

GLOBAL BENCHMARKING SURVEY 2020

Benchmarking the competitiveness
of the global animal health industry

EUROPE

AUSTRALIA

BRAZIL

CANADA

CHINA

INDIA

JAPAN

MEXICO

RUSSIA

SOUTH AFRICA

USA



Contents

- Key outcomes 3
- Key recommendations 3
- 1. Executive summary 4
 - Summary of key outcomes 4
 - Summary and recommendations 7
 - Changes since the GBS 2015 Survey 8
- 2. Introduction and background 9
- 3. Outline methodology 10
- 4. The findings for Europe 11
 - Section A – Financial data 11
 - Section B – IMPACT OF REGULATIONS ON INNOVATION 14
 - Section C - COMMERCIALISATION OF EXISTING PRODUCT 32
 - Section D - REGULATORY PREDICTABILITY & QUALITY 38
 - Section E - REGULATORY TRENDS 41
 - Section F - HOPES AND EXPECTATIONS FOR THE NEXT 5 YEARS 45
 - Section G - REGULATORY COOPERATION AND SPECIAL PRODUCT CATEGORIES 49
- Glossary of Abbreviations 51

Key outcomes

The key outcomes in the Executive Summary are condensed into the following set of bullet points:

- AnimalhealthEurope member companies spent an average of 7.8% of their revenue on R&D (range 6% to 9.4%), which is consistent with previous benchmarking surveys.
- The protection of technical documentation is important for stimulating investment in new product development and undermining intellectual property through public access to documents policies is damaging to innovation in the European Union (EU).
- The regulatory framework is ill-adapted to biologicals, particularly the data requirements and the burden of the variations regulations.
- Faster approval times for certain vaccines are needed so that the industry can respond to rapidly changing disease situations in Europe.
- There is a very wide variation in the proportion of company R&D budgets spent on mandatory defensive R&D (range from <1% to 40%).
- The rate of increase of product development time over recent decades is slowing down and a small reduction in the time taken for the product registration step is noted.
- The centralised procedure is ranked highly as an enabling factor for innovation, and the Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP) are also seen as helpful.
- The biggest hurdle to innovation is environmental safety legislation, the resource intensive manufacturing inspections and the EMA policy on access to documents.
- The growing cost of pharmacovigilance systems has become a significant challenge.
- Post-authorisation efficiencies from grouping and worksharing variations are highly valued.
- Regulatory predictability and regulatory quality in the centralised procedure are highly valued.
- The many steps taken by CMDv to improve MRP/DCP are recognised and appreciated.
- Some significant beneficial changes have occurred in the EU regulatory framework since the previous survey in 2015, but there are many other improvements still needed; great hope lies in the successful implementation of Regulation (EU) 2019/6 to address some remaining issues.
- There is great concern that efforts by the European Commission to reduce administrative burden through the new regulation will be steadily eroded when implemented by the member states.
- Companies believe that international regulatory cooperation has a positive or very positive impact on their ability to innovate.

Key recommendations

- Continue the drive for greater harmonisation within the EU regulatory network
- Continue efforts to bring more efficient regulatory procedures and digitalisation
- Good implementation of the new regulation is a key short-term factor moving forwards, particularly to achieve the original objectives of the review of the legislation (such as reduced administrative burden for all parties, and support for innovation)
- Better adapted systems for biologicals
 - For example: variations, clinical trials, greater access to accelerated assessment for urgently needed vaccines, multi-strain dossiers and antigen master files
- Better adapted systems for novel therapies,
 - These often fall between two stools in relation to the data requirements for biologicals and pharmaceuticals, and need specialist knowledge
- Keep risk assessment procedures for environmental safety and antimicrobial resistance proportionate for the veterinary medicinal products sector
- Do not let pharmacovigilance become the next administrative mountain
- Continue to build more opportunities for dialogue between key stakeholders and work together for the most successful outcomes
- Pursue international regulatory cooperation and convergence

Global Benchmarking Survey 2020

Report for Europe

1. Executive summary

The HealthforAnimals Global Benchmarking Survey is run every 5 years and has now grown to include 11 countries in the 2020 survey. The purpose is to examine the interactions between industry and regulatory systems for veterinary medicinal products, particularly the impact of regulations on the animal health industry's ability to access markets, be innovative, continue to commercialise existing products and be competitive.

This report is the sixth for Europe. It summarises the data from 12 companies that are members of AnimalhealthEurope and examines key trends. The GBS2020 global overview report, published separately, draws comparisons with the other key markets surveyed.

Data was collected through questionnaires in Q4 2019, and then aggregated and summarised to allow discussion in a subsequent workshop. The key points from the workshop discussions are an integral part of this report, which follows the questionnaire structure with 7 separate sections.

Summary of key outcomes

Section A - Economics of the animal health sector

The global animal healthcare (i.e. medicines and ancillary healthcare products) industry continues to grow (\$24 billion in 2015 and \$41.5 billion in 2018); as part of this, the global veterinary pharmaceuticals market was estimated to be nearly \$33.8 billion in 2018. Europe is the second largest market, after USA, but remains a small fraction of the human medicines market. Company growth is driven by many factors. Acquisition is a common growth strategy to build competence and capacity in technologies, new science, new therapies and new geographies. The livestock and pet sector markets are themselves growing in size.

Eleven of the twelve AnimalhealthEurope member companies provided financial data (including 8 that are also members of HealthforAnimals). Their average annual gross turnover was \$461 million in 2018, with a range of approximately \$50 million to \$1 billion. They spent an average of 7.8% of their revenue on R&D (range 6% to 9.4%), which is consistent with previous surveys.

Section B - Impact of the EU regulatory environment on ability to innovate

The regulatory environment can be both an enabler and a disabler of innovation. In the veterinary medicines sector there is a continual tension between the small size of markets¹ and the need to provide sufficient technical data to support regulatory decisions that provide the necessary level of protection to public and animal health and the environment. Thus, key aspects become the extent and cost of data requirements, the level of acceptable risk in the veterinary medicines sector and the benefit:risk approach to registration. The data requirements must be finely tuned to this approach, and to the characteristics of the veterinary medicines sector.

The protection of technical documentation plays an important role in stimulating investment in new product development and undermining intellectual property through public access to documents policies is damaging to innovation in the EU. With the exception of the maintenance of the "global

¹ The veterinary medicines market is small (around 3% to 5%) in comparison to the human medicines market, and is highly fragmented by the need to address multiple species.

marketing authorisation principle”, there is optimism for the new provisions for protection of technical documentation in the new regulation (Regulation (EU) 2019/6).

It is not surprising, therefore, that the key factor relevant to innovation is the EU regulatory framework, and how it addresses or manages these issues.

A trend through many of these surveys is how the regulatory framework is ill-adapted to biologicals, particularly the data requirements (as defined in the annex to the primary EU legislation on veterinary medicines) and the burden of the variations regulations. Evolution of the regulatory framework to allow new regulatory approaches, such as new vaccines technologies platform, multi-strain dossiers and the Vaccine Antigen Master files, could help to relieve some issues; however it will need to be clearly defined and managed by well-trained assessors on this type of product. The most important thing is to get faster approval times for certain vaccines so that the industry can respond to rapidly changing disease situations in Europe.

The continual drain on R&D budgets from mandatory defensive R&D has been a key issue within Europe; as seen in previous reports, there is a wide range between companies. Concern remains with the increased focus on antimicrobial resistance and environmental safety. However, industry is thankful that at the time of the survey progress was expected on reducing administrative burden with the more efficient management of variations under Regulation 2019/6.

Other good news is the slowing down of the rate of increase of product development time and the small reduction in the time taken for the product registration step

This survey yielded insufficient data to identify any clear trend in product development costs; concrete observations are not possible due to the low sample size and high within-sample variance.

As in the previous surveys, the centralised procedure is ranked highly as an enabling factor, as is the protection of intellectual property. The Mutual Recognition Procedure (MRP) and Decentralised Procedure (DCP) are also seen as helpful (with the exception of the persistence of additional national requirements). The biggest hurdle to innovation is environmental safety legislation, the resource intensive manufacturing inspections and the EMA policy on access to documents.

Section C - Commercialisation of existing products

As with stimulating innovation, the Regulatory Framework is the most critical factor relevant to the exploitation of existing products, through the maintenance and extension of existing licences.

Pressure from competitors in a small and highly fragmented market and negative consumer attitudes continue to concern companies. In previous surveys the lack of data protection for investments into existing products featured high on the list of issues, but in 2019 this has become less of a concern thanks to the new Regulation adopted in January 2019 (which becomes applicable in January 2022).

The post-authorisation efficiencies brought by the centralised procedure are once again recognised, as is the sound business investment of good manufacturing practice. Requirements for environmental safety data and antimicrobial resistance data pose a threat to the renewal of existing products, and the frustrations caused by delays in variations for manufacturing changes is evident. The resources needed for packaging and labelling changes continue to be a major challenge. The growing cost of pharmacovigilance systems has become a significant challenge, with the view emerging that the cost of inputs has become disproportionate to the expected output of improved product safety in the veterinary sector.

Section D - Regulatory predictability and quality

The regulatory predictability and regulatory quality of the centralised procedure remains as a shining light in the European regulatory framework. The next survey, in 5-years' time will be a milestone for this factor, as the impact of opening up the centralised procedure to all products becomes evident.

The steps taken by the CMDv to improve the regulatory predictability and regulatory quality of the MRP/DCP are recognised, but there is still more work to do to bring greater efficiencies and overcome challenges. Not least is the need for more harmonisation and the removal of additional national requirements, that continue to add unnecessary administrative burden into the system, despite the efforts of the CMDv to tackle these. As with the centralised procedure, the next survey will be interesting, to see if the rating of the MRP/DCP improves, as we see both the impact of moving from a directive to a more-directly applicable Regulation, and the impact of the modified regulatory procedures.

Section E - Regulatory trends

Some significant beneficial changes have occurred in the EU regulatory framework since the previous survey in 2015, not least the structures and systems put in place to prepare for novel therapies, increased efficiencies in the management of variations (work-sharing and grouping), and increasing digitalisation, including the implementation of e-submissions and the E-application form. The cost of defensive R&D, as estimated by this sample of companies, has been found to have a wide range from <1% to 40% of the total R&D budget. This probably reflects different company portfolios and business strategies. The large majority of companies reported that their expenditure on defensive R&D had increased.

There still remains a long list of areas where there has been unrewarded expectations of change. Additional national requirements remain a continual battle; it seems as some are eliminated, other new ones appear. Applicants also believe that we still have not reached the full spirit of mutual recognition within the EU. There are several provisions for biologicals that were anticipated but did not materialise, such as the vaccine antigen master file system and the reduction in the need for efficacy field trials for vaccines where this is justified.

The developments that cause the most problems are the continued cost of environmental risk assessments (ERA) and AMR, the double-edged sword of new or revised CVMP guidelines, that on the one hand improve transparency in expectations for data requirements, but on the other hand continue to increase requirements and the cost of product development. GMP inspections are costly, and duplicated inspections are a tremendous waste of resources. Companies are questioning the overall value of the escalating cost of pharmacovigilance and there have been some major complaints about the disproportionate cost of variations that affect multiple dossiers, such as changes to the 'detailed description of the pharmacovigilance system'.

Section F - Hopes and expectations for the next 5 years

The top most helpful trends and most unhelpful trends

The survey asked companies to consider some trends or changes in regulatory approach that have been taking place recently and the expected impacts of these on business in the next 5 years. The top most helpful trends were the move from a zero-risk to a benefit-risk assessment approach, the increased use of more efficient procedures for the management of variations (work-sharing and grouping) and the move towards greater use of electronic submission and efficient data management.

The top most unhelpful trends were the increasing transparency with respect to data disclosure (access to documents policies), the continued use of the Global Marketing Authorisation concept

(article 38.3 of Regulation 2019/6) and the increasing requirements for post-marketing surveillance and pharmacovigilance.

These top helpful and unhelpful trends remain the same as in the 2015 survey.

Expected impact of the new Regulation 2019/6

The new regulation was published in January 2019, before this survey was conducted, but it does not become applicable until January 2022. There is a mixed response from industry to the new regulation, reflecting the mixed outcome of the review of the legislation. While overall positive towards the progress that has been made, there is a general feeling that it was a missed opportunity to make significant inroads into the high administrative burden of EU regulations. However, the true impact depends on the content of the secondary legislation and supporting guidance. There is an unprecedented number of implementing and delegated acts to be drafted and adopted, as part of the implementation of the new regulation. While this brings uncertainty in the short term, it is also an opportunity to further deliver the objectives of the review of the legislation, such as reducing administrative burden. Equally, there is the risk that the secondary legislation and guidance further erode any gains in reduced administrative burden.

Change still wanted

Short term, the industry is calling for the practical implementation of the new regulation, and better implementation of existing principles, such as mutual recognition and fully harmonised approaches across MSs. Understanding how regulatory science should evolve to prepare for new technologies and new therapeutic paradymes will be critical to supporting future innovation. There should be more opportunities for industry and regulators to really work together to deliver the best outcomes on challenges facing all stakeholders in the EU regulatory network.

Medium term, regulation that is better adapted, where appropriate, to the characteristics of the veterinary medicines sector is a common objective (e.g. more veterinary specific aspects to GMP).

Long term the industry is looking globally towards greater harmonisation between regions and more mutual recognition agreements.

Section G - Regulatory cooperation and special product categories

Regulatory cooperation

All respondents responded positively that their EU regulatory authorities engage in cooperation with other regulatory bodies at a global level and that international regulatory cooperation has a positive or very positive impact on a company's ability to innovate.

Special product categories

In EU legislation there is a raft of provisions allowing a flexible approach to data requirements in special situations. This is an expected outcome within a market sector that is both small and highly fragmented and also heavily regulated, necessitating adaptations of the rules to take into consideration different needs and special situations.

Summary and recommendations

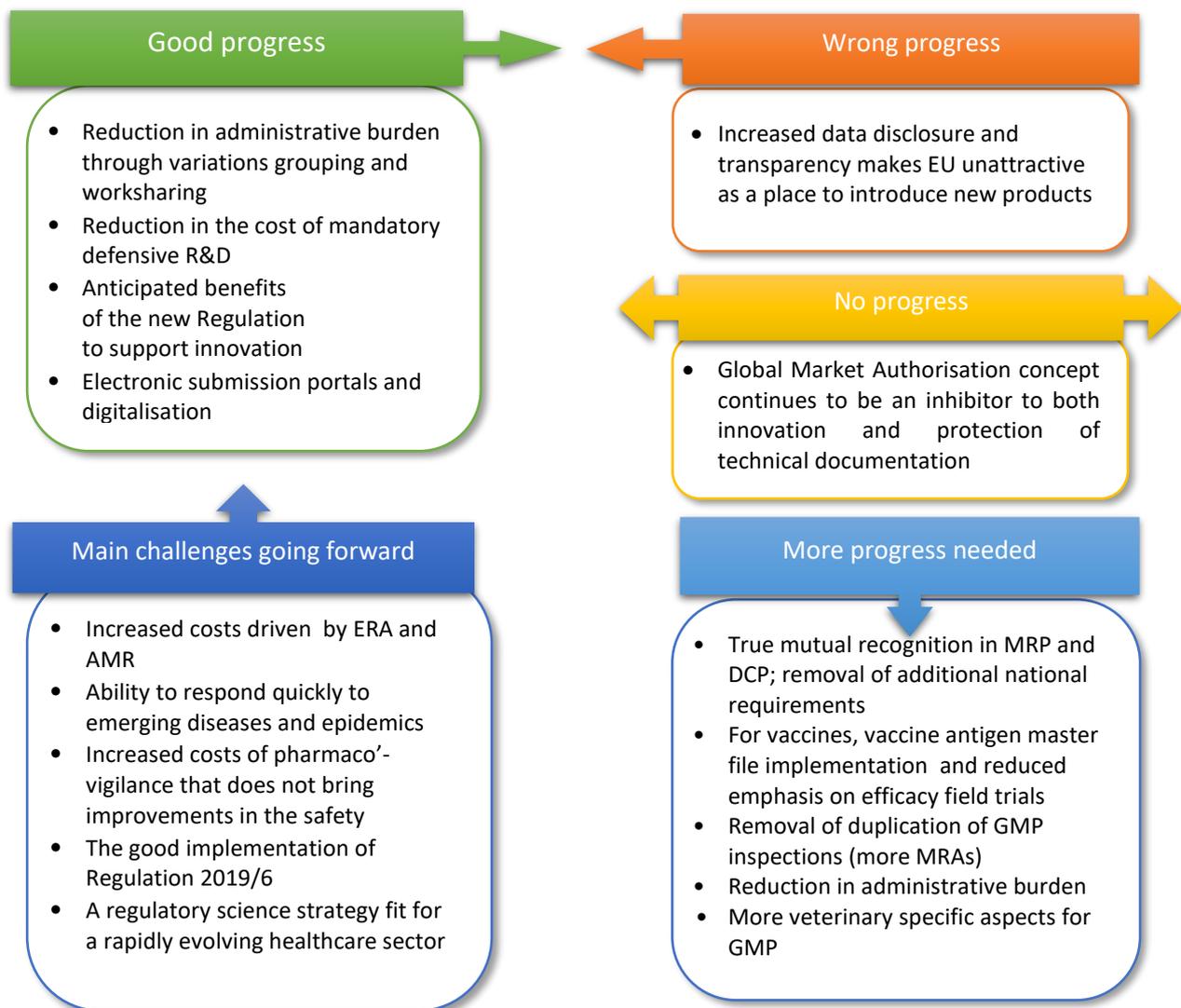
The regulatory environment only evolves slowly, and many of the issues, hopes and expectations identified in previous surveys are carried forward in this one. However, in the EU we are at a milestone moment, on the eve of the implementation of a new regulation, which brings some raised optimism towards increased support for innovation, but also a concern that the objectives of the review of the legislation will not be sufficiently met for the reduction in administrative burden.

The costings data in this survey has been highly variable, forestalling any firm observations. The impact of the cost of defensive R&D requires a more in-depth study and a better understanding of the variables.

The EU regulatory environment is unique, as it is composed of a network of national regulatory agencies; this brings unique challenges in devising efficient and cooperative regulatory systems across the EU, and building harmonised implementation of common rules and erasing national divergencies in decision-making. Progress has been made in some areas of the regulatory system, but the drive for greater harmonisation must continue.

The key recommendations have been summarised on page 4, and the major changes since the previous Benchmarking Survey in 2015 are summarised in the graphic below.

Changes since the GBS 2015 Survey



2. Introduction and background

The purpose of the HealthforAnimals Global Benchmarking Survey is to examine the interactions between industry and regulatory systems for veterinary medicinal products, particularly the impact of regulations on the animal health industry's ability to access markets, be innovative and be competitive. This includes the ability to bring new products to the market, as well as to retain and exploit existing products on the market and thus the impact on the availability of veterinary medicinal products.

