODUCT 1			
1/artwork preparation	1485	990	248
2/costs of the printed material	571	285	233
3/packaging operations	1442	759	569
Line clearance between runs			
Total Cost	3498	2034	1050
reduction of costs comparing to monolingual pack		**-42%**	**-70%**
PRODUCT 2			
1/artwork preparation)	1485	990	248
2/costs of the printed material	380	541	424
3/packaging operations	2555	1433	984
Line clearance between runs			
Total Cost	4420	2964	1656
reduction of costs comparing to monolingual pack		**-33%**	**-62.5%**
PRODUCT 3			
1/artwork preparation	1485	990	248
2/costs of the printed material	98	215	105
3/packaging operations	3149	1125	367
Line clearance between runs			
Total Cost	4732	2330	720
reduction of costs comparing to monolingual pack		**-51%**	**-85%**

Conclusion

Trilingual packs would produce savings of 33-51%, and 6-language packs 62.5-85%. These savings are highly significant.

Case study 4 – small vial and 500ml vial packed with leaflet in a carton

- US manufacturing site costs, using 10,000 units/lot, 20,000 units/lot and 60,000 units/lot.
- Two different products based a small vial and a 500ml vial packed with leaflet in a carton.
- The costs are not all inclusive and are based on averages. The costs include direct costs and personnel costs.
- The artwork preparation/creation covers from word text to the colour pdf.
- Warehousing costs will not be impacted by the changes so these are not included.
- The Batch Test and release costs are not included, but the savings would be pro-rata to the number of batches reduced.

The overall costs are shown in the table below, together with the level of savings that can be achieved using multi-lingual packaging. The unit costs are shown in the table overleaf.

Table 20: Summary of packaging costs for packaging case study 4

Activity / Cost	1 language on 6 different packs (6 Lots of 10,000 units/lot)	3 languages on 2 different packs (3 lots of 20,000 units/lot)		6 languages on 1 pack (1 lot of 60,000 units)	
Small vial sterile liquid					
Package initiation process	$600.00	$600.00		$600.00	
Cost of small vial and labels	$3,600.00	$3,600.00		$2,400.00	
Carton costs	$20,400.00	$18,000.00		$12,000.00	
Artwork initiation process	$1,200.00	$1,200.00		$1,200.00	
Line clearance between packaging runs	$2,400.00	$900.00		$600.00	
Total Cost including FTE	**$28,200.00**	**$24,300.00**		**$16,800.00**	
Savings 3 Lots vs 6 Lots		**-14%**	**-$3,900.00**		
Savings 1 Lot vs 3 Lots				**-31%**	**-$7,500.00**
Savings 1 Lot vs 6 Lots				**-40%**	**-$11,400.00**
Non- Sterile Liquid 500 ml full label					
Package initiation process	$600.00	$600.00		$600.00	
500 ml Bottle and label	$2,700.00	$2,400.00		$1,200.00	
Carton costs	$4,800.00	$4,200.00		$2,400.00	
Artwork initiation process	$1,200.00	$1,200.00		$1,200.00	
Line clearance between packaging runs	$7,140.00	$3,600.00		$1,800.00	
Total Cost including FTE	**$16,440.00**	**$12,000.00**		**$7,200.00**	
Savings 3 Lots vs 6 Lots		**-27%**	**-$4,440.00**		
Savings 1 Lot vs 3 Lots				**-40%**	**-$4,800.00**
Savings 1 Lot vs 6 Lots				**-56%**	**-$9,240.00**

Conclusion

The use of multi-lingual packaging can reduce the cost of packaging for small vials by 14% (for bilingual packs) to 40% (for 6 language packs). For 500ml bottles the use of multi-lingual packaging can reduce the cost of packaging by 27% (for bilingual packs) to 56% (for 6 language packs).

