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

1. About the benchmarking survey

1996

2001

2006

2011

2015

2020

The Global Benchmarking Survey is run every **5** years by HealthforAnimals 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.

The 2020 report is the **6th** for Europe. It summarises the data from **12** European based international companies and examines key trends. The GBS2020 global overview report, published separately draws comparisons with the other key markets surveyed.

11 countries

6th report

12 companies

Abbreviations used in this report

AMR: antimicrobial resistance
CMDv: Coordination Group for Mutual Recognition and Decentralised Procedures – Veterinary
CVMP: committee for veterinary medicinal products
DCP: decentralised procedure
EMA: European Medicines Agency
GMP: good manufacturing practice
HMA: Heads of Medicines Agencies
MA: marketing authorisation
MRP: mutual recognition procedure
SPCs: summary of product characteristics
VMP: veterinary medicinal products

This brochure provides an insight into the contents of the Global Benchmarking Survey 2020 Report for Europe, which was prepared by AnimalhealthEurope as part of a HealthforAnimals initiative to support informed policy making in the animal health sector globally.

2. Key conclusions

Economics

The global animal healthcare industry continues to grow:

- Europe is the second largest market, after USA
- Acquisition is a common strategy for growth (to build competence and capacity in technologies, new science, new therapies and new geographies) and to adapt to a rapidly evolving marketplace
- AnimalhealthEurope companies spent on average 7.8% of their revenue on R&D (range 6% to 9.4%)

Impact of the regulatory environment on innovation

- The regulatory environment can be both an enabler and a disabler of innovation
- Key aspects include 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 **protection of technical documentation** plays an important role in stimulating investment in new product development
- EU Policies on **public access to documents** undermines the protection of intellectual property and is damaging to innovation in the EU

The regulatory framework is ill-adapted to biologicals

- Particularly the data requirements[1] (the 'annex') and the burden of the variations regulations
- Faster approval times for urgently required vaccines are necessary so that the industry can respond to rapidly changing disease situations in Europe

Efficient procedures and the cost of the product life-cycle

- As in the previous surveys, the centralised procedure is ranked highly as an enabling factor
- The mutual recognition and decentralised procedures (MRP/DCP) are also seen as helpful, but the persistence of additional national requirements remains a concern
- Mandatory defensive R&D costs have reduced but concern remains with the increased focus on antimicrobial resistance and environmental safety data requirements
- Progress has been made on administrative burden with the more efficient management of variations

Innovation

The biggest hurdles to innovation are:

- The cost of environmental safety requirements
- Resource intensive manufacturing inspections
- The EMA policies on access to documents

Hope for the new Regulation (EU) 2019/6

- With the exception of the "global marketing authorisation principle" (article 38.3), there is optimism for the new provisions for protection of technical documentation in the new regulation
- The annex to the new regulation could help to relieve some issues for biologicals, particularly the vaccines technologies platform, vaccine antigen master files and multistrain dossiers

[1] As described in the annex to Directive 2001/82/EC as amended.

3. Key recommendations

- Continue the drive for greater harmonisation within the EU regulatory network
- Continue efforts to bring more efficient regulatory procedures (e.g. Regulatory Optimisation Group)
- Good implementation of the new regulation is a key short-term factor moving forwards
- Better adapt systems for biologicals and novel therapies
- Keep risk assessment procedures for environmental safety and AMR* proportionate for the VMP* 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

Changes since the GBS 2015 Survey

Good progress

- Reduction in administrative burden through variations grouping and work-sharing
- Reduction in the cost of mandatory defensive R&D
- Anticipated benefits of the new Regulation to support innovation
- Electronic submission portals and use of IT

Main challenges going forward

- Increased costs driven by environmental safety and antimicrobial resistance data requirements
- Ability to respond quickly to emerging diseases and epidemics
- Increased costs of pharmaco-vigilance that does not bring improvements in the safety
- The good implementation of Regulation 2019/6
- A regulatory science strategy fit for a rapidly evolving healthcare sector

Wrong progress

- Increased transparency and data disclosure makes EU unattractive as a place to introduce new products

No progress

- The Global Marketing Authorisation concept continues to be an inhibitor to both innovation and protection of technical documentation

More progress needed

- True mutual recognition in MRP and DCP; removal of additional national requirements
- For vaccines, vaccine antigen master files and reduced emphasis on efficacy field trials
- Removal of duplication of GMP* inspections (more Mutual Recognition Agreements)
- Reduction in administrative burden
- More veterinary specific aspects for GMP

* See abbreviations listed on page 2.