This report is the sixth for Europe. It summarises the data from 12 European based international companies.

The survey originally benchmarked the European Union and USA regulatory systems but has since evolved to include the main VICH markets and has now grown to include 11 countries in the 2020 survey (see box).

The evolution of the Global Benchmarking Survey

1. 1996: Europe, USA
2. 2001: Europe, USA
3. 2006: Europe, USA, Japan, Australia, Canada
4. 2011: Europe, USA, Japan, Australia, Canada
5. 2015: Europe, USA, Japan, Australia, Canada, China, Brazil
6. 2020: Europe, USA, Japan, Australia, Canada, China, Brazil, India, South Africa, Russia, Mexico

The survey is run every 5 years with the cooperation and involvement of the HealthforAnimals national member associations. The purpose reaches beyond simple benchmarking, to include monitoring of trends and to identify the emerging issues in the regulatory environment that may have an impact on competitiveness, ability to do business and medicines availability. The survey is also a useful tool to gain insight into the expectations of the industry over the next 2-3 years in response to current regulatory dynamics and to provide information that allows development of clear action plans for meeting any identified challenges.

The outcome of this survey provides a wealth of information to support informed policy decisions in the continual search for best regulatory practice and opportunities for improvement.

3. Outline methodology

The previous Benchmarking Survey **questionnaire** from 2015 was updated to reflect the requirements for the 2020 survey, including: retention of core questions important for global benchmarking and long-term trend analysis; removal of less useful questions; addition of new questions reflecting known new developments within regulatory systems; and addition of selected ‘local’ questions of importance to an individual country for local versions of the questionnaires.

The survey was divided into two parts. Part 1 covered financial data and product development costs and was sent to the headquarters of each company (so regional offices were not involved). Part 2 covered the regulatory environment and its impact on innovation and competitiveness. The Part 2 questionnaire was adapted to the situation in each of the 11 surveyed markets and was completed by the country offices of companies active in those markets.

The national associations were responsible for requesting their membership to complete the questionnaires, to collect and collate the results using a standard template, and to organise a local 1-day **workshop** with those companies participating in the survey. At the workshop an aggregated summary of the data for each question was presented and discussed in order to explore and record different views and the local context important for an understanding of the reasons behind a particular outcome.

The assimilated questionnaire data and the workshop ‘narrative’ explaining the findings formed the basis of each **country report**. The **report structure** follows the list of questions, which are used as sub-headings. The questions are reflected in the subheadings and are reproduced at the beginning of each section in a box below each sub-heading.

The GBS2020 survey covers 11 markets: Europe, United States of America, Japan, Canada, Australia, China, Brazil, India, Russia, South Africa and Mexico.

Final output: The country reports and a global overview report will be published on the HealthforAnimals website: <https://healthforanimals.org/global-benchmarking.html>

Details for Europe

In Europe AnimalhealthEurope collected completed questionnaires from **12 corporate² member companies** during September and October 2019, and **7** of these companies participated in the European workshop on 13th November 2019.

For more information on the AnimalhealthEurope membership please visit: <https://www.animalhealtheurope.eu/>

Companies participating in the GBS2020 report for Europe were (companies 1 to 8 are also members of the global industry trade association HealthforAnimals):

- | | |
|---------------------------------------|----------------------|
| 1. Bayer Animal Health | 7. MSD Animal Health |
| 2. Boehringer-Ingelheim Animal Health | 8. Vetoquinol |
| 3. Ceva Santé Animale | 9. Dopharma |
| 4. Elanco | 10. Huvepharma |
| 5. Virbac | 11. Orion |
| 6. Zoetis | 12. Syva |

² A corporate member is a company with direct membership of AnimalhealthEurope. National associations are also members of AnimalhealthEurope, thus many companies are indirect members of AnimalhealthEurope through their national association. These indirect companies were not involved in the survey in Europe.

4. The findings for Europe

Section A – Financial data

Economics of the animal health sector

A market analysis of the economics of the animal health sector is beyond the scope of this report. Estimations of market size can vary significantly, depending upon what is included within the scope of ‘animal health’ (some data also include cosmetics and nutrition). However, the following published key figures and market indicators are reported to provide some context for this report.

In 2018 the global animal healthcare market (pharmaceuticals, vaccines, feed and diagnostics) was estimated in several reports to be worth in excess of \$40 billion as follows:

- \$41.5 billion with a forecast compound annual growth rate (CAGR) of 6.3%³; 45% of this market is for pharmaceuticals
- \$43.55 billion and CAGR of 5.9%⁴
- \$45.8 billion⁵ (versus \$24 billion in 2014); 60% of this market is for pharmaceuticals
- These values represent 3.5% to 3.8% of the size of the human pharmaceuticals industry⁶.
- The largest segment of this market is the veterinary pharmaceuticals market, which was estimated to be nearly \$33.8 billion (with CAGR of 11.9% since 2014).

This strong growth has a number of drivers. Companies are increasingly collaborating and partnering with other players to drive product innovations, and to enter into new geographies. Collaborations and acquisitions in new biotechnology, novel therapies, new technologies and big data supporting diagnosis prediction, disease diagnosis and other healthcare management systems are driving growth. Examples are therapeutic antibodies for companion animals, chewable tablets, *in ovo* vaccination and new vaccine technologies.

Other drivers include the rise in incidence of food borne and zoonotic diseases, the growing livestock sector in many parts of the world, with the increased demand for protein, and increasing pet ownership.

The GBS2020 Part 1 report - the global context

The GBS2020 Part 1 report ‘Financial data’ is published separately and covers the 2018 full financial year. All data is presented in US dollars (\$). The data was provided by the 10 multi-national companies that are members of HealthforAnimals, the global trade association.

Key findings from that report are cross-referenced where relevant in this report for Europe, such as in the sections on product development trends and defensive R&D.

The 10 HealthforAnimals company members had combined revenue of \$22.7 billion in 2018, representing approximately 50% of the global market value, and an average of \$2,274 million, of which 7% was invested in research and development.

³ [Fortune Business Insights](#), Animal Health Market, report ID: FBI102371

⁴ <https://www.globenewswire.com/news-release/2019/05/07/1818679/0/en/Global-Animal-Health-Market-To-Reach-USD-70-01-Billion-By-2026-Reports-And-Data.html>

⁵ [Market Research Reports - https://www.marketresearchreports.com/blog/2019/09/05/world%E2%80%99s-top-10-animal-health-companies](https://www.marketresearchreports.com/blog/2019/09/05/world%E2%80%99s-top-10-animal-health-companies)

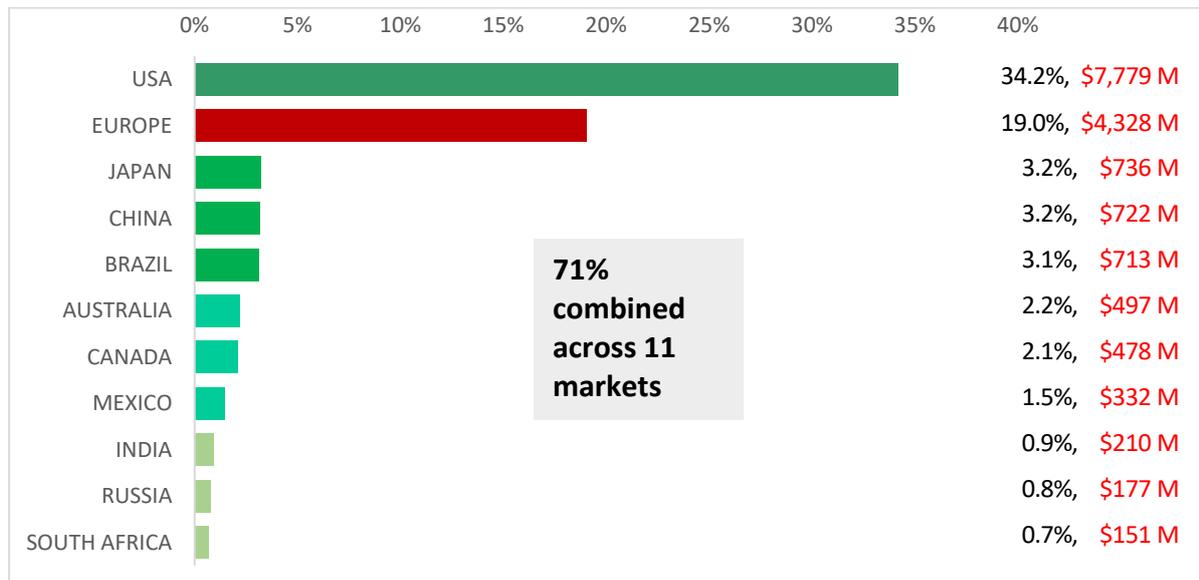
⁶ The global market for pharmaceuticals reached \$1.2 trillion in 2018 and will grow by 4-5% CAGR, Report on The global market for pharmaceuticals, available at www.IQVIAInstitute.org.

Multi-national company growth is often driven by acquisitions. The effect of greater concentration in animal pharma on overall innovation in the sector is uncertain.

The 11 benchmarked markets accounted for 71% of HealthforAnimals companies’ global revenues (Figure 1), with Europe representing 19% of that revenue.

Overall, the HealthforAnimals companies directed their R&D spending mostly towards pharmaceutical (62%) and biological (24%) products. Investment in pesticide-based medicines remained a small segment of product portfolios (4%). The R&D share for the two principle animal segments was 51% for companion animals and 49% for major food animal species.

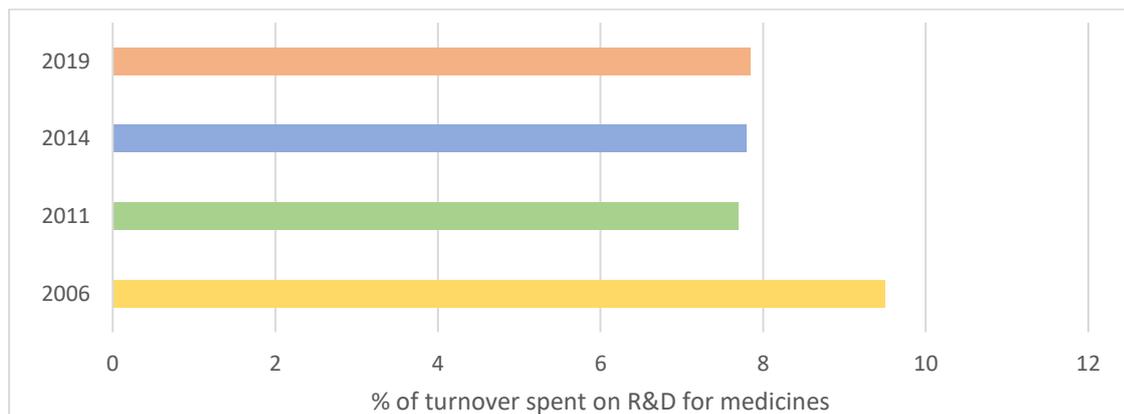
Figure 1: Estimated market share of HealthforAnimals companies global revenues in 2018 (in %)



AnimalhealthEurope member companies

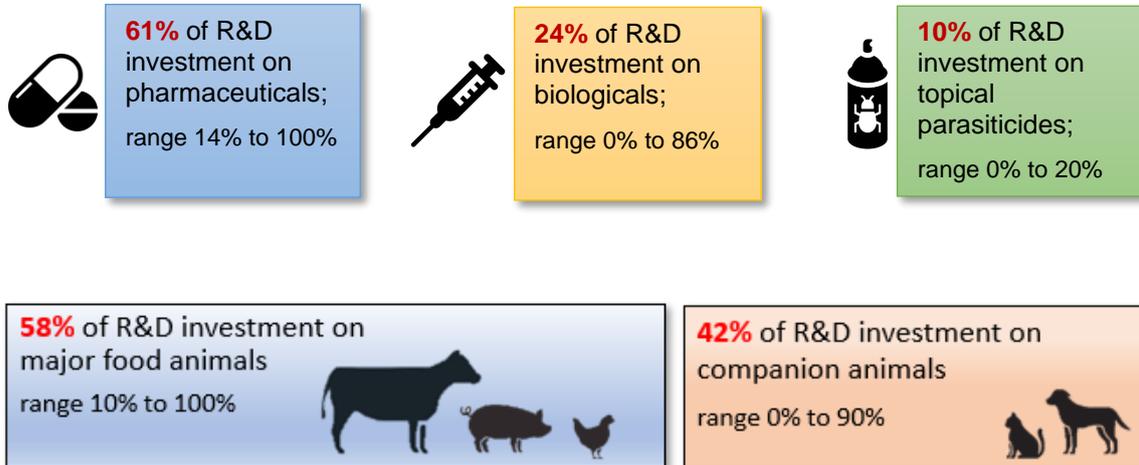
Eleven AnimalhealthEurope member companies provided data for Europe (8 also members of HealthforAnimals) and had an average annual gross turnover in Europe of \$461 million, with a range of approximately \$50 million to \$1 billion. They spent an average of 7.8% of their revenue on R&D (range 6% to 9.4%); the average spend in previous surveys was 7.8% in 2014, 7.7% in 2011 and 9.5% in 2006 (Figure 2).

Figure 2: % of turnover spent on R&D for veterinary medicines by AnimalhealthEurope companies



Product development

AnimalhealthEurope companies spent 61% (range 14% to 100%) of R&D investment on pharmaceuticals, 28% on biologicals and 10% on topical parasiticides (ectoparasiticides) for pesticide-based regulatory submissions (such as in USA via the Environmental Protection Agency). The split between major food animals and companion animal R&D projects was 58% to 42%.



Observations on the cost of mandatory defensive R&D and on the cost of product development are reported in Section B.

Section B – IMPACT OF REGULATIONS ON INNOVATION

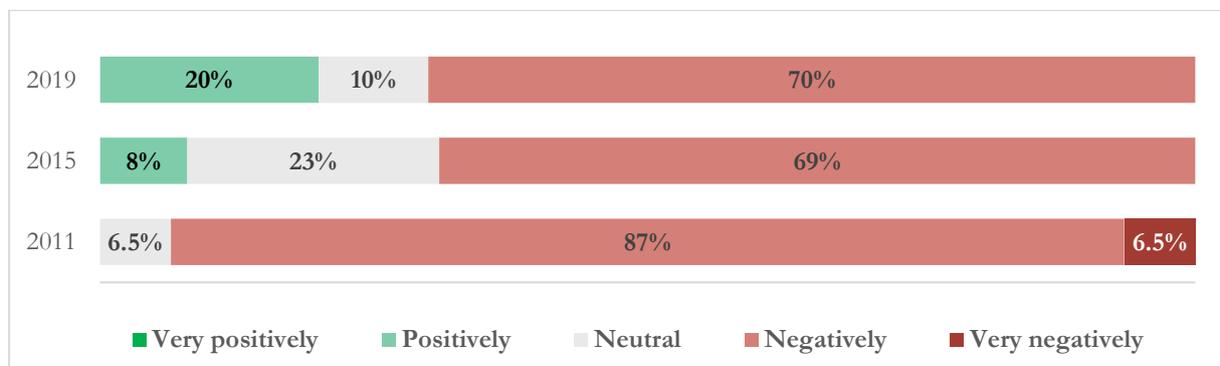
1. Impact of the EU regulatory environment on ability to innovate

How does the regulatory environment in Europe impact your ability to innovate?

Although the majority of responses were negative (70%, vs 20% positive) in 2019, companies recognise, in relation to their other markets, that the EU regulatory environment is a long-term driver of innovation, especially through the provision of technical guidelines and scientific advice which increase the predictability of the authorisation process. But in their daily activities, they are confronted with a high administrative burden, and rising costs, hindering their global developments. This negative side of the EU regulatory framework dominates industries thinking towards ability to innovate, as can be seen in the section 2 below.

The changes in views between the last three surveys shows a trend to a more positive outlook (Fig 3).

Figure 3: Impact of the EU regulatory environment on ability to innovate; from 2011 to 2019



Trend analysis

In the [2011 Global Benchmarking report](#) for Europe, the EU regulatory framework was cited as the major obstacle to innovation, with insufficient protection of technical documentation (“data protection”) the main factor. It was also noted that the new legislation introduced in 2004 significantly favoured generic products. The continual growth in negative consumer attitudes were also seen as indirectly negatively influencing the EU Regulatory framework and the willingness to invest in certain products or technologies.

In the [2015 Global Benchmarking report](#) for Europe, the negative views are attributed to a period of high increasing costs due to pharmacovigilance, environmental safety data demands and lack of harmonisation between national agencies. However there was a more positive outlook, perhaps because the positive effects of a new variations Regulation (applicable from 2010) and a new MRL Regulation (applicable from 2009) had been realised, or perhaps because industry had a more positive outlook following the release of an European Commission proposal in 2014 for a new regulation governing VMPs, that was, on balance, largely welcomed by the industry.

In this [2020 Global Benchmarking report](#), the positive impacts of EU regulation, such as the centralised procedure, are further explored later in this chapter. However, the overall negative viewpoint may partly stem from the frequent mentions of the adverse impact of (a) the EMA policy on access to documents, and (b) the “global marketing authorisation concept” on the effectiveness of the data protection provisions (see section 10).

A common thread over these decades is the increasing cost of doing business in a small highly regulated market, triggering an on-going high level of merger and acquisition activity in an endless drive for scale and efficiencies and an increasing globalisation of the market place.

2. Factors relevant to innovation in the animal health industry

Below is a list of factors relevant to innovation in the animal health industry. Which of these, if any, are significant for innovation in your business in Europe? Rank from 1 (highest significance) to 11.

When the average ranking scores for each of the 11 listed factors are calculated, the factors become ranked in order of priority as shown in Table 1, and fall into 4 groups. More detail of the ranking choices can be seen in Figure 4. The factors listed under the open option “Other” are listed in Table 2 with their individual rankings.

The EU regulatory framework and legislative environment is the highest ranked factor, by a clear margin, having the most (negative) impact on innovation. As noted in the previous section, companies have a split relationship with the EU regulatory framework, which is seen as both a hurdle to innovation (when it doesn’t get it right), but never-the-less essential to stimulate innovation (with the necessary regulatory framework).

The next factors having the most impact on innovation are the small size of market segments, negative consumer attitudes and the EMA policy on access to documents (required to implement Regulation (EC) No 1049/2001 on public access to documents).

It was felt that negative consumer attitudes were particularly driven by antimicrobial resistance and attitudes towards vaccination or immunological products. Previous studies have also identified the concerns of the general public to genetically modified organisms and other new biotechnologies.