Table 21: Unit packaging costs for Case study 4 – small vial and 500ml vial packed with leaflet in a carton

Activity / Cost	1 language on 6 diff. packs Assumes 6 Lots of 10,000 units/lot			3 languages on 2 diff packs Assumes 3 lots of 20,000 units/lot			6 languages on 1 pack Assumes 1 lot of 60,000 units		
	Units	Cost/Unit of Production	FTE	Units	Cost/Unit of Production	FTE	Units	Cost/Unit of Production	FTE
Small vial sterile liquid									
Package initiation process	**FTE**	$0.01	0.01	**FTE**	$0.01	0.01	**FTE**	$0.01	0.01
Cost of small vial labels	10,000 units/Lot	$0.06		20,000 units/Lot	$0.06		60,000 units/Lot	$0.04	
Carton costs (one-pack cartons)	Cost/Unit of Prod	$0.34		Cost/Unit of Prod	$0.30		Cost/Unit of Prod	$0.20	
Artwork initiation process Cost/Prod unit and FTE	FTE	$0.02	0.01	FTE	$0.02	0.01	FTE	$0.02	0.01
Line clearance between packaging runs Based on lot size	Cost + FTE	$0.04	0.05	Cost + FTE	$0.02	0.02	Cost + FTE	$0.01	0.01
Product (SKU) Warehouse cost for 3 months	Cost	Not enough units to generate a cost savings impact.		Cost	Not enough units to generate a cost savings impact.		Cost	Not enough units to generate a cost savings impact.	
Non- Sterile Liquid 500 ml full label									
Package initiation process	**FTE**	$0.01	0.01	**FTE**	$0.01	0.01	**FTE**	$0.01	0.01
500 ml Bottle and label	10,000 units/Lot	$0.045		20,000 units/Lot	$0.04		60,000 units/Lot	$0.02	
Carton costs	Cost/Unit of Prod	$0.08		Cost/Unit of Prod	$0.07		Cost/Unit of Prod	$0.04	
Artwork initiation process	FTE	$0.02	0.01	FTE	$0.02	0.01	FTE	$0.02	0.01
Line clearance between packaging runs	Cost + FTE	$0.12	0.21	Cost + FTE	$0.06	0.07	Cost + FTE	$0.03	0.04
Product (SKU) Warehouse cost for 3 months	Cost			Cost			Cost		

[return]

Annex 7: Disproportionate costs to pioneer companies due to legislation (impact on 'level playing field')

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The introduction of the 'European Reference Product'[47] concept to facilitate the marketing authorisation process for generic products was intended to remove regulatory hurdles for generic procedures caused by disharmonisation in Europe. However it has had some unintended consequences, with a direct and serious impact on the 'level playing field' within the marketplace for veterinary medicinal products. Typically the originator (owner of the European reference Product) must now follow more difficult and costly procedures in order simply to obtain SPCs that are fully harmonized with those obtained by the generic. The steps to be followed by the originator to recover parity with the SPC of the generic depend in part on the circumstances and route of the initial registrations and are complex; the difficulties may be best demonstrated using a number of detailed examples.

The following 7 case studies show how the generic procedure benefits from use of a European Reference Product, but the originator (i.e. the owner of the European Reference Product) cannot compete without incurring significant additional costs:

- Case 1: European Reference Product: the originator must incur significant costs to update the original marketing authorisation dossier.
- Case 2: European Reference Product: the originator must incur significant costs running a repeat use MRP.
- Case 3: European Reference Product: the originator will incur costs and a period of competitive disadvantage because the 'treatment withdrawal period' must be harmonised with the generic product.
- Case 4: European Reference Product: the originator must incur significant costs applying for a 'Line extension' for the original product in some member states.
- Case 5: The cost of market distortion caused by national law.
- Case 6: The cost of lost opportunity when the originator is denied access to a MS market, then a generic obtains access via the European Reference Product system.
- Case 7: The cost of an article 34 referral to harmonise the conditions of use of the product (as defined in the 'Summary of Product Characteristics' of the marketing authorisation).

These case studies were prepared by individual companies based on their own experiences, and then 'verified' by the peer review of a working group of regulatory experts from 14 companies.

Case study 1: Data to show additional cost of Type II variation for the pioneer in addition to cost of initial registration.

Assume the Pioneer product is registered nationally in Members States (MS) A, B & C.
The generic product, using a mutual recognition procedure (MRP) based on a European Reference Product (ERP), can apply for a marketing authorisation in MS 'D'. If the pioneer company wants to do the same, the level and cost of the data dossier required for a type II variation by the regulatory authorities is significantly higher, particularly since the originator has already borne the cost of the original data dossier.

[47] Article 13 of Directive 2001/82/EC as amended by Directive 2004/28/EC.