Change still wanted

Short term

Better implementation of existing principles, such as mutual recognition.

Fully harmonised approaches across Member States.

More opportunities for industry and regulators to work together to deliver the best outcomes on challenges facing all stakeholders in the regulatory network.

Medium term

Evolution of regulatory science to prepare for new technologies and new therapeutic paradigms will be critical to supporting future innovation.

Regulation that is better adapted to the characteristics of the veterinary medicines sector (e.g. more veterinary specific aspects to GMP*).

Long term

Greater harmonisation between regions globally and more mutual recognition agreements.

International 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.

4. Core findings

Critical factors for commercialisation of existing products

Positive impact

Post-authorisation efficiencies of the centralised procedure are recognised, as is the sound business investment of good manufacturing practice.

Main challenges

1. The Regulatory Framework for the maintenance and extension of existing licences
2. Pressure from competitors in a small and highly fragmented market and consumer influences
3. Environmental safety and antimicrobial resistance data pose a threat to existing product renewals
4. Delays in variations for manufacturing changes is an issue
5. The resources needed for packaging and labelling changes continue to be a major challenge
6. The growing cost of pharmacovigilance systems has become a significant challenge

Regulatory predictability and quality

The regulatory predictability and regulatory quality of the centralised procedure is appreciated.

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.

Improvements to the regulatory predictability and regulatory quality of the MRP/DCP* are recognised, but there is still more work to do to remove inefficiencies.

Not least is the need for the removal of additional national requirements, that continue to add unnecessary administrative burden into the system.

Regulatory trends

Beneficial changes

- The structures and systems put in place to prepare for novel therapies
- Increased efficiencies in the management of variations (work-sharing and grouping)
- The implementation of e-submissions and efficient data management
- The cost of defensive R&D has fallen, but a wide range in company experiences remains
- The move from a zero-risk to a benefit-risk assessment approach

Unrewarded expectations of change

- Continued appearance of additional national requirements in MRP and DCP
- New provisions for biologicals, e.g. the vaccine antigen master file system and the reduction in the need for efficacy field trials for vaccines where justified

Biggest challenges

- GMP inspections are costly and duplicated inspections are a waste of resources
- The disproportionate cost of variations that affect multiple dossiers
- The continued use of the Global Marketing Authorisation concept hampers innovation
  - » See article 38.3 of Regulation (EU) 2019/6

Most unhelpful trends

- The continued rise in requirements and cost of AMR* and environmental safety requirements
- The increasing transparency and data disclosure (access to documents policies)
- The overall value and benefit of the escalating cost of pharmacovigilance, with the view emerging that the cost of inputs now exceeds benefits from improvements in product safety

Mixed response to impact of the new Regulation (EU) 2019/6

Industry is **overall positive** towards the progress that has been made.

BUT

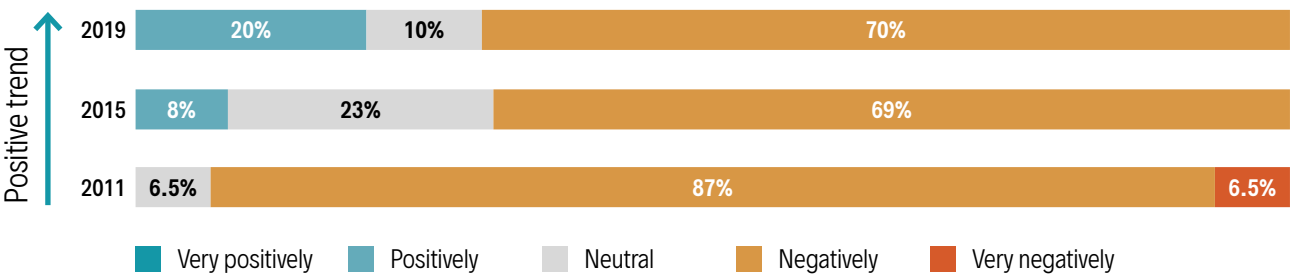
Sees a **missed opportunity** to fully address the high administrative burden of EU regulations.