It was considered that the EMA policy on access to documents is being abused by people with specific agendas, sometimes leading to publication on social media (such as pharmacovigilance reports). The large majority of freedom of information requests come from competitor companies, or their lawyers. By making the data publicly available in the EU also means it is available to the rest of the world and accessible to competitors. This is of particular concern in regions that do not have effective policies on protection of technical data.



The highly-ranked “Other” relevant factors reported in Table 2 highlight issues caused by the increasing cost of product development and manufacturing (see also heading 7 to 12), lack of harmonisation within EU and globally (also affecting costs), and lack of flexibility in applying rules and guidelines (increasing costs for studies and for variations). The lack of an EU regulatory framework for vaccine platform technologies, a concept that does exist in the USA (recognised by USDA), is also hindering innovation. It is also reported that the Nagoya Protocol is causing projects to be stopped due to the uncertainties surrounding the legal ownership of certain biological materials (e.g. new diseases).

The importance of being able to balance high investments with an acceptable level of risk in business decisions is underlined by one company view in Table 2 (‘High investment with significant risk of failure’).

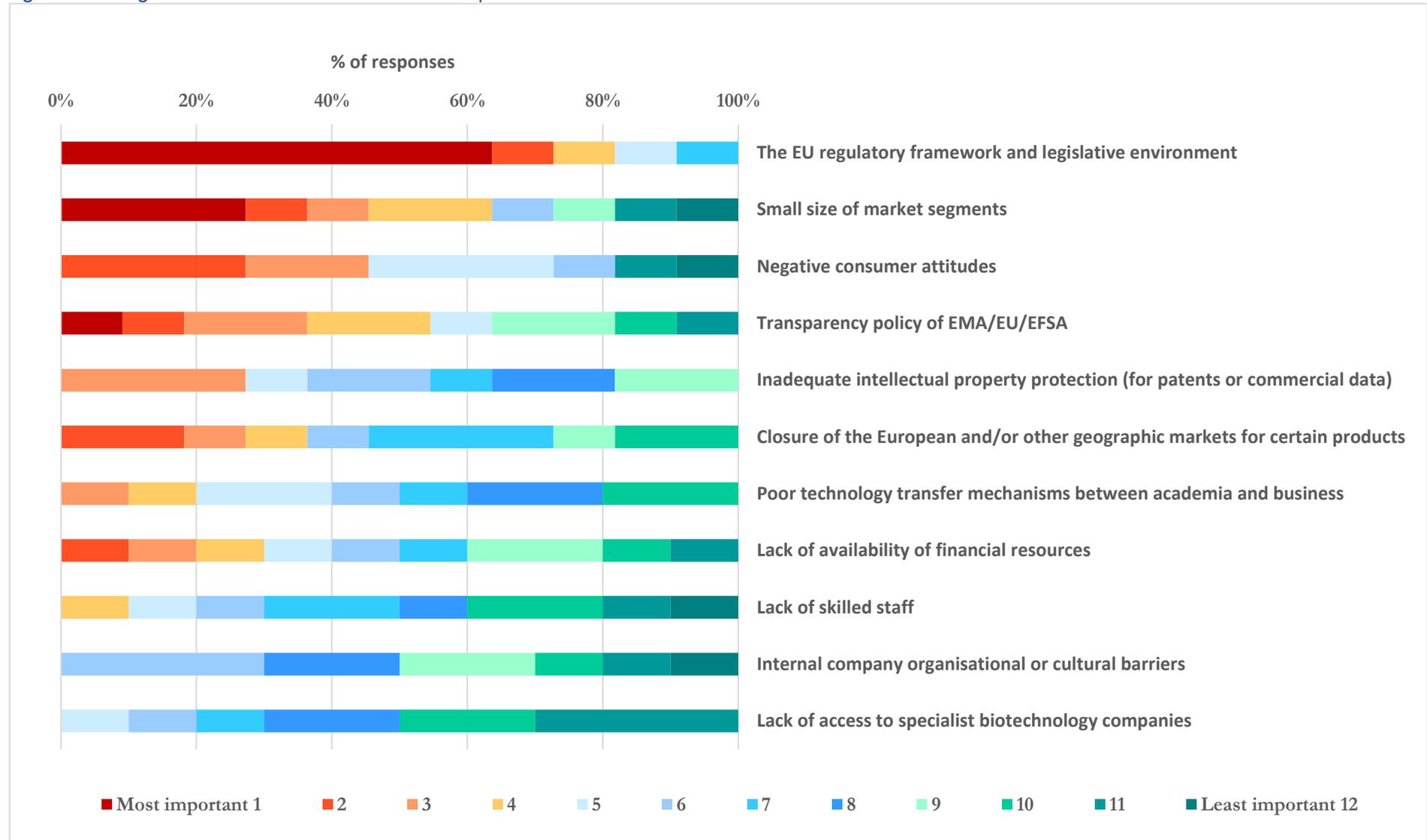
Table 1: Ranking of factors relevant to innovation

Factors relevant to innovation Ranked in order of negative impact	Average ranking score
1. The EU regulatory framework and legislative environment	2.3
2. Small size of market segments in the veterinary medicines sector	4.9
3. Negative consumer attitudes	5.1
4. Transparency policy of EMA/EU/EFSA	5.5
5. Inadequate intellectual property protection (for patents or commercial data)	6.1
6. Closure of the European and/or other geographic markets for certain products	6.1
7. Poor technology transfer mechanisms between academia and business	6.6
8. Lack of availability of financial resources	6.6
9. Lack of access by companies to skilled staff in the employment market	8.0
10. Internal company organisational or cultural barriers	8.5
11. Lack of access to specialist biotechnology companies	8.7
12. Other.....	See Table 2

Table 2: Other factors reported relevant to innovation

Other factors reported	Ranking
• Lack of international harmonisation, even within EU	1
• Cost and duration of studies required in EU	1
• Cost of GMP, lack of sufficient adaptation for veterinary products	1
• Lack of flexibility in the regulation for variations for immunological products	1
• Lack of development structures (between academia and business), in particular for virology	1
• Platform regulatory framework (e.g. for vaccines)	1
• Lack of flexibility in application of the EU rules driving need for unjustified studies in animals	2
• High investment with significant risk of failure	2
• Nagoya Protocol	3
• Lack of alignment between regions hindering global developments	4
• Tendency to apply risk adverse approach (precautionary principle) for novel products, when not well understood by Regulators	5

Figure 4: Ranking of factors relevant to innovation for companies



3. Expenditure on mandatory defensive R&D

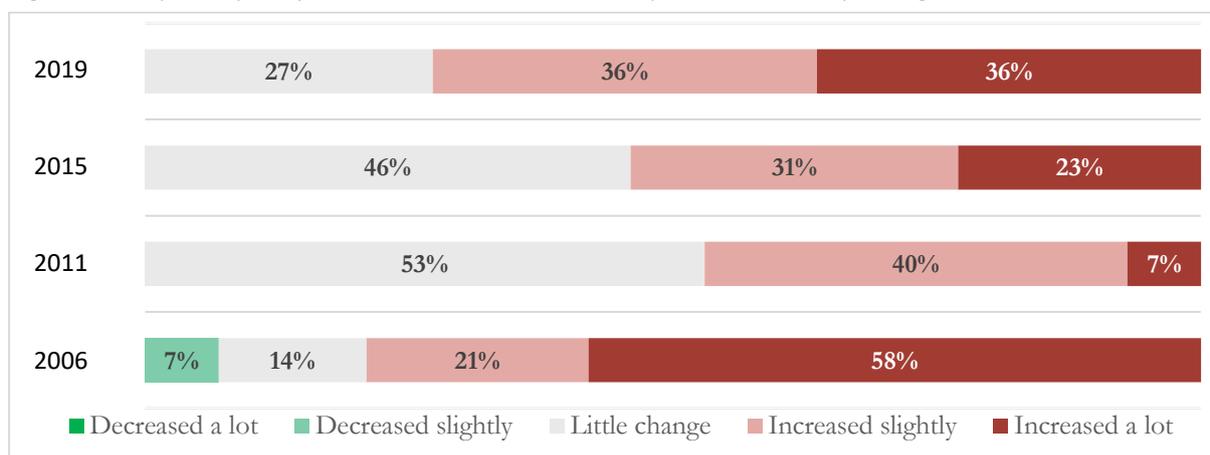
Which of the following statements best indicates how your expenditure on mandatory defensive R&D in Europe has changed since 2015?

In 2019, the majority of companies (73%) reported that their expenditure on defensive R&D had increased either slightly or a lot (Figure 5).

Mandatory defensive R&D is defined as the cost of additional studies to maintain a product on the market, demanded by the regulatory authority, either at renewal, or during other regulatory activity (such as product reviews or referrals). It does not include additional studies conducted voluntarily by the marketing authorisation holder post-authorisation.

The picture in 2006 was very negative, following the implementation of the new 2004 legislation (Directive 2004/28/EC). There was a significant improvement in perception in the next survey in 2011, but since then perceptions have worsened, as seen in Figure 5.

Figure 5: Companies' perception of the burden of mandatory defensive R&D spending since 2006



Expenditure on mandatory defensive R&D has persisted as a significant problem in EU through-out previous Global Benchmarking Surveys, and when benchmarked with other regions of the world, the EU was a particular area of concern for the industry. Important contributing factors include variations, product reviews, renewals and referrals. The high cost of Mandatory Defence (MD)-R&D diverts company resources away from R&D and can impact the retention of products on the market.

In 2019 the worldwide average cost of MD-R&D reported for 7 of the 10 HealthforAnimals companies was 14.5%, but with a large range from less than 1% to 40% (the ranges in 2015 and 2010 were 6 to 50% and >20% to 80% respectively). Three HealthforAnimals companies did not respond to this question. The wide range reflects both company portfolios and company regulatory strategy (e.g. to focus resources on new products and not on maintaining existing products).

The companies that are members of AnimalhealthEurope and are not members of HealthforAnimals reported mandatory defensive R&D levels from 1% to 25%. The wide range and small sample size, and a change in survey methodology, does not permit comparison or trending with previous surveys. This may be subject to a follow-up enquiry.

The authorities have also made efforts to address the issue and further improvements are expected. For example, the new Regulation in the EU will no longer require a 5-year renewal of a marketing authorisation and will provide a legal framework to help reduce the resources required for variations.

The factors causing a change in expenditure on MD-R&D are explored under heading 4 overleaf.

4. Factors causing the change in expenditure on mandatory defensive R&D

The factors reported as causing an increase or decrease in expenditure on mandatory defensive R&D (MD-R&D) are listed in Tables 3a and 3b.

Three factors are reported that can reduce expenditure on MD-R&D:

- Pharmaceutical dossiers already upgraded through national review procedures;
 - Explanation: following the harmonisation of EU legislation, member states (MSs) each undertook a review of the products on their market, to bring them in compliance with the harmonised rules; for companies, the review process lasted decades, as each MS was on a different timeline; it is only recently that the last product reviews are in the final stages of being completed in the last MSs.
- Work-sharing procedures for variations
- Referral procedures (focusing on existing data, not requiring additional experimental data)

A greater range of factors are reported that increase the cost of MD-R&D, and these have been grouped into the following regulatory areas:

- Retrospective application of increased data requirements
- Referrals and variations
- Pharmacovigilance
- Antimicrobial resistance (AMR) and environmental risk assessment (ERA)
- Manufacture

The EU regulatory authorities have taken steps to reduce the sometimes disproportionate resource costs of variations, particularly when one change affects a large number of marketing authorisations, by introducing grouped variations and work-sharing procedures. These have had a significant positive impact on reducing the cost of maintaining existing products on the market.

Furthermore, a decline in the costs for mandatory defensive R&D can be expected when a pharmaceutical product dossier has already been upgraded. The national review procedures for old products are (almost) finalized in the last remaining countries. In the past these triggered high product maintenance costs (dossier upgrades were a significant negative impact factor in earlier surveys, e.g. 2006).

Additional product maintenance costs can also be avoided if referral procedures focus on existing data, and do not require additional experimental data (e.g. the referrals for gentamicin and tylosin involved extrapolation of existing data). This depends on the type of referral, as some can trigger a request for new studies. Increased costs can also be caused by referrals linked to generic registrations. It was also noted that there is more demand for more detail in the dossier, which creates a need for more variations.

Antimicrobial resistance and environmental risk assessments are strong triggers for increased costs of product maintenance. Increasing regulatory expectations on safety and efficacy means it becomes increasingly less attractive to develop or defend products where AMR and environmental topics are likely to play a central role. In addition, the retrospective application of increased requirements, and the evolving fields of pharmacovigilance and manufacturing control all contribute to the issue.

Table 3a: Factors causing a decrease in expenditure on mandatory defensive R&D

Factors causing a decrease in expenditure on mandatory defensive R&D
<ul style="list-style-type: none"> • Pharmaceutical dossiers already upgraded through national review procedures • <u>Work-sharing</u> procedures for variations • Referral procedures (focusing on <u>existing data</u>, not requiring additional experimental data)

Table 3b: Factors causing an increase in expenditure on mandatory defensive R&D

N.B. The repetition of topics in the statements in this table is left to provide an indication of how frequently a factor is raised in the individual company responses.

Factors causing an increase in expenditure on mandatory defensive R&D	
<ul style="list-style-type: none"> • Authorities applying new standards to well-established products • Ph.Eur. monographs updates (vaccine dossiers) • Increased level of requirements, in particular more efforts needed to support existing products • Additional requirements and different interpretation of existing requirements • In addition to an overall increase, with less innovation, the ratio of new to existing products changes, with a higher proportion of “old” products. This in turns changes the balance of R&D spending. 	Retrospective application of increased requirements
<ul style="list-style-type: none"> • <u>Referral</u> procedures • Variations to keep products up to date complying with current regulation • More demanding effort for maintenance in terms of number of <u>variations</u> • Increase of requirements for marketed products leading to <u>variations</u> requested by authorities • Increase of details on SmPC (c.f. single tier label claim in US) leading to <u>variations</u> to remain competitive • Requirements for <u>variations</u> for “cosmetics changes” in the product information (e.g. use of new pictograms (target species), • new QRD statements to be implemented right after a <u>variation</u> and/or after renewal 	Referrals and variations
<ul style="list-style-type: none"> • <u>Pharmacovigilance</u> – PSUR assessments and questions: lack of good co-ordination between MSs; questions are sometimes triggered by single cases or general issues rather than product specific effects. Even with good argumentation from companies, MSs insist (usually driven by a single MS) on variations and label changes. • Phv.: Increased questions around product safety/performance/benefit-risk 	Pharmacovigilance
<ul style="list-style-type: none"> • Antimicrobial resistance & Environmental Risk Assessments • Increasing requirements about Environmental Risk Assessment • Increased issues around environmental impact assessment • Antimicrobial resistance related changes 	AMR and ERA
<ul style="list-style-type: none"> • Issues concerning active ingredient suppliers leading to the need for second or different source to be identified and registered. The work entailed in gaining approval of a second source, especially where there is no CEP, is high. • Tendency for assessors to apply the latest rules to the new active ingredient source (e.g. elemental impurities, residual solvents) and starting materials, and defining where GMP applies from (with tendency to go further back down the synthetic pathway). 	Manufacture

5. TIME to gain registration for a major new product in Europe

Please state the AVERAGE LENGTH OF TIME it takes you to gain registration for a major new product in Europe, from submission of the marketing authorisation dossier to first-market product approval. Please make separate estimates for major livestock species, companion animals and minor species and for the product types of pharmaceuticals and biologicals.

For the registration step the average length of time in 2019 is reported to be shorter by one or two months for every category of product compared to the recent previous surveys (see Table 4 and Figure 6). There is no significant difference between pharmaceuticals and biologicals, or category of target species.

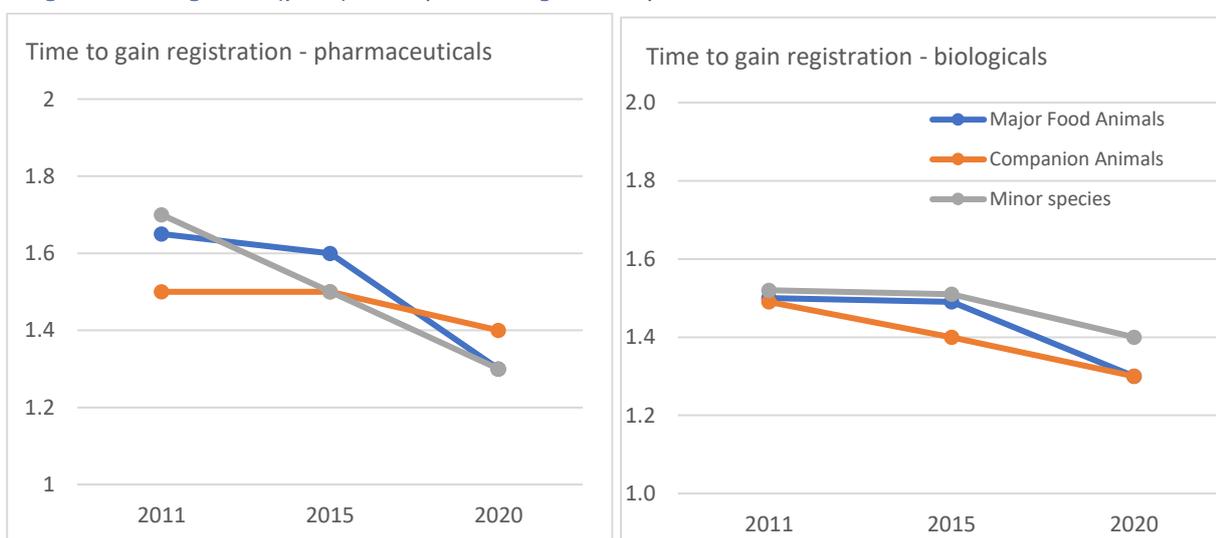
The registration step (i.e. the marketing authorisation procedure) is well defined in the EU, with time limits set in the legislation (7 months). However, there is typically a ‘clock stop’ when a list of questions is sent to the applicant from the assessor, which can affect the overall length of the registration procedure, depending on how quickly the applicant can respond.

For food-producing animals an MRL must first be obtained for the pharmacologically active ingredients. The MRL dossiers should be sent to the regulatory authority 6 months before the product dossier; this avoids delays in the assessment of the product application.