For example:

Pioneer Product	Generic product
Cost of original dossier.	
Ask for MRP from MS 'A' to MS 'D'	*Submit an MRP application using an ERP*
An updated full dossier is required:	*Prepare a generic dossier*:
- Updated Part II	- Full Part II
- Updated part III	- Generic Part III
- toxicology	- bioequivalence
- residues studies	- residues studies if needed
- environmental safety, if needed	- environmental safety, if needed
- Updated part IV	- Generic Part IV
- dose determination studies	- Justification of exemption - Bioequivalence
- updated clinical trials	

Additional factors to consider for the calculation of the cost of the updated dossier include: the target species (livestock vs. companion animal), compound type (antibiotic or antiparasitic), tissue residues (technological progress, new methods and therefore new validation data), environmental safety (pasture, soil degradation), time of first registration (as this would determine the degree of update that will be necessary).

While the generic would have to invest in an appropriate Part II of the dossier (Quality/manufacturing) and bioequivalence only, for the originator, the time and cost would be increasingly disproportionate the older the original registration is. As generics are allowed to file applications only 10 years after the registration has been granted to the originator, a minimum of 10 years would be considered for the update period.

In the last decades, substantial new requirements were introduced in EU veterinary legislation via directives/regulations and guidelines. In fact, in most cases the initial registration is based on a dossier established 15-20 years ago. Given this, originators would have to invest in new (residue) safety and efficacy research for a new marketing authorisation in a MS, which would request data to comply with current standards.
Updating the dossier would take two to three years at a significant cost (> € 1 million).

Examples of typical costs would be:

Updating dossier part II , III & IV:	500,000€
Environmental safety package:	300,000€
Clinical update (if any):	250,000€
Fees for the type II variation:	100,000€
Total:	1,150,000€

Case Study 2: Cost of a repeat-use procedure with prior harmonisation of the SPC

Assume the Pioneer product is registered via MRP in Member States (MS) 1 to 12.
The Generic product based on an ERP can apply for a MA in MS '13'.

If the pioneer company wants to do the same, a repeat-use procedure is necessary to add MS '13'.
In addition to the cost differences described in case 1 above, and the cost of the repeat-use procedure itself, 2 additional costs appear:

- Pay fees in the MSs concerned by the first procedure (this requirement is not clear in some MS. It can be estimated to be between 10,000€ to 20,000€ per MS requesting it). Average of 6 MSs requesting it = 90,000€.

- A type II variation may be required in the first range of MS in order to harmonise the SPC in all Member States involved in the MRP. Assume 1500€ fee per MS, and 10 MSs = 15000€; the human resources (4-5 days); the impact on packaging, updating mock-ups, destruction of "old" packaging (9-10 days). Total 13 - 15 days (at 1,000€ per day = 15,000€) and 30,000€ to 40,000€ in costs.

Updating the dossier would take two to three years at a significant cost (> € 1 million) (see case study 1).

Case study 3: The period of competitive disadvantage following a ERP procedure

Assume the Pioneer product is registered nationally in Member States A, B & C with different SPCs and withdrawal periods (WP) based on the same original dossier (i.e. the same dossier resulted in different national decisions in the national authorisation procedures). For example, MS 'B' and 'C' may have added a longer safety span to the results of the tissue residue studies leading to disharmony in the length of the WP.

The Generic product starts a MRP based on the national reference product in these 3 MSs with MS 'A' as Reference member State (RMS). He will obtain an SPC with the WP used in MS 'A'. This gives a significant advantage to the generic product in MSs 'B' and 'C'.

To get the same WP in MSs 'B' and 'C', the owner of the pioneer product is required to submit a type II variation. We may consider that the studies presented originally are not acceptable anymore and that new residue studies, following updated guidelines, should be conducted. This type II variation will also trigger the need to also include an environmental safety package, as this requirement has been introduced since the original national registration. If the predicted environmental concentration exceeds the defined trigger level (i.e. PEC is > to 100) this means a full "phase II" environmental safety package will be required.

Additional costs:

- Fees per MS for the type II variation 1,500€ per MS
- New tissue residue depletion study 90,000 – 120,000€
  - Manufacturing of C_{14} material (45,000 – 60,000€)
  - New analytical methods and validation
  - Animal phase
- Potential environmental safety package phase I: 10,000€
- Potential environmental safety package phase II: 260k-390 k€
  (in case of Tier B 500,000€-750,000€)
  - Testing of environmental fate of the compound and its degradation products in soil and water
  - Testing of chronic effects on plants, water or dung organisms

Approximate Total Costs:	500,000€ to 1,000,000€

Additional time:

- Time to develop environmental safety package 12 – 18 months (soil degradation can take up to 12 months)
- Time to develop the residues study 6 months
- Time to get the variation 3 months
- Time to implement it, communicate etc. 3 months

Total time of competitive disadvantage for the pioneer:	two to three years

In total, this results in more than two years of delay and 500,000€ regulatory costs before it is possible for the pioneer product to compete with the generic on equal terms.