Table 4: Time (years) to gain registration for a major new product in Europe

		Average 2011	Average 2015	Average 2019	Range 2019	N 2019
Major Food Animals	Pharmaceuticals	1.65	1.6	1.3	1.0 - 1.5	8
	Biologicals	1.5	1.5	1.3	1.2 - 1.5	4
Companion Animals	Pharmaceuticals	1.5	1.5	1.4	1.0 - 1.7	8
	Biologicals	1.5	1.4	1.3	1.1 - 1.5	4
Minor species	Pharmaceuticals	1.7	1.5	1.3	1.0 - 1.5	3
	Biologicals	1.5	1.5	1.4	1.25 - 1.5	2

Figure 6: Average time (years) of the product registration phase



This improvement is attributed to a faster turn-around in addressing the lists of questions; this may be because the questions are less time consuming to address (fewer delays from triggering new studies) and perhaps because companies are improving their dossiers. There are two likely reasons for this. Firstly, the body of regulatory guidance continues to grow, both on scientific requirements and on the regulatory procedural steps. Secondly, there has been an increase in the use of the EMA/CVMP scientific advice procedure. Both these aspects increase the transparency of the process and an improved understanding of what is expected. However, other factors may also come into play, such as fewer new compounds being registered, and a greater use of the centralised procedure.

6. Impact of Regulations on TIME to develop a major new product

(a) Have regulatory factors caused a change in the average length of time it takes you to develop a major new pharmaceutical product (from initial research to final market authorisation), compared to 2015? Please make separate estimates for major livestock, companion animals and minor species.

(b) Have regulatory factors caused a change in the average length of time it takes you to develop a major new biological product (from initial research to final market authorisation), compared to 2015? Please make separate estimates for major livestock species, companion animals and minor species.

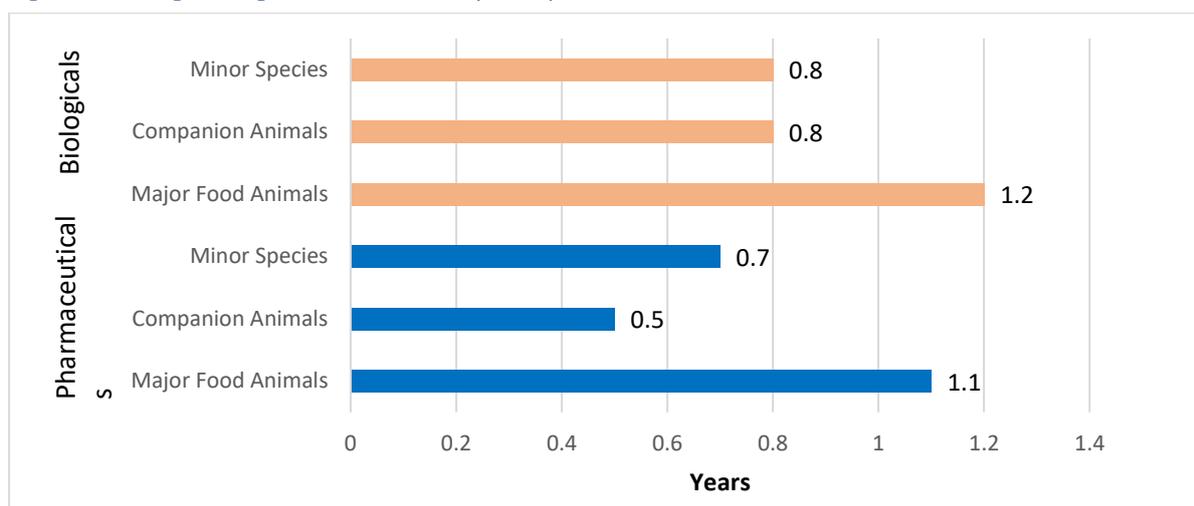
For the product development phase, the average changes in the time it takes to develop a major new pharmaceutical product and a major new biological product since the previous survey in 2015 are shown in Table 5 and Figure 7. The number of companies on which the 2019 average is based is also shown ('N').

In all categories, the majority of respondents reported an increase (typically 0.5 to 2 years) or 'little change' (typically 0 to 0.4 years) in the length of time it takes to develop a major new product.

Table 5: Impact of Regulations on changes in the TIME to develop a major new product since 2015

Product category	Target species category	Average change (years)	minimum (years)	maximum (years)	N
Biologicals	Minor Species	0.8	0.2	1.5	4
	Companion Animals	0.8	0.2	1.5	4
	Major Food Animals	1.2	0.2	2	5
Pharmaceuticals	Minor Species	0.7	0.4	1	7
	Companion Animals	0.5	0.3	1	5
	Major Food Animals	1.1	0	2	4

Figure 7: Average change in TIME to develop new products since 2015



The product development step can vary widely in length. Every product is different, and so is the length of the product development programme. One significant variable is the category of product under development. The data requirements, and thus the R&D programme, are different for a pharmaceutical and a biological. Likewise, the data requirements are different for a food-producing species, and companion animal species, and for species classified as “minor species”.

Data requirements can evolve over the years, as regulatory science evolves, affecting the length or cost of the product development process. More time is now spent on human safety and user risk assessments, and more data is generally needed for environmental risk assessments.

Trends in the change in time to develop new products

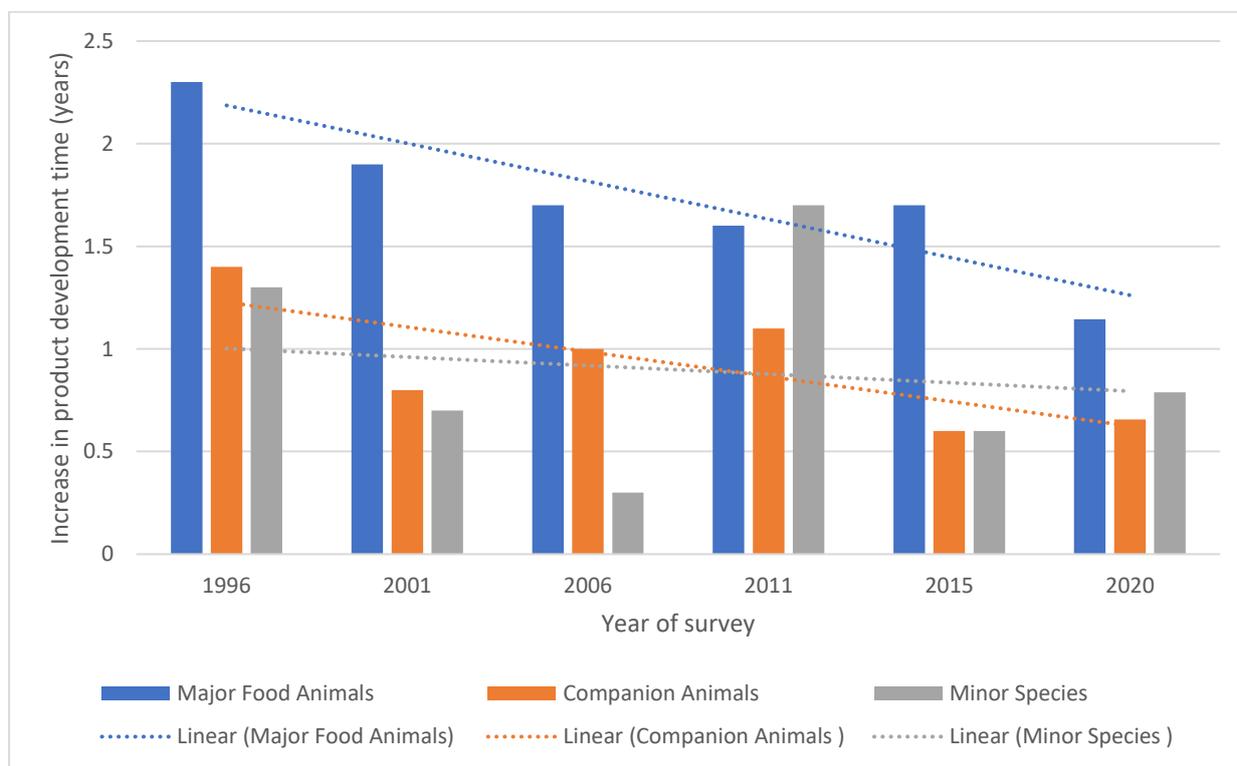
The trend lines in Figure 8 indicate that overall, for the 30-year period from 1990 (the starting point for the 1996 survey) to 2019, perception of *the rate of increases* in time to develop new products has been falling for all three categories (major food animals, companion animals and minor species).

There have been some fluctuations in the trend, as might be expected from different surveys covering different selections of product development portfolios.

N.B.: This data, collected since 1996, is regarded as indicative, and is not sufficiently precise to allow the data to be summated across all six surveys. Doing this would appear to indicate that the product development time has increased over this 30-year period by 10.4 years for major food animals, by 5.6 years for companion animals and by 5.4 years for minor species. This is not the case.

However, the key outcomes are that the product development time continues to increase, but the rate of increase is slowing down, as judged by data covering a 30-year period (Figure 8).

Figure 8: Trend line: Changes in the *rate of increase* in time it takes to develop a major new product (pharmaceuticals plus biologicals); in each survey respondents were asked to estimate how much the product development time had increased over the previous 5 years.



The steady increase in the time of product development increases the importance of the protection period for the technical documentation, before it can be utilised by competitors for generic versions. The increase in product development time means that the effective protection by a patent is reduced, placing more emphasis on the marketing authorisation protection. This is a theme that is also experienced in the human pharmaceuticals sector (see Box below).

Key statements from a ‘Study on the economic impact of supplementary protection certificates, pharmaceutical incentives and rewards in Europe’⁷

- We find that the effective protection period for the medicinal products in our dataset has declined from an average of 15 years to 13 years during the period 1996 to 2016.
- We speculate that part of the reason for this decrease may be attributed to the increase in regulatory requirements both at the EU and national level.
- The average development time of a medicinal product – defined as the time that elapses from the first patent filing protecting the molecule to the first marketing authorisation of the final product in the EU – has increased from 10 years to 15 years in the analysed period
- The results from our statistical modelling point to a positive relationship between the effective protection period and the level of pharmaceutical research and development. Specifically, we find that when medicinal products experience a longer effective protection period in the markets where they are sold, pharmaceutical companies increase their innovation efforts.
- We find some evidence to suggest that the regulation spurs innovator-on-innovator competition. We base this insight on the previous finding that the regulation stimulates innovation, and that more innovation, all else equal, leads to more medicinal products, which eventually result in more innovator-on-innovator competition.

7. COST of developing a major new PHARMACEUTICAL product

Thinking about the AVERAGE COST of developing a major new PHARMACEUTICAL product in the EU (from initial research to approval) for all possible species and indications for that product, compared to 2015 have REGULATORY FACTORS caused this cost to change in real terms? Make separate estimates for major livestock species, companion animals, and minor species.

For all categories of species, none of the respondents reported that the cost of developing a major new PHARMACEUTICAL product in the EU (from initial research to approval) had reduced compared to 2015 (see Figure 9).

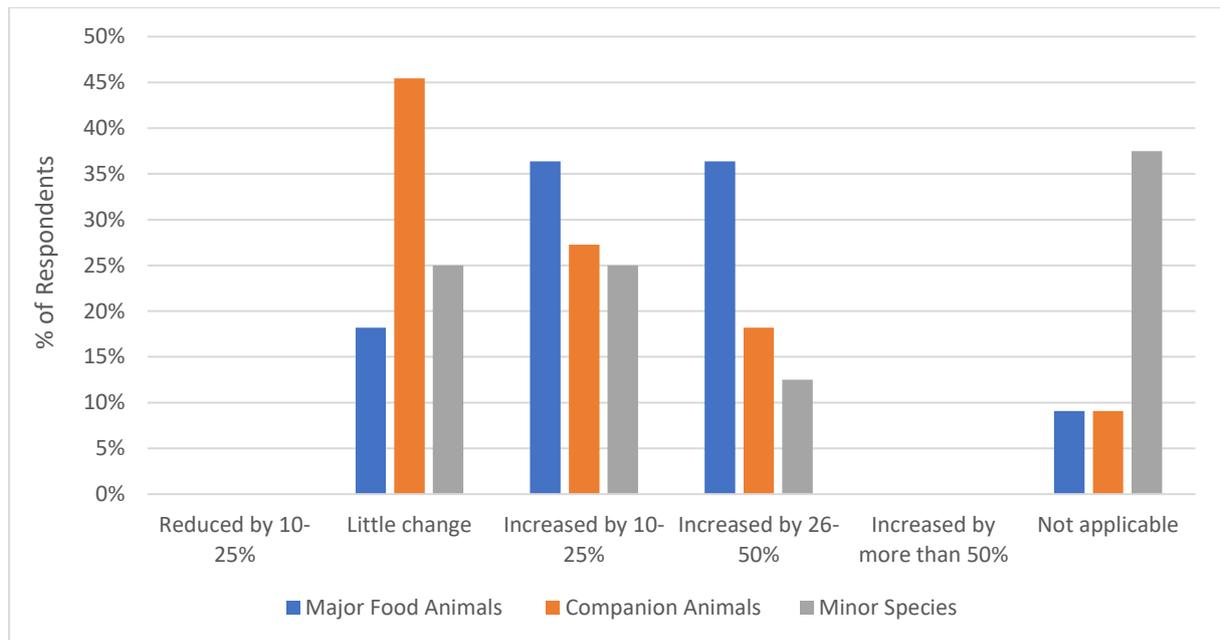
The large majority (85%) of respondents report that the cost of developing a major new pharmaceutical product for major livestock species has increased between 10% to 50%.

A large proportion (45%) of respondents report that the cost of developing a major new pharmaceutical product for companion animals has seen little change (less than 10% increase). Two companies believe the costs have increased by 26-50%.

The large majority of respondents report that the cost of developing a new pharmaceutical product for minor species has increased a little or up to 25%. One company believes the costs have increased by 26-50%. These increases have been seen despite the updated “MUMS” guidelines from the CVMP.

⁷ Copenhagen Economics, May 2018; commissioned by European Commission Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs, available at https://ec.europa.eu/health/sites/health/files/human-use/docs/pharmaceuticals_incentives_study_en.pdf

Figure 9: Perceived change in COST to develop new pharmaceutical product (versus 2015)



8. COST of developing a major new BIOLOGICAL product

Thinking about the AVERAGE COST of developing a major new BIOLOGICAL product in the EU (from initial research to final market authorisation) for all possible species and indications for that product, compared to 2015, have REGULATORY FACTORS caused this cost to change in real terms? Make separate estimates for major livestock species, companion animals, and minor species.

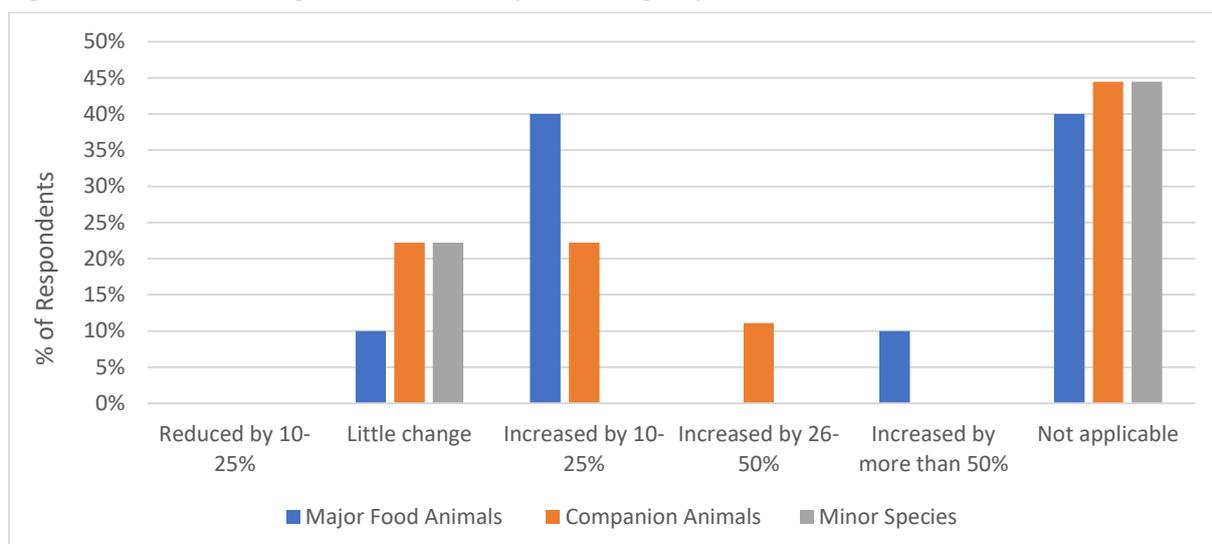
A large proportion (40 to 45%) of respondents were not involved in the development of biologicals. For all categories of species, none of the respondents reported that the cost of developing a major new BIOLOGICAL product in the EU (from initial research to approval) had reduced compared to 2015 (see Figure 10).

The large majority of respondents report that the cost of developing a major new biological product for major livestock species has increased between 10% to 25%. However one company believed costs had seen little change, while another company believed costs had risen more than 50% since 2015.

The large majority of respondents report that the cost of developing a major new biological product for companion animals has seen little change or up to 25% change since 2015. However one company believed costs had risen between 26% to 50% since 2015.

The few respondents with experience of developing a new biological product for minor species report little change in the costs since 2015.

Figure 10: Perceived change in COST to develop new biological product



Key outcomes for COST of developing a major new product:

No companies reported a decrease in costs for any of the product categories; the largest perceived increase in costs are seen for both pharmaceutical and biological products for major food animals. Trends: Costs for both are rising

In Part A of the GBS2020 questionnaire companies were asked to provide the total development cost of a new product for several product categories. Several examples were provided but the data is characterised by (a) low sample numbers per category and (b) high variance; the high variance is assumed to be a combination of specific product development needs, different company strategies for product development and different accounting methods.

Consequently, the data is not reported and will be the subject of a more in-depth follow-up enquiry.

An independent study by the Economic Research Service of USDA⁸ estimated that the cost of developing veterinary pharmaceutical products had risen by 159% during the period 1990 to 2011.

9. Impact of Regulations on ABILITY TO INNOVATE

Thinking about Regulations in Europe, how would you assess the impact of each of the areas of regulation listed below on your ABILITY TO INNOVATE successfully?

The overall ranking of the impact of each of the areas of regulation, that were listed in the question, on a company’s ability to innovate successfully are shown in Figure 11. The top 5 most helpful and unhelpful areas of regulation are summarised in Table 6 (with their rankings from previous surveys).

The five most helpful areas of regulation all fall within two important areas that help to bring new innovations to market: firstly, functional marketing authorisation procedures, and in particular the high regard in which the centralised procedure for obtaining a marketing authorisation, run by the European Medicines Agency, is held; and secondly, the importance of the protection of intellectual property to stimulate investment in new products and technologies.

⁸ Incentivizing New Veterinary Pharmaceutical Products to Combat Antibiotic Resistance, Stacy Sneeringer and Matt Clancy (Economic Research Service, USDA), Applied Economic Perspectives & Policy, 12 September 2019

The quality and predictability of the centralised procedure are further examined in chapter D of this report, and section 10 below examines the different elements of the regulatory provisions to protect technical documentation in a marketing authorisation application.

Table 6: The most and least helpful areas of regulation in 2019 and rankings from previous surveys

Top 5 most helpful areas of regulation					Top 5 most unhelpful areas of regulation				
	2019	2015	2011	2006		2019	2015	2011	2006
Centralised Procedure	1	1	1	1	Environmental safety regulations (ERA)	1	1	1	1
Protection of Intellectual Property - patents	2	3	3	3	Manufacturing - GMP Inspections	2	4	-	-
Mutual Recognition Procedure	3				EMA access to documents policy	3	-	-	-
Protection of Intellectual Property – MA data	4	9	8	6	Good laboratory practice	4	7	5	6
Decentralised Procedure	5				Maximum residue limits	5	5	6	3

The five most unhelpful areas touch upon three distinct issues. Firstly, the large cost hurdle of complying with the data requirements, particularly for environmental risk assessments for veterinary medicines, but also for Good Laboratory Practice and for Maximum Residue Limits. This significant investment by the veterinary medicines sector in the protection of the environment is a positive message to the wider public and should be better communicated.

Secondly, the high-resource impact of GMP inspections is identified; these inspections can take several days and soak up the time of numerous staff before, after and during the inspection. This issue is compounded when inspections are duplicated by several national authorities from outside the EU.

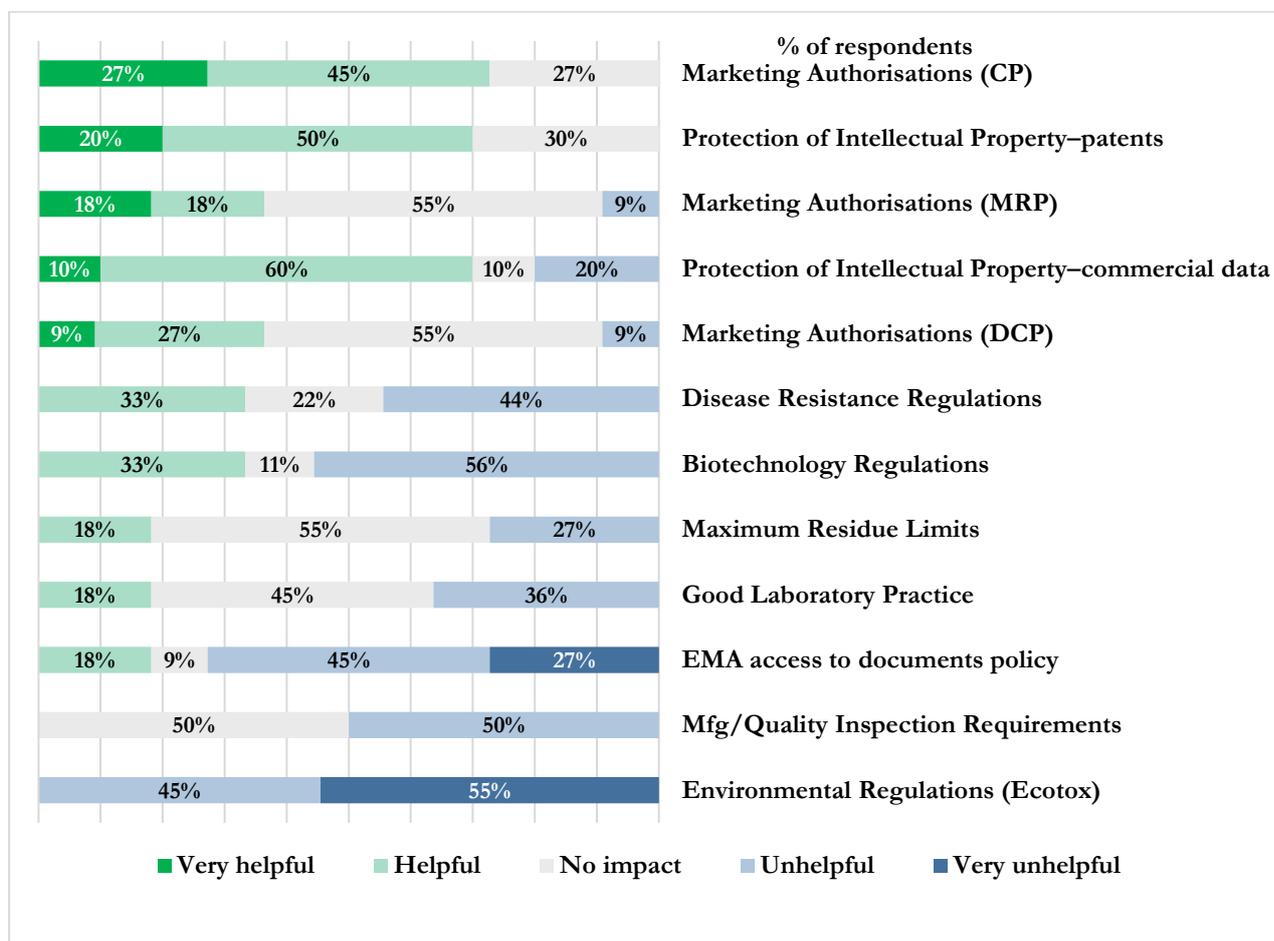
Thirdly, the EMA policy on access to documents is regarded as a significant disincentive to bringing innovations to the EU first. There is concern that the bulk of freedom of information (FOI) requests come from competitors. There is also a concern that the resources of the EMA are overloaded by numerous FOI requests and diverted away from their core tasks (the authorisation of medicines and contribution to the protection of animal and public health). Two companies did regard the EMA access to documents policy as helpful, but probably from the perspective of a competitor.

The biotechnology regulations address the additional burden of complying with the GMO regulations. Issues are also caused by a lack of clarity of definition of the scope of the regulations, which can mean that some excipients get drawn into the GMO assessment, causing delays.

The impact of ‘disease resistance regulations’, which refers to both antimicrobial resistance and antiparasitic resistance data requirements, received a mixed response, part helpful and part unhelpful. This is because good regulatory practices to manage resistance can be helpful for sustaining key products on the market, but the cost of additional data and monitoring is a large hurdle, and equally can cause the loss of products from the market.

Another key aspect to consider is that it is challenging for the regulatory network and regulatory science to keep abreast of new science, including access to suitable scientific expertise within regulatory agencies. This can slow down innovation, particularly if innovative approaches are used. An innovation is new by definition; accordingly not all aspects can be known at the time of product authorisation. It is important that regulators feel able to accept a certain level of risk if the data demonstrate a positive benefit-risk balance.

Figure 11: Impact of EU regulation on ability to innovate



10. Is EU legislation on protection of technical documentation an incentive?

- a) Thinking about the current EU legislation on protection of technical documentation (Directive 2001/82/EC as amended), to what extent do you consider it to be an incentive?
- b) Thinking about the future EU legislation on protection of technical documentation (Regulation (EU) 2019/6), to what extent do you consider it to be an incentive?

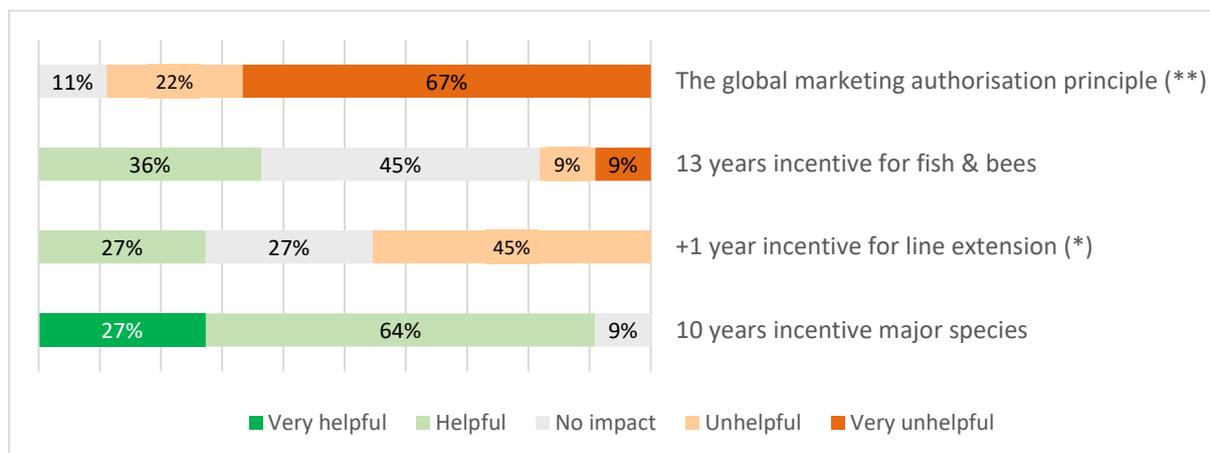
(a) The provisions for the protection of technical documentation in Directive 2001/82/EC,

Directive 2001/82/EC, as amended by Directive 2004/28/EC, will be superseded by Regulation (EU) 2019/6 in January 2022 (see next section).

Directive 2001/82/EC, as amended, includes several provisions for the protection of technical documentation, beginning with a standard 10 years’ protection for a new product (article 13(1)). If the product is extended to an additional food-producing species, then the 10-year period is extended by +1 year (giving 11 years). This can be done 3 times for livestock species to a maximum of 13 years, provided the 3 line extensions are for food-producing species and are obtained within 5 years of the first marketing authorisation (MA). If the original product is for fish or bees, then 13 years protection is awarded straightaway. During these periods of protection a generic version of that product cannot cross-refer to the product and benefit from a derogation to provide certain safety and clinical data.

The respondents to this survey almost universally agree that the 10 years of protection for the first product is a helpful incentive for investment. However all the other provisions (the +1 year extensions and the 13 years for fish and bee products) received a mixed response (Figure 12).

Figure 12: The relative helpfulness of protection of technical documentation in Directive 2001/82/EU



The ‘positive’ view is that these other provisions are ‘better than nothing’. The negative view is that the markets for fish and bee products are very small, and a much longer term of protection is needed to obtain a return on investment. The additional +1 year is also largely insufficient to cover the cost of a line extension to an additional species, but is also negatively viewed because (a) only food-producing species are in scope, thus excluding line extensions for companion animals, and (b) the restrictive 5-year window in which to obtain up to 3 line extensions to additional species.

But the most damning view is directed at the “global marketing authorisation concept” in article 5.2 of the Directive (as amended in 2004), which includes the restriction: “All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 13(1).” See box below for the full text.

This means that any investment in research to improve the product through new strengths, pharmaceutical forms, administration routes and presentations will not benefit from any protection period for the new data. This effectively stifles new incremental developments and innovation.

Article 5, 2nd paragraph: “When a veterinary medicinal product has been granted an initial authorisation in accordance with the first subparagraph, any additional species, strengths, pharmaceutical forms, administration routes, presentations, as well as any variations and extensions, shall also be granted an authorisation in accordance with the first subparagraph or be included in the initial marketing authorisation. **All these marketing authorisations shall be considered as belonging to the same global marketing authorisation, in particular for the purpose of the application of Article 13(1).**”

(b) The provisions for the protection of technical documentation in Regulation (EU) 2019/6

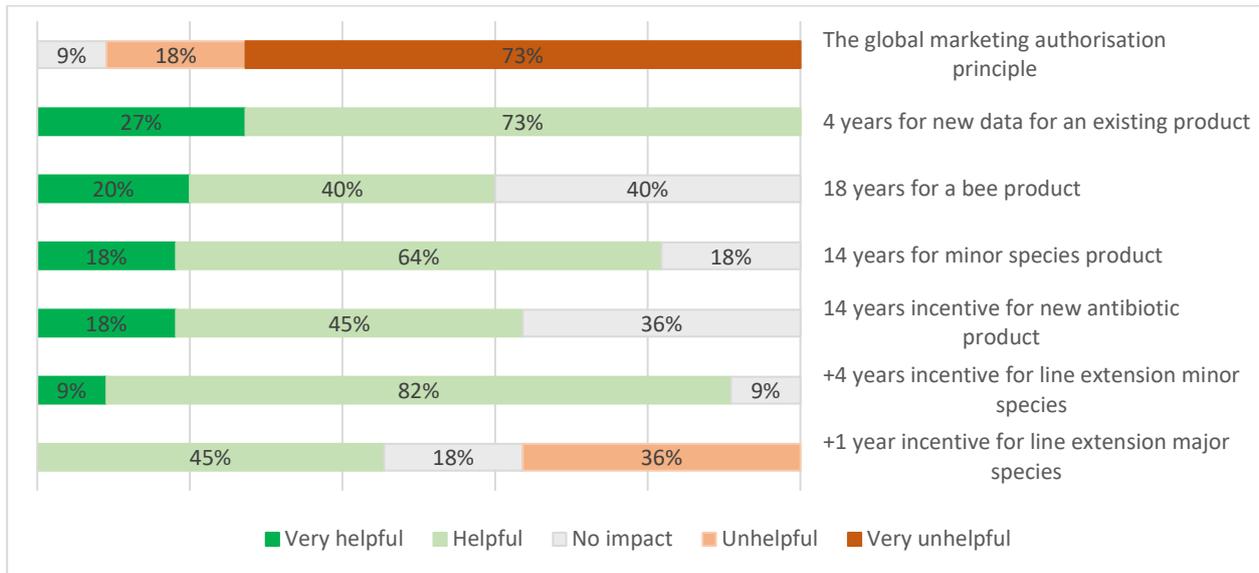
Regulation (EU) 2019/6 becomes applicable in January 2022 and will supercede the current legislation (Directive 2001/82/EC, as amended by Directive 2004/28/EC (see previous section).

Following a review of the legislation, the new regulation was published in January 2019 and therefore was available for inclusion in this survey. It contains improved provisions for the protection of technical documentation, as listed in Figure 13, and it can be seen that these are seen as either helpful or very helpful, with two exceptions:

- firstly, almost universal dissatisfaction is expressed that the “global marketing authorisation concept” has been retained, with 91% of companies regarding this as unhelpful (of which 73% said ‘very unhelpful’); and
- secondly, dissatisfaction is expressed that the +1 year was retained for a line extension to a major species, when experience with Directive 2001/82/EC (as amended) shows this is an insufficient incentive.

The new provision for 4 years protection for new data to an existing ‘well-established’ product is positively welcomed, even though this new provision is restricted to new data that brings improvements either to preventing the development of antimicrobial or antiparasitic resistance, or to the product’s benefit-risk assessment. Enforcing this protection might also prove difficult.

Figure 13: The relative helpfulness of protection of technical documentation in Regulation (EU) 2019/6



In the GBS2020 workshop discussions the general sentiment was positive but sad that it took so long to persuade the authorities that the specifics of the veterinary medicines sector, particularly the difficulties in obtaining a return on investment due to the small and fragmented market (through multiple species) necessitated more extensive provisions to stimulate investment. In the words of one company delegate “It is a shame we had to wait so long for it.”

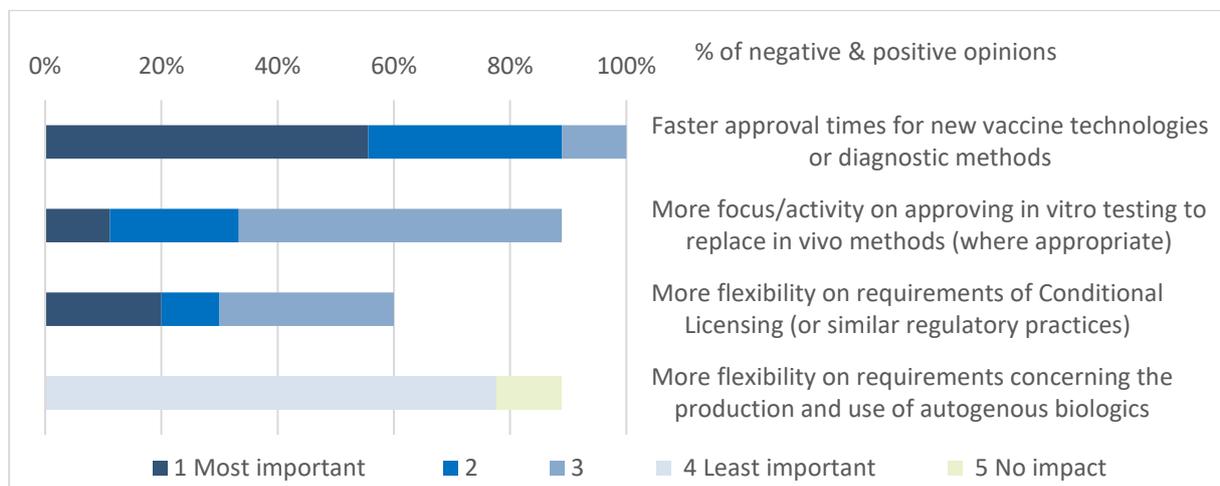
It will be interesting to see the initial responses to the implementation of these provisions in the next Global Benchmarking Survey in 5 years (2025), 3 years after these new provisions became applicable.

11. Stimulation of innovation for biologicals

Regarding biologics, which of the following choices would be best for regulators to focus on to stimulate/promote innovation in this area?

The view of the respondents on where regulators should focus to stimulate innovation for biologicals is shown in Figure 14. The primary recommendation was to focus on faster approval times for new vaccine technologies and diagnostic methods. The new vaccine platform technologies (now accommodated in the technical annex of Regulation (EU) 2019/6) could bring significant improvements to the vaccine development process, but the requirements and regulatory approach should be clearly defined and managed by well-trained assessors on this type of product. Therefore training of assessors and access to suitable/sufficient experts within the EU regulatory network is also a key parameter to support innovation in this area.

Figure 14: Focus points to promote innovation in biologics



More focus on improving the approach to the replace of *in vivo* tests with *in vitro* tests and more flexibility in the requirements for conditional licencing were also seen as important.

During the GBS2020 workshop discussions it was also pointed out that manufacturing ‘quality by design’ is easy to justify for the manufacture of pharmaceuticals, but this concept is much harder to build-in to the manufacturing of vaccines.

More flexibility on requirements for the production of autogenous vaccines was not regarded as helpful to promote innovation in licenced vaccines, although harmonisation of autogenous vaccines regulation within EU was considered necessary.

Other suggestions included:

- GMO scope – avoiding unnecessary capture of substances/products into the scope of the GMO regulations, as this causes extensive additional requirements.
- Improved management of variations for biologicals (supporting quality by design with relevant guidance and not taking the default position that any variation for a biological product needs an assessment by the Authorities, even simple variations).

Section C - COMMERCIALISATION OF EXISTING PRODUCT

1. Factors relevant to the commercialisation of existing products

Below is a list of 12 potential factors relevant to the exploitation of existing products in the animal health industry in the EU. Which of these, if any, are significant for the exploitation of your existing products? (Please rank from 1 for ‘most important’ to 12 for ‘least important’).