The regulatory costs have been estimated but, as the length of the WP can be a critical issue in livestock production, this may also cause significant sales losses as the pioneer product may loose significant market share.

If the more favourable SPC has been accepted for the generic, why can it not be accepted for the pioneer? The solution is to allow a simpler and less costly (no requests for new data) 'administrative variation' for the pioneer product based on the harmonisation given to the generic. This would reduce the time and costs to a more reasonable scenario and avoid the competitive distortion in the marketplace.

Case Study 4: Costs arising from line extension request

In case study 3 the SPCs had different withdrawal periods. In this case study the difference in the national SPCs of the ERP is an additional route of administration (i.e. a different method of giving the medicine to the animal) or an additional species (i.e. the medicine can be used to treat a broader range of animals).

As before, assume the pioneer product was registered nationally in several MSs. In some MSs the additional claims (i.e. for an additional form of administration or an additional species) were rejected. Therefore the resulting SPCs in each MS were different. In some MSs the use of the pioneer product is more restricted.

The generic can apply via the MRP using the 'best' SPC of the pioneer product as its ERP. The result is that the generic obtains the broader use of the product in all MSs, placing the generic at a competitive advantage over the pioneer in those MSs that restricted the use of the pioneer.

To get an equivalent product the pioneer product must ask for a line extension of its product; the cost and the timeline are higher than for a type II variation.

Additional cost:

- Fees per MS for the line extension procedure	10,000 – 20,000€
- Development of a new residue study (see comment above)	90,000 – 120,000€
- Potential environmental safety package	300,000€
(in case of Tier B:	50,0000 -750,000€)
- A new clinical trial (field study) will be needed to justify the additional species or additional route of administration (as the original studies will not comply with the latest guidelines)	20,000€
- Updated dose determination and target animal safety studies	10,000€
- New user safety studies and any other new requirements…	30,000€
Total Costs to update of the dossier:	460,000 to 800,000€

Additional time:

- Time to develop environmental safety package	12 – 18 months
- Time to develop new clinical trial	12 months (even more if seasonal product)
- Time to develop the residues study	6 months
- Time to get the line extension	12 months (210 days procedure)
- Time to implement it, communicate etc ..	3 months
Total time of competitive disadvantage for the pioneer:	not less than two years

In all the cases this delay may result in the pioneer never recovering its market share.

Case Study 5: to illustrate the market distortion caused by national law (e.g. Germany)

The following scenario applies (see also case 3):

Based on national licences issued well before 1998 (i.e. before the use of the MRP became mandatory) there are different withdrawal periods assigned by each MS for the product SAMPLE® of the company PIONEER. The company ME-TOO follows the concept of the European Reference Product (ERP) taking the ERP with the shortest withdrawal period (WP). It achieves the approval for SAMPLE-METOO® in all EU MSs including those where the WP is significantly longer.

"Best" case for PIONEER: see case study 3.

"Worst" case for PIONEER - e.g. Germany: Based on national law, the shortening of a WP is only possible if there has been a change of the maximum residue limit (as defined in the MRL Regulation 2377/90) for the particular Active Pharmaceutical Ingredient (API). If this is not the case a full new marketing authorisation application will be necessary.

Option one:
National application in Germany only: This will require investment of several million Euros[48] to redevelop the product as Germany – like all EU MSs – will only accept efficacy and safety studies according today's standards. The time needed for completion of the task is around 4 years (conducting state of the art studies, registration process, re-launch). It is also questionable whether SAMPLE® can be introduced again into the market as SAMPLE-METOO will quite rapidly replace the originator because of the shorter WP.

Option two:
PIONEER applies for an auto-generic, i.e. PIONEER files a generic application of its own product to avoid the requirements for a full new marketing authorisation application. This will mean that PIONEER re-enters the market only after approximately one year as compilation and registration process will take at least 1 year. Again it is questionable whether SAMPLE® can be re-introduced at all into the market as SAMPLE-METOO will have become established. Also, the PIONEER cannot compete price-wise as the auto-generic application will cost additional money (compilation, copying, distribution, fees).