In the question a list of 11 factors relevant to the commercialisation of existing products were presented (with an “Other” option to add a 12th factor). The overall ranking of the potential factors is shown in Figure 15, ranked from most important at the top, to least important at the bottom. The “Other” option was not used and is not shown.

The top most important factors relevant to the exploitation of existing products, and their rankings in previous surveys, are:

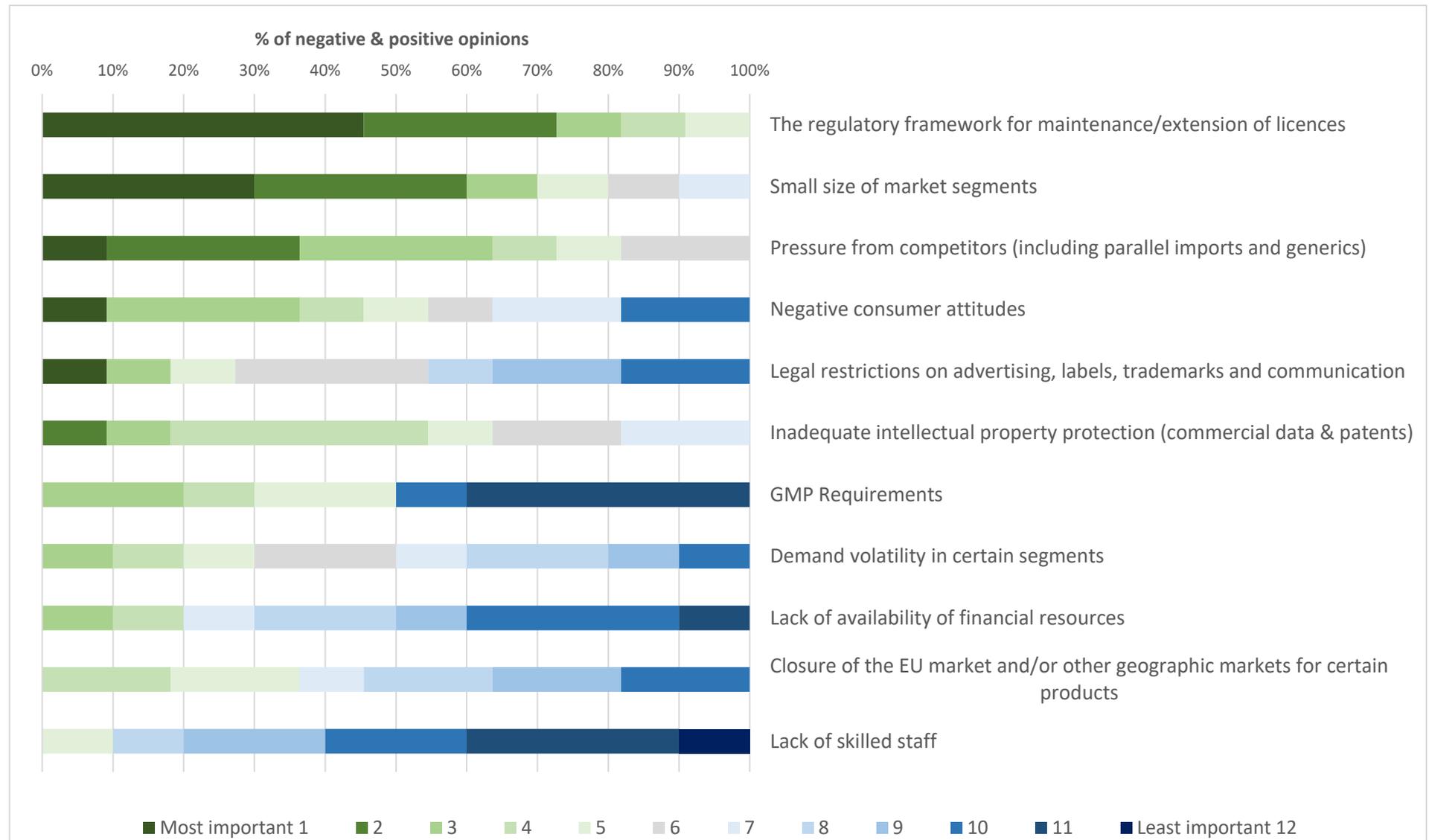
Ranking of most important factors relevant to the exploitation of existing products					
		2019	2015	2011	2006
	Regulatory framework for maintenance/extension of licenses	1	1	1	1
	Pressure from competitors (including parallel imports and generics); differences in SmPCs are important	2	4	2	3
	Small size of market segments; the market for veterinary medicines is highly fragmented.	3	3	3	2
	Negative consumer attitudes	4	5	6	6
	Inadequate protection of intellectual property	5	2	4	4

How the regulatory framework governing the lifecycle of existing products is implemented is of fundamental importance to a company’s ability to continue to commercialise existing products. There can be a reluctance to submit variations to a product dossier because of the risk of having the dossier opened and things found that are not state-of-the art, leading to the requirement to update data to current guidelines. Therefore, most of the decisions to maintain a dossier are based on cost.

This risk is also relevant for line extension: the business decision is difficult if some parts of the original dossier do not comply with recent guidance. Subsequently the SmPC will need to be updated or changed, putting the originator at a competitive disadvantage if the SmPCs of generic or me-too products (such as biologicals) are not updated at the same time. There is also a risk that a variation assessment overflows into other areas, with consequences for other related products.

New demands from consumers can close the market for certain products (e.g. hormone-based products in the EU). Consumer pressure can also have an influence when it comes to antimicrobial restrictions. Lack of knowledge or trust in the regulatory environment may be a factor. This is very challenging as it is impossible for the industry to effectively communicate to the wider public. Some negative consumer attitudes are partially fuelled by the media, and can be amplified quickly on social media. Local initiatives of governments or retailers can also have an impact (for example green labelling of food in Germany). However, it is hoped that new debates around ‘sustainability’ may bring some more balanced views to the fore.

Figure 15: Relevant factors to exploit existing products



2. Impact of regulation on ability to commercialise existing products

Thinking about Regulations in Europe, how would you assess the impact of each of the areas of regulation listed below on your ABILITY TO COMMERCIALISE EXISTING PRODUCTS successfully?

Respondents were presented with 13 areas of regulation to rank in order of impact on a company's ability to successfully commercialise existing products. The top most helpful and most unhelpful areas of regulation, and their rankings from previous surveys, are summarised in the Table below, and are shown ranked from most to least helpful in Figure 16.

Rankings for most helpful					Rankings for most unhelpful:				
	2019	2015	2011	2006		2019	2015	2011	2006
Centralised Procedure licence maintenance	1	1	1	1	Environmental safety regulations	1	1=	1	1
Incentives for Line Extension (new species)	2	-	-	-	Variations regulation - manufacturing changes	2	1=	6=	5
Good Manufacturing Practice in general	3	2	3	3	Disease resistance regulations	3	3=	6=	4
MRP/DCP licence maintenance	4	-	-	-	Packaging/labelling modification rules	4	3=	2	3

Helpful aspects

The **Centralised Procedure** is seen as the most helpful aspect of EU regulations for the maintenance of marketing authorisations, although two companies thought it unhelpful, so there is probably room to seek further improvements in these procedures. This mirrors the outcome in section B above, where the centralised procedure was regarded as the most helpful aspect of regulations enabling innovation. Also mirroring the results of section B, the **protection of technical documentation** is again ranked high in importance, this time for helping to commercialise existing products by adding line extensions. However 4 companies felt this aspect was unhelpful, because the +1 year data protection awarded for line extensions is seen as insufficient and is limited to livestock species.

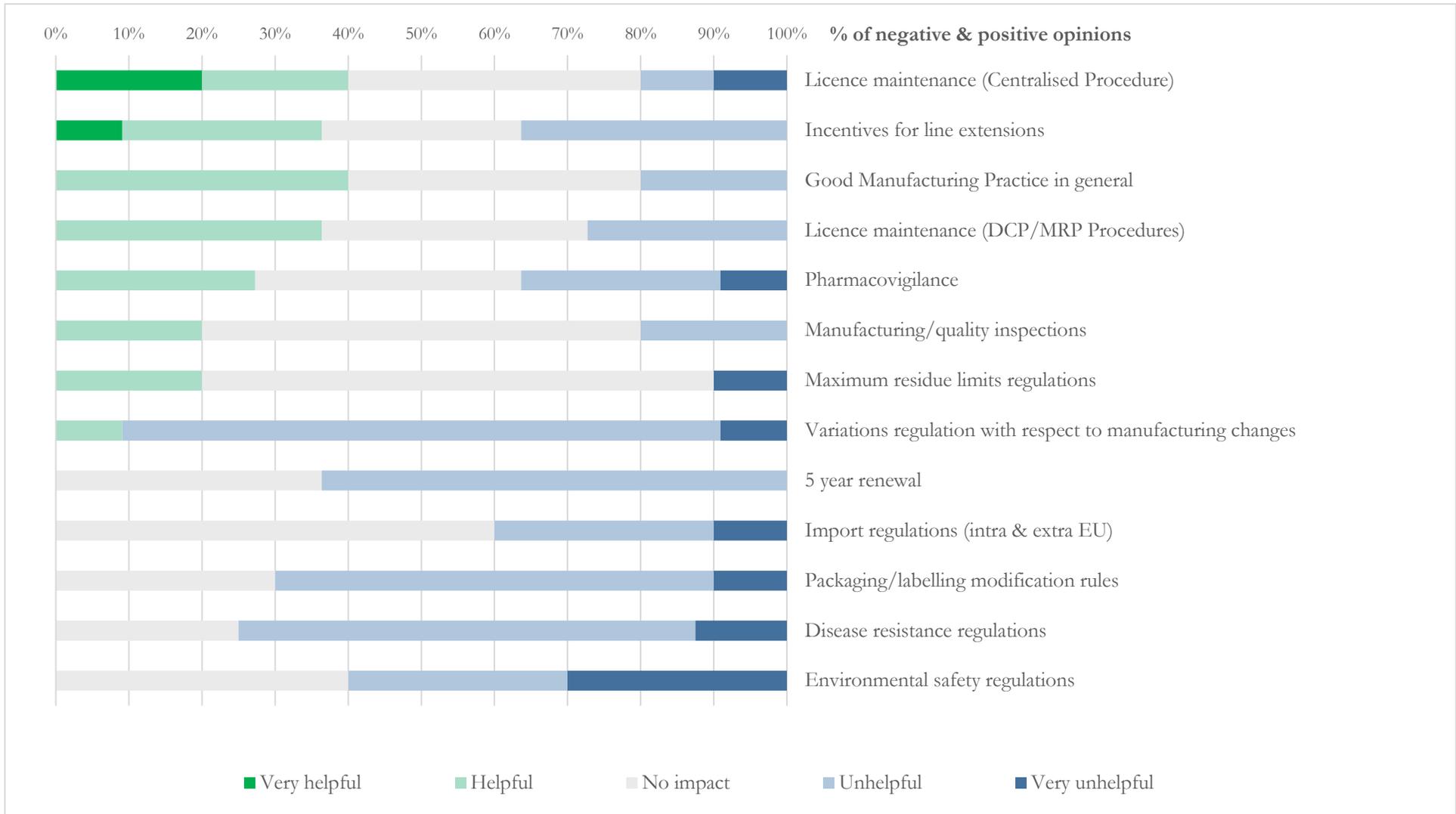
Good manufacturing practice rules receive a reasonably positive response as they are seen as good business practice by providing assurance of the quality of a company's products and is a standard that is generally accepted worldwide, giving a good balance between inputs and outcomes. As one company commented "Industry is not against rules when they are proportionate and helpful". However, again a couple of companies see GMP as unhelpful, because it is a significant business cost, but also because it is felt the GMP rules are insufficiently adapted to the veterinary medicines sector.

A similar story is reflected in the response to **pharmacovigilance**. It is positive for companies to be assured they will quickly detect issues with their products in the field; but the administrative burden is high and companies report that the cost of maintaining a compliant pharmacovigilance system has risen steeply since the last Global Benchmarking Survey. There is now considered to be a heavy imbalance between the cost of inputs and the value of outputs towards improved safety (Table 7).

Unhelpful aspects

Turning to the least helpful aspects, once again it is the **environmental safety** regulations that top that list with the highest 'very unhelpful' score, as in other sections of this report. The data requirements for **disease resistance** (antimicrobial resistance and parasiticide resistance) have a high cost impact, threatening the continued maintenance of existing products.

Figure 16: Impact of European regulations on ability to commercialise existing products



The **licence maintenance**, including the variations procedure, in the decentralised and mutual recognition procedures (DCP/MRP) receives a mixed response. However the variations procedures with respect to **manufacturing changes** were seen as unhelpful by 91% of respondents. The main issue is that the procedure runs at the speed of the slowest member state. This means that manufacturing changes become significantly delayed as these cannot be implemented until the variation has been approved in the slowest MS. This is contrary to the variations work-sharing procedure where the timeline of implementation is the one of the reference member state (RMS).

The cost of updating or changing packaging and labelling is also seen as prohibitive to progress (see Figure 17 below). This is a very big incentive not to change packaging, which prevents or delays improvements in packaging that could be a benefit to end-users.

Import Regulations (intra- and extra- EU) can become an issue when sourcing certain constituents for vaccines from outside the EU (can occur also for pharmaceuticals); companies are also currently concerned about the impact of the UK exit from the EU.

Figure 17: Packaging/Labelling Modification Rules



Table 7: The pros and cons of Pharmacovigilance

The pros of Pharmacovigilance	The cons of Pharmacovigilance
Reassures the public that products are safe and are continually monitored	Cost of PHV has increased significantly creating a heavy imbalance between cost of inputs versus the small value of outputs
Data can be used for internal assessments to decide whether or not to put a product on the market*	It is resource intensive, triggers label changes, and does not collect data on positive impact of the product
Compared to US, it allows for the identification of some issues earlier	The value is diminished as regulators do not allow data to be used in technical dossiers

* It is important to have the data as pharmacovigilance plays an important internal role; MAHs want to be the first to know of any problems with a product, particularly if a line extension or other investments are planned.

3. Impact of regulation of autogenous vaccines on innovation in vaccines

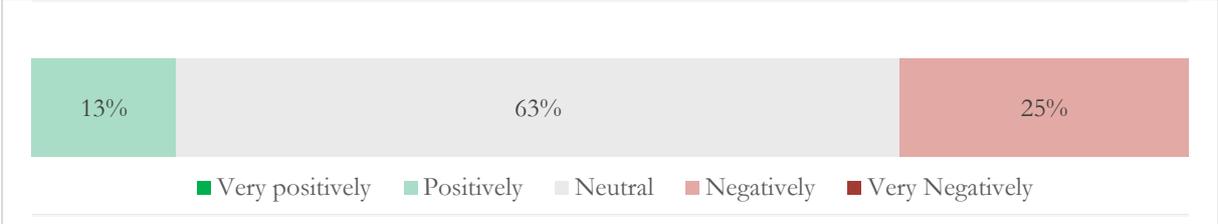
How does the regulation of autogenous vaccines in Europe affect your ability to bring new innovative vaccines to market?

The rise in the use of autogenous vaccines, particularly in some EU member states, has generated discussion around the need for more regulatory control, and the potential impact of their use on the incentive to develop authorised vaccines. This is a new question for the GBS2020 report.

When presented with the question ‘How does the regulation of autogenous vaccines in Europe affect your ability to bring new innovative vaccines to market?’ the respondents in this survey generally had a neutral or negative response (Figure 18). The neutral companies will include those that sell autogenous vaccines as well as licenced vaccines. The negative companies believe that the rise in the market share of autogenous vaccines undermines the value of the high cost of full product development and marketing authorisation of a vaccine.

However all companies recognise that autogenous vaccines have a role to play in the local control of diseases in livestock animals.

Figure 18: Impact of the regulation of autogenous vaccines on ability to bring new innovative vaccines to market



Section D - REGULATORY PREDICTABILITY & QUALITY

1. Predictability of EU regulatory procedures

Does the EU Centralised Procedure (CP), the decentralised procedure (DCP) or the mutual recognition procedure (MRP) as currently managed provide you with the regulatory predictability that you need and the regulatory quality you expect?

The outcome of the questions on regulatory predictability and regulatory quality are shown separately in Figures 19 and 20. The Centralised Procedure (CP) is regarded as predictable with good regulatory quality, achieving these attributes “always” or “mostly”. The decentralised procedure (DCP) and the mutual recognition procedure (MRP) do not always deliver these attributes, achieving them “mostly” or “sometimes”. The reasons for these perceptions are discussed below.

These aspects of the regulatory system can have a significant impact on a company’s ability to bring products to the market. For example, the predictability of a regulatory system can have a large influence on a company’s willingness to invest. Predictability of timelines is important, for example to enable planning for product launches.

But of even more importance for large investments is being able to predict the successful outcome of a registration process if the regulatory requirements are satisfied. This is achieved by transparency in the registration requirements and the expectations of the regulatory authorities, through a comprehensive set of technical guidelines, and through accessibility of the regulatory assessors via channels such as pre-submission meetings and scientific advice. This aspect is particularly important when new technologies and novel therapies are involved.

Trend

Although this outcome is similar to previous surveys in 2015 and 2011, this is an important timepoint to benchmark these aspects of the regulatory environment under the current legislative framework, so that it can be compared with the situation in 5 years’ time (i.e. GBS2025) when Regulation (EU) 2019/6 will have been operational for several years.

Centralised Procedure

The CP is important for innovation (particularly new technologies) and is mandatory for biotechnology derived products. Obtaining a single decision valid across all EU markets is highly valued. The access to the best regulatory expertise within the EU is appreciated.

However, half of the companies questioned do see room for improvement and chose the “mostly” option. The missing factor is open discussion at different steps of product development to obtain more informal discussion on dossier content and product development strategy. More dialogue is desired, which cannot be achieved via the scientific advice procedure (too formal) or from pre-submission meeting (where focus is on ‘procedure’). Scientific advice is sometimes too slow, and companies have moved on to the next step of the development process by the time the answers arrive. More technical and scientific meetings with the rapporteur and the co-rapporteur would be useful in place of the current formal ‘list-of-questions’ system. However, following the European Ombudsman recent challenges to the EMA’s procedures for interacting with applicants, companies fear that creating more opportunities for open dialogue will not be possible.

Companies regard the excessive scrutiny around the new technologies as unhelpful (suspecting an influence from human medicines legislation/guidelines) and would appreciate an opportunity for more dialogue to be able to explain their technologies.