[48] Here we may take IFAH-Europe figures from recent surveys (average development costs). However, we should reduce the total costs by the costs for PART 2 as this part is usually already state of the art.

Case Study 6: to show the cost of 'opportunity lost' when the ERP is denied access to a specific CMS or group of CMS.

Introduction

Prior to the change in the medicines legislation in 2001 the national route to obtaining marketing authorisations was the predominant procedure. Within the EU, a pioneer company would typically apply for a range of national licences. This range would vary considerably depending on the product and whether it made claims for a major indication in a major animal species.

Such applications would typically be made in between 15 to 20 Member States (as opposed to all of the EU countries) based largely on commercial considerations. Assume that 20 MS were selected by the Applicant for regulatory submissions. It would not have been uncommon for about 15 of these applications to be successful and the remaining 5 to have suffered rejection or have been withdrawn by the Applicant because of the potential high cost to respond to questions from the assessor. Furthermore, it would not have been uncommon for some MSs to come to different opinions about the wording in the Summary of Product Characteristics (SPC) of the national marketing authorisation.

Under Directive 2001/82 (as amended) the route to generic entry was greatly simplified. A generic applicant could now select the MS which possessed the best SPC/label of the pioneer product to use as the European Reference Product (ERP).

The amended legislation also introduced a new regulatory route, the Decentralised Procedure (DCP), which reduced the attractiveness of the national route. Although the DCP route did represent progress for both pioneer and generic companies, the outcome of a generic application via the DCP could be a generic authorisation in all 27 MS with the optimal SPC and label.

Clearly this process discriminates against the pioneer company, which was denied access to certain EU markets while the generic enjoyed unhindered access free of competition. The revenues lost as a result could be very considerable. It should be noted that the generic received its authorisation based on the safety and efficacy data of the pioneer ERP. **Therefore one has the extraordinary situation whereby the pioneer is excluded from some markets because those MS deem the data to be deficient while a generic enjoys full access in those markets based on the identical data set of the pioneer!**

Estimated cost of 'denied sales'

Pioneer product is registered nationally in Members States 1 to 18
Generic product based on ERP obtains registrations in all 18 MS plus MS '19' via the DCP route.

Consider also that MS '19' represents a significant market opportunity in which the pioneer MA application was originally rejected.

Now we have the scenario whereby a generic product is marketed in a significant market that was originally denied to the pioneer. The generic product is marketed in MS '19' without any competition from the pioneer.

In addition the generic authorisation is based on the **same** data set that MS '19' had rejected from the pioneer.

This market size could range from €1- 5 million.
The pioneer is therefore losing revenues of €1-5 million p.a.
Since the MS now has accepted the data package, the cumulative loss in denied sales for the first ten years (i.e. the period of data protection) are 10-50 M€.

Case Study 7: The cost of an Article 34 Referral to harmonise a SPC

Introduction

During the scientific assessment of a generic application via a Decentralised Procedure (DCP), it is possible that one MS may take a divergent opinion to the other MSs and call an Article 34 Referral to arbitrate on the matter. This involves the CVMP conducting a review of the data generated by the pioneer. The outcome of the CVMP review leads to a harmonisation of the pioneer and generic Summary of Product Characteristics (SPC). This process involves the pioneer in retrieving all the relevant data requested by CVMP and defending it during oral hearings. This involves expending considerable resources in terms of deployment of experienced personnel and cash resources.

Case Study

Scenario: a generic company applies for marketing authorisations in several countries via the DCP. One of the CMS calls a referral to CVMP on the basis of divergent decisions during the procedure. The referral is accepted and the pioneer is requested by CVMP to harmonise his SPC across all MSs.

Table 22: Activities and Costs involved, case study 7

Activity	Man days	Out-of-pocket cost €
Collation and review of all the SPCs in the EU	12	
Detail an exhaustive list of differences between the SPCs	4	
Review all sections of the SPCs	2	
Suggest appropriate changes where divergences exist	1	
Propose a harmonised SPC, label and PL	3	
Provide all available data to support the changes	5	
Internal experts to review the data	4	
Preparation of the Response Document	4	
Compilation and publication of the dossiers (in hard copy, 30 plus CDs, couriers)	7	6,000
Review of the Referral Assessment Report	3	
Response to the AR	6	
Revised AR review	3	
Compilation of Additional information requested by CVMP	10	
Resources for Internal and/or external experts; travel, hotels etc	6	15,000
Preparation for the Oral Explanation	6	
Written response to List of Outstanding Issues	3	
Draft Opinion review	3	
Comments on draft Opinion	3	
Adoption of CVMP Opinion	1	
Translations of SPCs, label texts and PLs into 23 official languages	3	20,000
EC Decision and standing committee written procedure	0	
Droit de regard for the EP	0	
Publication of EC Decision in OJ	0	
Start of the national variation phase		
Preparation of Type II variations to all MS	18	9,000
Regulatory national fees* (based on average €1,000)		18,000
Creation of label mock ups	18	
Creation of new labels for all MS	18	
Write off of label inventory, packaging		120,000
Cost of new labels, label development		120,000

Total man days	**137**	
Total € (Man days costed at €1,000 per day)	**137,000€**	**308,000€**
Overall cost	**445,000€**	
Overall timeline	**18-24 months**	

All these costs are basically incurred because of the original different decisions by the competent authorities. Yet the costs are not (fully) absorbed by them.
A pro-active referral as requested by the authorities would add a cost of 37,700 € to this overall cost.

Of course it is recognised that a MAH can refuse the opportunity offered to work with the CVMP on harmonising its SPC. In that situation, the CVMP will undertake the harmonisation itself which will inevitably result in a SPC of the lowest common denominator. This will have a wider impact of removing label claims particularly for minor indications/species. However some companies may decide that the cost of defending a harmonised SPC for some products is too great with claims and/or products being lost to the European market.

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Annex 8: Poland case study

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Regrettably, there are problems throughout the EU. Looking at Poland as an indicative example illustrates the challenges and burdens resulting from fragmentation. The fragmentation is mainly caused by the inappropriate application of human legislation by national authorities; an example of unnecessary additional national requirements complicating the Mutual Recognition and Decentralised Procedures and impeding validation of a marketing authorisation (MA) application.

The Polish legislation "KPA-Codex of Administration Proceeding" requires all documents listed below to validate an application:

- Extract from Chamber of Commerce for the applicant authenticated by RP consul in the country of origin or by apostille, equipped with original of sworn translation to Polish language. For each new procedure another original (or notary certified copy) of apostille and sworn translation must be provided. Such document is valid until changes are implemented and it must be replaced afterwards by a new set of documents.
- Notary certified copy of Power of Attorney: letter of authorisation for local representative for communication and to act on behalf of the applicant, furthermore this letter should be signed by two persons according to Extract from Chamber of Commerce for the applicant. The same letter of authorisation is required for the person authorised to communicate and to act on behalf of the applicant during the procedure.
- A signed commitment that all the translations attached to the application and all copies are exactly the same as the originals (one statement for all the translations and copies will suffice).
- A signed declaration that the same documentation is submitted in all CMS.

Based on examples of best practice in other member states we consider all these requests as superfluous and not appropriate for the conduct of MA procedures, because they do not add any benefit to the evaluation. These requirements are purely bureaucratic and result from the restrictive interpretation of the Polish administrative legislation.

The Polish authorities base their request on the Hague Convention[49] (1961) regarding foreign public documents. This is outdated now that Poland has acceded to the EU and the EU directive prescribes the documents that must be submitted with an application.

For example, Art 12 of Directive 2001/82 says (para. 3) that the application for a MA shall include all the administrative information and scientific information necessary for demonstrating the quality, safety and efficacy of a product. The file shall be submitted in accordance with Annex I. The annex to Directive 2001/82 exactly describes the documentation to be submitted. It refers also to the Rules governing medicinal products in the European Community (including the Notice to Applicants). In the NtA the national Polish requirements do not include the above mentioned extra requirements.

Furthermore, the Directive states explicitly (article 30 last para.) that the applicant is responsible for the accuracy of documents and data submitted and (article 83 paragraph f) that the MA can be suspended/revoked if the application documents are incorrect.
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[49] This abolished the requirement of legalization for foreign Public Documents (legalisation substituted by an apostille). Poland became a Convention signatory on 19.11.2004. Since then, or rather after Poland joined the EU, the Polish authorities required apostilles. A legal opinion suggests that the Polish requirements are contrary to the principle of mutual recognition, are obstacles to the free movement of medicinal products in addition to being disproportionate and unfair.

Annex 9: Detailed tables of each information obligation of the marketing authorisation procedures (annex to chapter 8)

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