Figure 19: Regulatory predictability under Centralised, Decentralised & Mutual Recognition procedures

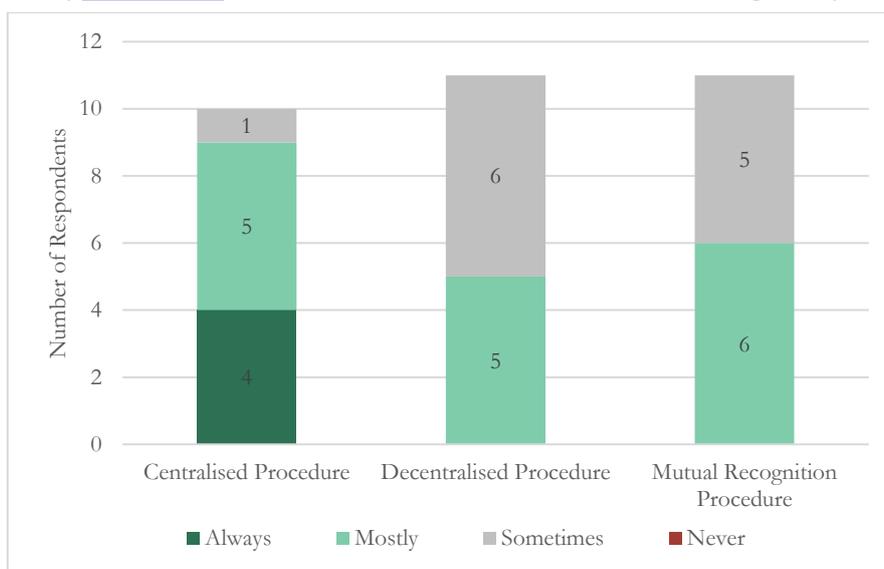
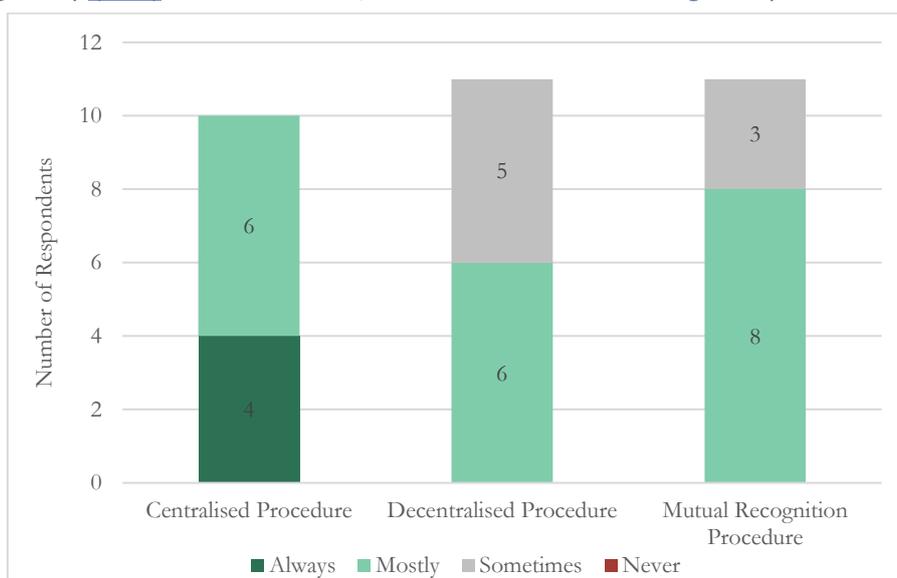


Figure 20: Regulatory quality under Centralised, Decentralised & Mutual Recognition procedures



Decentralised Procedure

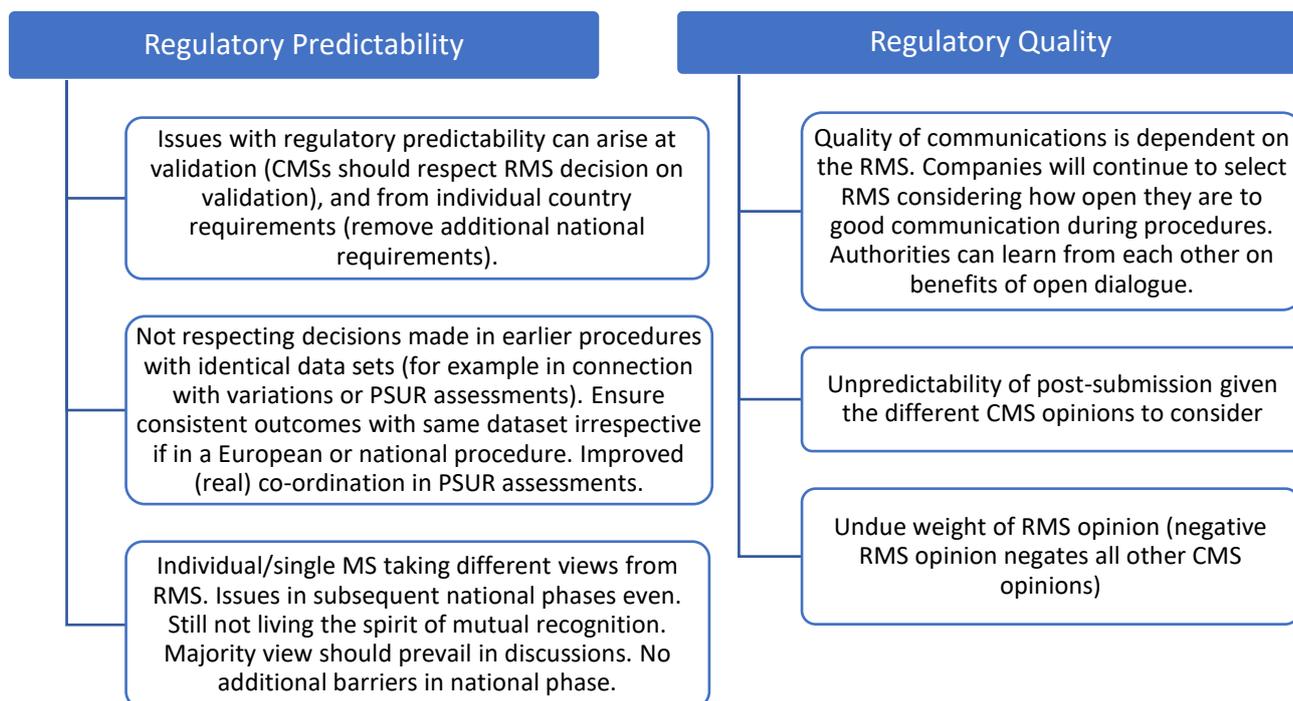
The DCP received a split view between ‘mostly’ and ‘sometimes’; the choice of the “sometimes” option is associated with the unpredictability of post-submission steps and the effort required to address the different concerned member state (CMS) opinions and the different additional national requirements. There is a large discrepancy between the time it takes the different member states to issue the marketing authorisation and agreeing the national packaging can be complex, particularly for multilingual packs. This all creates a feeling of ‘more work and more rush’.

Sometimes a DCP can be blocked by a single or a few MSs. This situation would be avoided if the assessment of the reference member state (RMS) is followed by the CMDv by consensus. The principle should be not to have multiple assessments within 1 procedure by individual MSs. However, there also needs to be a system where CMS consensus can over-ride the single viewpoint of the RMS. Currently there is a legal void in that if the RMS opinion is negative there is no

procedural way back foreseen in the legislation, even if the CMS opinions are positive. [N.B. This issue is resolved in Regulation (EU) 2019/6, which becomes applicable in January 2022]

The active engagement of the RMS is seen as key to a good procedure, particularly to endeavour to find consensus between CMSs concerning the issues raised. The divergent interpretation of regulations, directives and some guidelines by some member states, contradictory opinions, or even ‘hobby horses’ of involved member states creates problems. As a consequence, issues are being discussed until the last day of the procedure and one CMS can have a major influence on the outcome.

Table 8: Key issues with regulatory predictability and regulatory quality



Mutual Recognition Procedure

The MRP received more “mostly” votes than the DCP as it is felt there is more time for better exchanges with the RMS, compared to the DCP, through the 1 on 1 process of the first assessment by the RMS. During this first phase the CMSs do not influence the RMS’s final decision and RMS and applicant have enough time to work through the principal questions before submission to the MRP.

The MRP is not seen as a favourable approach for existing vaccines; thus companies prefer to maintain EU wide auto-generic or biosimilar applications to promote medicine availability with a fair cost and risk/benefit balance.

As with the DCP, divergent interpretation of existing regulations can cause problems in MRP (for example, generic procedure for antibiotics). The validation of the packaging artworks by some countries in the national phase can cause delays (these types of issues have been resolved in the CP).

Section E - REGULATORY TRENDS

1. Recent beneficial changes to EU regulatory frameworks

What beneficial changes have occurred in regulatory frameworks SINCE 2015?

The EU regulatory network has brought welcome improvements to areas such as novel therapies, new guidelines, improved variation procedures and improved E-submission tools. These items are recorded in the table below.

✓ ADVENT group for novel therapies - reaching out for input, then releasing Q&As on some topics
✓ Various HMA/CMDv initiatives to develop more efficiency in the EU regulatory system within the current regulatory framework, i.e. without waiting for the future VMP Regulations
✓ Development of guidelines helping to clarify authority expectations improves predictability (although some GLs are not beneficial and can make life more difficult)
✓ Improvement of the procedures for variations (especially the work-sharing procedure, but also grouping/super-grouping and type II umbrella variations)
✓ Improvements concerning procedures for generic applications
✓ Improved CVMP and European Pharmacopoeia guidance (<i>in vitro</i> assay allowance, animal safety/toxicity testing, harmonization and improved guidance on viral purity requirements)
✓ Implementation of e-submission

2. Expected changes that have NOT occurred in EU regulatory frameworks

What expected changes have NOT occurred in regulatory frameworks SINCE 2015 despite expectations of change?

As the new Regulation was delayed and has a long implementation period (not until January 2022), all the benefits already expected from the 2015 survey are delayed. These include: improved technical data protection, reducing information on labels, removal of renewals, removal of sunset clause, and opening up the scope of the centralised procedure. The lack of reduction of the administrative burden from additional national requirements was mentioned multiple times.

The responses from the surveyed companies are summarised below under 3 headings. As these are individual company responses, they may be contradictory to the overall conclusion of the report, but are never-the-less captured as a record individual reflections.

Pre-authorisation

- Certain Member States have been slow to remove unnecessary national requirements; these reduce harmonisation and decrease efficiency of EU decentralised regulatory procedures
- The full spirit of mutual recognition between some Member States in DCP/MRP is still missing
- Benefit risk assessment based on product data, not a check-box approach on regulatory principles. For example, a variation was refused by a RMS due to lack of full compliance with a guideline, while the CMSs considered the data was sufficient to address any safety issues.
- Streamlined process for national phases
- Labelling & packaging simplifications
- Reduction of the administrative burden (in fact it increased due to environmental safety, AMR, and slow development of a workable electronic application form, with data capture and re-use)
- Reduction of requirements of well-known molecules in terms of Environmental Risk Assessment and in the case of new molecules
- Insufficiently developed regulatory science strategy for new technologies; current approach is too much in 'silos' (e.g. pharmaceutical experts versus biological experts)

Post-authorisation

- No decrease in the defensive R&D costs in the product lifecycle
- An easy process for harmonisation (e.g. conversion to MRP; harmonisation of Part II for biologicals; the CMDv “10 critical points for harmonisation of Part II” does not always work and a fully harmonised Part II may be required)

Biologicals

- Evolution in Ph.Eur. purity testing to waive extraneous agents tests from final products towards a benefit-risk-based approach, while continuing to recognise well established reference methods (2.6.24 & 2.6.25 & 5.2.5, IVMP production & control GL-Former Eudralex vol 7.B)
- Reconsideration of the need for field efficacy trial requirements for veterinary vaccines, despite very broad authority agreement that they are frequently of no value
- MUMS Guideline for vaccines: missed opportunity (increased requirements while the opposite was expected)
- The vaccine antigen master file (VAMF) concept was not implemented

3. Recent changes to EU regulatory frameworks causing the most problems

What regulatory changes SINCE 2015 have given you the most problems and why?

The responses from the surveyed companies are summarised under 6 headings as follows:

Increased environmental requirements

- The negative influence of environmental safety legislation and its interpretation during regulatory procedures (e.g. there was the first rejection of MA application for a product for food-producing animals on the grounds of environmental safety)
- New CVMP guidelines on environmental risk assessment raised unsurmountable hurdles that resulted in several projects being abandoned

New or revised CVMP guidelines

- Involvement with the development and registration process of a new biotech product – registration process rather chaotic with positive CVMP opinion turned down by the Council and approval obtained only with several months of delay
- Review of new technology – who should review – pharma expert or bio expert; when something new comes along CVMP is not sufficiently prepared
- Increasing quality requirements often aligned with ICH guidelines (elemental impurities, residual solvents, genotoxic impurities, definition of starting material) that are not fully relevant to animal health.
- New guidelines concerning extraneous agents testing resulting in re-testing of master seeds and cell banks for existing products, whereas these seeds and cell lines have been used for products which are on the market for prolonged periods of time: risk for existing product portfolio.
- MUMS: high requirements considering low return of investment (MRL establishment, extrapolation from major species, the safety and efficacy requirements not much reduced)

Development of resistance

- The impact AMR policies in several MSs on AM residues following the use of antibiotics in vaccine manufacturing
- Impact on existing products and important constraints for the development of new antibiotics, often due to political pressure (the assessment not is based solely on science and benefit-risk; this creates uncertainty and unpredictability)

Pharmacovigilance

- PSUR assessment timelines introduced – 14 days to answer queries in the preliminary report (before no timelines applied) with no consolidation/alignment of these questions in the report

GMP inspections of API manufacturers

- EU GMP inspections of API manufacturers outside Europe resulting in non-compliant statuses : This is an important topic and causes major problems, as it is not linked to regulatory change but to changes in the way of implementation with increased scrutiny
- Trigger unexpected deletion or suspension of API manufacturers in MA dossiers, which can result in unavailability of VMPs in the market

Post-authorisation

- Disproportionate level of fees for variations (e.g. change in DDPS), especially for administrative change; this can negatively influence decisions to conduct variations and prevent innovation and product lifecycle management
- Increase in administrative burden, including from issues with the new E-application form and Brexit, to some extent
- More and more country rules on reporting out of stock situations, and all of these being different, such as when you have to report, for what, how etc.

4. Impact of EU regulatory frameworks on major business decisions

Have regulations played a major role in influencing you to take any of the following major decisions over the last five years?

Respondents were asked to consider a list of 23 potential major business decisions, and whether regulations played a major role in influencing these over the last five years. The options were often in pairs, looking at both the upside and the downside of a business decision. Many of these decisions have other multiple factors other than regulations, including other regulations related to business operations. The outcome is shown in Figure 21, and the top 4 decisions taken where regulations played a significant role were:

1. Avoid certain product technologies in Europe (significant in 36% of decisions)
2. Invest in production outside Europe (significant in 27% of decisions)
3. Introduce more breakthrough products in Europe (significant in 27% of decisions)
4. Reduction of product range in Europe (significant in 22% of decisions)

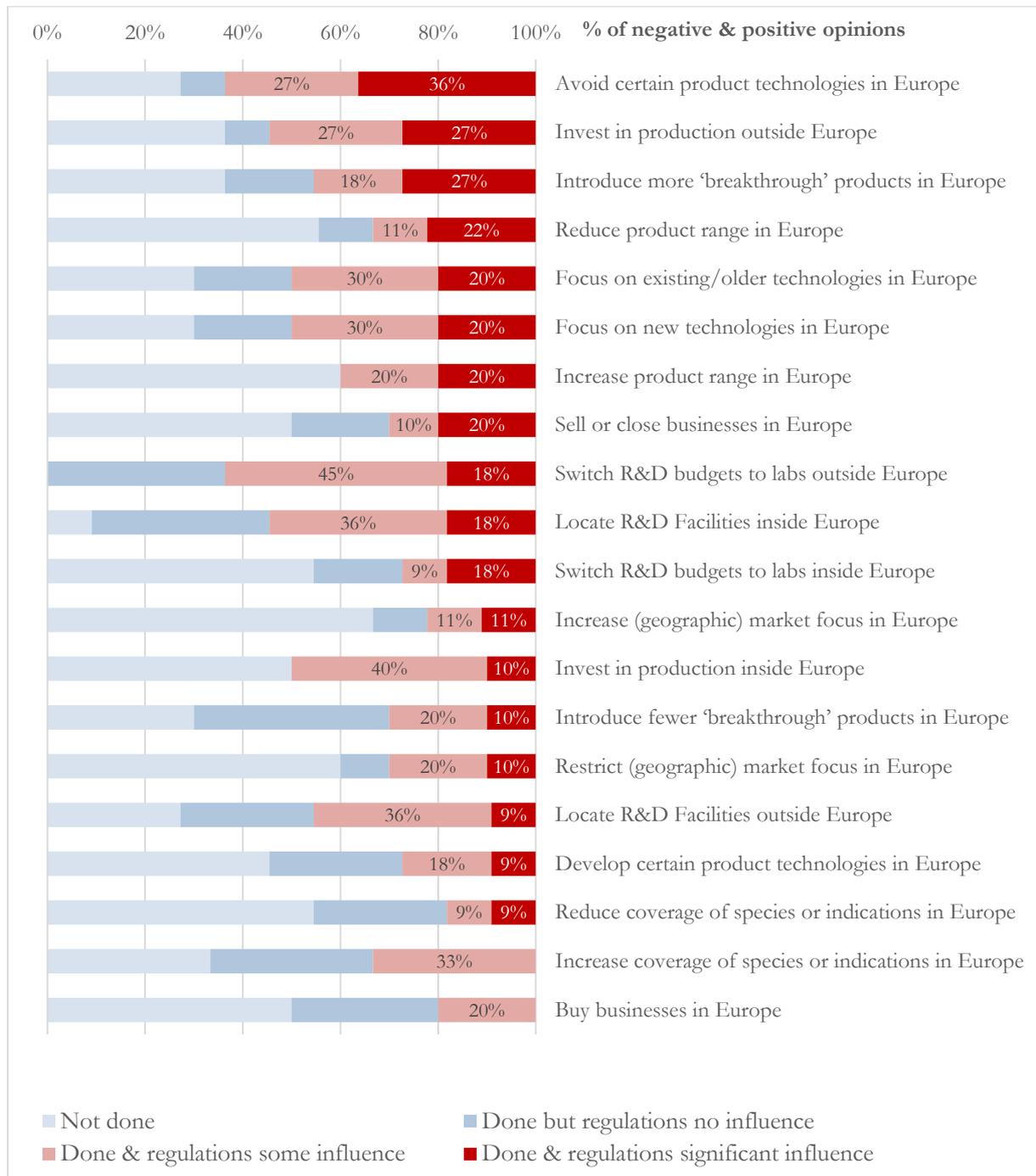
It is notable that the majority of paired options produced a divergent outcome (see Table 9), with the exception of decisions to “Focus on new technologies in Europe” and “Focus on existing/older technologies in Europe”, which were equally influenced by regulations (20% ‘significant’ and 30% ‘some’). Other options where regulations had a similar level of significant influence were: Restrict / increase (geographic) market focus in Europe’, Increase/Reduce product range in Europe, and Switch R&D budgets to labs inside/outside Europe.

Table 9: Paired business decisions where regulations drive a divergent business decision

Paired business decisions, with clear divergent answers, are shown in the same row.

More significant impact on business decision	%	Less significant impact on business decision	%
Reduce coverage of species or indications in Europe	9	Increase coverage of species or indications	0
Locate R&D Facilities inside Europe	18	Locate R&D Facilities outside Europe	9
Sell or close businesses in Europe	20	Buy businesses in Europe	0
Introduce more ‘breakthrough’ products in Europe	27	Introduce fewer ‘breakthrough’ products in Europe	10
Invest in production outside Europe	27	Invest in production inside Europe	10
Avoid certain product technologies in Europe	36	Develop certain product technologies in Europe	9

Figure 21: Major decisions taken in the last 5 years as influenced by regulations



Section F - HOPES AND EXPECTATIONS FOR THE NEXT 5 YEARS

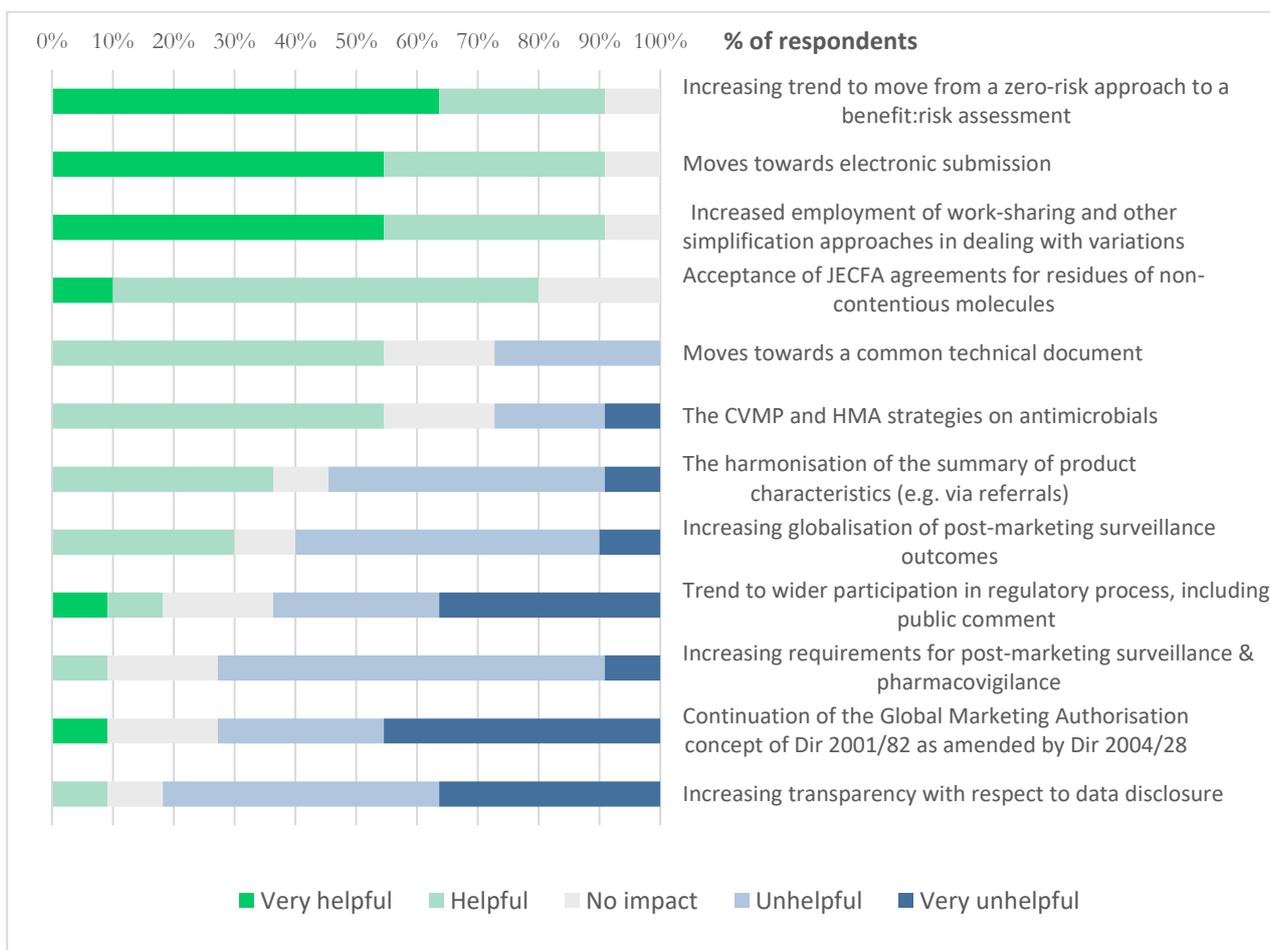
1. Expected impacts of recent trends or changes in EU regulatory approach

The following trends or changes in regulatory approach have been taking place recently and may well have an impact in future. What impacts do you expect these to have on your business in the next 5 years?

The top 4 most helpful and most unhelpful trends are summarised in the Table below and remain the same as in the 2015 survey; the responses to all the options are shown in Figure 22.

Top 4 Helpful Trends 2019:	2015	Top 4 Unhelpful Trends 2019:	2015
1. Move from zero-risk to benefit-risk assessment approach	1=	1. Increasing transparency data with respect to disclosure (access to documents policies)	2=
2. Increased use of work sharing to deal with variations	1=	2. Continued use of the Global Marketing Authorisation concept	1
3. Move towards greater use of electronic submission	1=	3. Increasing requirements for post-marketing surveillance & pharmacovigilance	3
4. Acceptance of JECFA agreements for MRLs	4	4. Trend to wider participation in the regulatory process	2=

Figure 22: Impacts of regulatory trends



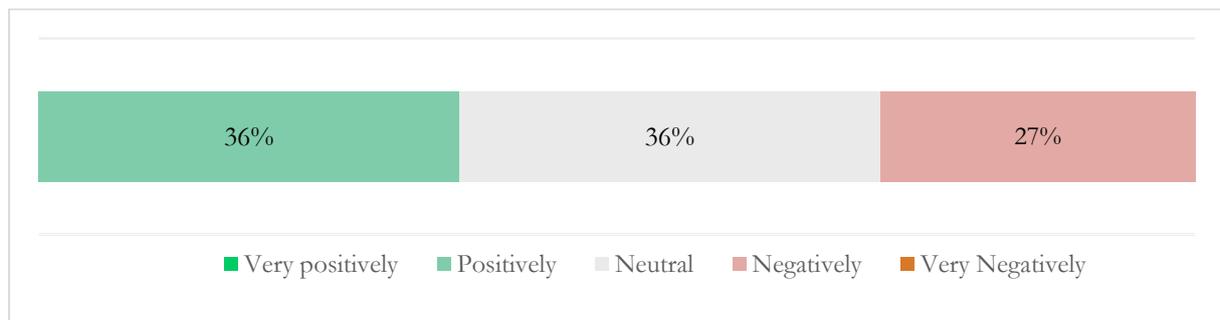
2. Expected impacts of the new veterinary medicinal product regulation

What impacts do you expect the new veterinary medicinal products regulation to have on your business and why?

The view of companies on the impacts of the new veterinary medicinal products (VMP) Regulation (Regulation (EU) 2019/6) is summarised in Figure 23. There is a mixed response, perhaps reflecting the mixed outcome of the review of the legislation leading to a balance between pros and cons. Nobody took a very positive or a very negative view. A company's viewpoint can also be influenced by individual experiences, and expectation of the impact of the implementation of the new Regulation in January 2022, depending on the company product portfolio. The Regulation contains a mix of gains and losses. However, the true impact depends on the content of the secondary legislation and supporting guidance.

As the objective of the review of the legislation was to bring a significant overall improvement, it is interesting to consider whether a balance is a good outcome. However, the view of other key stakeholders, particularly the view of the regulatory authorities, needs to be added to the mix.

Figure 23: Impacts of new veterinary product regulations



The positive and negative outcomes of the review of the legislation, in the eyes of the companies participating in the workshop, are discussed below. Respondents were split over whether the new Annex 2 (covering the data requirements), currently being drafted, would have positive or negative effects. The overall trend, however, leans ultimately towards positive expectations.

Positive outcomes of the new Regulation

- Opening up of the scope of the centralised procedure to all products, allowing pan-EU decisions
- More harmonised and efficient approach across the EU resulting in less administrative burden and less duplication
- Innovation on existing products rewarded (data protection for line extension)
- Protection of technical documentation: more incentive for minor species, but insufficient incentive for major species; 4 years of protection for new data for an existing product
- Increased clarity on biological product requirements in annex 2 of the regulation including: use of vaccine antigen master file (easier changes for different products), inclusion of vaccine platform technology, the multi-strain dossier approach possible for pathogens when justified,
- Spirit of openness and support in the development of innovative medicines by including novel therapies in annex 2, while trying to keep flexibility and predictability
- Post marketing activities (grouped variations, work-sharing, no renewals, no sunset clause)
- Better defined routes to approval for products for limited markets and exceptional circumstances
- A more harmonised approach to autogenous vaccines
- Union Product Database (despite anticipated high administrative burden to get it established)

Negative outcomes of the new Regulation

- Too many uncertainties, such as pharmacovigilance signal management, SmPC harmonisation procedure and variation management, particularly with the high number of implementing measures
- Increased requirements are anticipated on adjuvants, novel technologies, including nanotechnologies
- No clear decrease on existing expensive data requirements that contribute little; for example: efficacy field trials for vaccines, GLP for all safety studies, use of serology; these need to be reconsidered during the redrafting of Annex II
- Increased uncertainty especially towards antimicrobials
- Insufficient reduction in administrative burdens (may yet be further influenced by the implementing measures)
- PBT as legal ground for refusal, potential requirement for environmental studies for companion animal products, linked to the implementation of monographs

Opportunity

The uncertainty over the true impact of the new VMP Regulation is also an opportunity, as there is an unprecedented number of implementing and delegated acts to be drafted and adopted, as part of the implementation of the new Regulation. Therefore, it is possible, given the right implementation of the details of the Regulation, to further improve the regulatory systems and deliver the objectives of the legislative review to reduce administrative burden and increase medicines availability.

Focus needs to be on major areas such as the SmPC harmonisation of existing products, efficiently managed databases, variations management, antibiotic and endectocide product life cycle and new registrations and Annex II.

The opportunity must be taken to bring registration improvements concerning new technology products. The survey respondents remained concerned that important resources will continue to be divested from innovation to defending existing products.

3. Changes still wanted in EU regulatory approach

What changes do you still want to see and why?

The industry wish list is arranged below in short, medium, and long- term goals.

Short term changes

EU vs Member States

- All Authorities, irrespective of their available resource and country of origin, living the spirit of mutual recognition
- Avoidance of divergent decisions on the same data package, e.g. national variation procedures.
- Practical implementation of the new Regulations, with well-developed supporting infrastructure e.g. fully functional Union Product Database, Eudravigilance Vet
- Simple harmonisation procedure
- Ensure medicines availability by the recognition of national MAs after renewal in all EU
- Increase in predictability success factors, e.g. avoid divergent opinions etc NVR does not change predictability – that is down to good implementation
- Authority assessors receiving good training on new technologies; avoidance of reliance on closest regulatory precedent especially where the precedent is not relevant

Product development and assessment

- Always base assessment conclusions on individual product data rather than on strict regulatory principles (i.e. a check-box approach)
- Reduce the complexity of new product assessments, by better recognition of assessments
- Greater flexibility in variation assessment/timing
- Risk and science-based decisions for more predictable assessment
- One scientific evaluation resulting in MA across the EU
- No repeat registration procedures
- Further expansion of e-submission
- The simplification of artwork/labelling under the new Regulation is anticipated: - less required text and extension of the use of pictograms to address space limitations

Post-authorisation and pharmacovigilance

- Decrease defensive R&D costs allowing existing products to be maintained on the market
- Greater dialogue opportunities with regulatory authorities, including on pharmacovigilance
- Opportunities for industry and regulators to really work together to deliver the best outcome e.g. detailed implementation of signal detection

Medium term changes

- GMO rules clearer on scope (substances and products) and limit additional requirements to where it is really justified and are not already taken care of in the usual benefit:risk assessment
- GMP rules (annex IV and V) suitably adapted where appropriate to the specificities of veterinary medicines sector whilst ensuring an appropriate level of control
- Harmonisation of autogenous vaccines regulation within EU to reduce fragmentation in the market and inclusion of viral vaccines
- Fully harmonised approaches across MSs, e.g. electronic submission, to exploit fully the advantages from working within one EU legal framework
- Conditional licenses system needs improving, such as allowing with ‘reasonable expectation’ of efficacy; conditional licenses at the EU level will shorten the time-to market for pivotal products
- Improved approval processes for novel therapies with greater authority dialogue opportunities.
- Reduce constraints around products authorised in the centralised procedure (which will be open to all products) and allow more flexible lifecycle management. For example, to allow a product first authorised in the CP to have duplicates in the NP, MRP or DCP procedures
- More flexibility for variations for immunological products; simplification of the variation guideline, limit the number of type II variations and provide the possibility to file umbrella variations to update dossiers which will facilitate lifecycle management

Long term vision

- Deletion of the global marketing authorisation principle
- Majority voting in the decentralised procedure
- Greater cross-region (e.g. EU with USA, China, Japan) authority discussion on new technologies to align early on studies and requirements
- Harmonisation between regions (US, Europe...) and more mutual recognition in scientific assessment and inspections

Section G - REGULATORY COOPERATION AND SPECIAL PRODUCT CATEGORIES

1. Engagement in regulatory cooperation

Does your regulatory authority engage in any forms of regulatory cooperation, such as joint reviews or parallel assessment, with another (non-EU) regulatory authority?

All respondents responded positively that their regulatory authorities engage in cooperation with other entities.

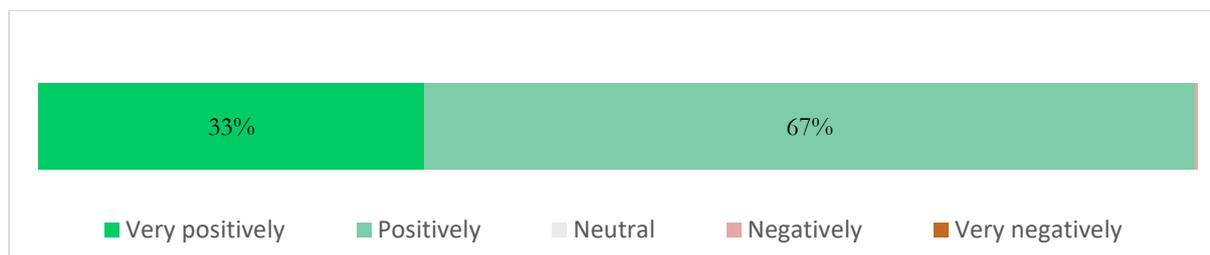
2. Impact of regulatory cooperation on your ability to innovate

If yes, how do joint reviews or parallel assessment between EU and another country impact your ability to innovate?

There is an unanimous view that regulatory cooperation has a positive or very positive impact on ability to innovate (Figure 24).

The impact of joint reviews or parallel assessment between EU and another country depends on the authorities involved. The potential negative impact of a national stringency or reluctance to certain products must also be considered, especially for biologicals.

Figure 24: Impacts of regulatory cooperation on innovation



3. Do “special categories” of product exist?

In your country do “special categories” of product exist, such as “minor species”, or “generic” for which there is an exemption from certain data requirements (e.g. registration can be obtained with an abbreviated or abridged data dossier)?

The respondents listed the following special categories of products in the EU, which often allow certain derogations from the provision of a full-data dossier:

- Generics and hybrid abridged dossiers with derogation from full safety and efficacy data
- MA exemption (under conditions) for aquarium fish, cage birds, homing pigeons, terrarium animals, small rodents, and ferrets and rabbits kept exclusively as pets (*this exemption is currently inconsistently applied across the EU member states*).
- ‘MUMS’, products intended for minor use / use in minor species
- Informed consent applications (copycats)
- Exceptional circumstances
- Fixed combination product (of known active ingredients)
- Well established veterinary use
- Specific initiatives at country level (e.g. UK provisional MA & limited MA)

Acknowledgements

A great deal of thanks and appreciation is offered to all the company personnel who had to find the time within their busy schedules to complete the questionnaire for the GBS2020 survey. A hearty thanks is also due to the dedicated staff within the HealthforAnimals national industry associations around the world, for the enormous effort in driving this project in their regions and delivering the data and analysis on time.

Glossary of Abbreviations

ADVENT - Ad Hoc Expert Group on Veterinary Novel Therapies at EMA

AMR - Antimicrobial Resistance

CAP - Companion animal product

CMDv - Coordination Group for Mutual Recognition and Decentralised Procedures - Veterinary

CVMP - Committee for Medicinal Products for Veterinary Use at EMA

DCP - Decentralised Procedure

DDPS - Detailed Description of the Pharmacovigilance System

EFSA - European Food Safety Agency

EMA - European Medicines [Evaluation] Agency

EU - European Union

GBS - Global Benchmarking Survey

GLP - Good Laboratory Practice

GMO - Genetically-modified organism

GMP - Good Manufacturing Practice

HMA - Heads of Medicine Agencies

IVMP - Immunological Veterinary Medicinal Products

JECFA - Joint FAO/WHO Expert Committee on Food Additives

MA - Marketing Authorisation

MAH - Marketing Authorisation Holder

MD-R&D - Mandatory Defensive R&D

MFA -Major food animal

MRA - Mutual Recognition Agreement between countries

MRL[s] - Maximum Residue Limit[s] (or level[s])

MRP - Mutual Recognition Procedure

MSs - Member States (of the EU)

MUMS - Minor Uses-Minor Species

NP - National Procedure

NVR - New Veterinary Regulation (EU) 2019/6

PBT - Persistent, Bioaccumulative & Toxic PSUR - Periodic Safety Update Reports

R&D - Research and Development

SmPC - Summary of product characteristics

USDA - US Department of Agriculture

VICH - Veterinary International Cooperation on Harmonization (of Technical Requirements for Registration of Veterinary Medicinal Products)

VMP - Veterinary Medicinal Product

Report prepared by AnimalhealthEurope as part of a HealthforAnimals initiative to support informed policy making in the animal health sector globally.

This report and reports on the other markets included in the benchmarking survey are available at: HealthforAnimals.org/GBS2020