The **true impact** depends on the content of the unprecedented number of implementing and delegated acts and supporting guidance (short-term uncertainty but also an opportunity to refocus on the objectives of the review of the legislation, such as reducing administrative burden).

Impact of the EU regulatory environment on ability to innovate

Although the majority of responses were negative, there is **a long-term trend towards a more positive outlook**, and companies recognise that the EU regulatory environment is a long-term driver of innovation, especially through the technical guidelines and scientific advice provided which increases the predictability of the authorisation process.

But aspects of the regulatory environment also make it the biggest hurdle in certain areas. In their daily activities, they are faced with a high administrative burden, rising demands for product licence maintenance and compliance, diverting R&D budgets away from innovation and hindering their global developments.



A common thread over these decades is the increasing cost of doing business in a small (relative to the human medicines sector) yet heavily regulated market, triggering an on-going high level of merger and acquisition activity in a continuous drive for scale and efficiencies.

Factors relevant to innovation in the animal health industry

Top 5 factors with negative impact on innovation

1. The EU regulatory framework and legislative environment
2. Small size of market segments
3. Negative consumer attitudes
4. Policies on access to documents of the EU and its agencies
5. Inadequate intellectual property protection (for patents or marketing authorisation data)

> **"High investment with significant risk of failure"**

Other factors reported relevant to innovation

- Lack of international harmonisation, even within EU
- Cost and duration of studies required in EU
- Cost of GMP, lack of adaptation for veterinary products
- Lack of flexibility in the regulation for variations for immunological products
- Lack of development structures (between academia and business), in particular for virology
- Lack of regulatory framework for new technologies (e.g. vaccine platform technologies)

Expenditure on mandatory defensive R&D:

- Defensive R&D diverts funds away from new innovation
- Individual cost estimations are variable, but point to an overall reduction across industry
- Individual company perception is very mixed, and may depend on the company portfolio
- In 2019, the perception of 63% of companies was of no or little change, while 36% considered it had increased a lot

Factors that increase mandatory defensive R&D costs:

- Retrospective application of increased requirements
- Referrals and disproportionate cost of variations
- Increased pharmacovigilance costs
- Antimicrobial resistance (AMR) and environmental risk assessment (ERA) increased requirements
- Manufacture – issues concerning active ingredient suppliers and tendency for inspectors to go further down the supply chain

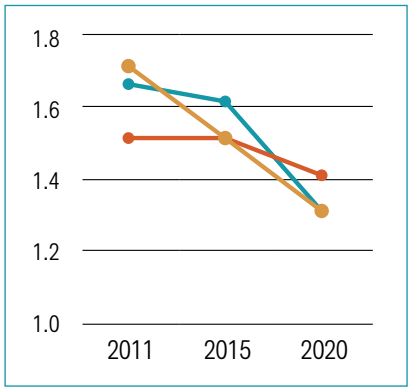
Factors that reduce mandatory defensive R&D costs:

- Pharmaceutical dossiers are already upgraded through national review procedures
- Work-sharing procedures for variations
- Referral procedures (focusing on existing data, not requiring additional experimental data)

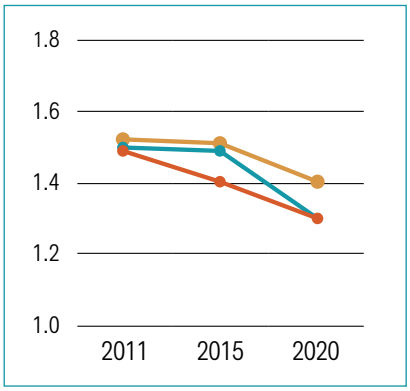
Time to gain registration for a major new product in Europe is decreasing

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. The average time (years) to gain registration for a major new product in Europe is approximately 1.3 or 1.4 years (range 1.0 to 1.7 years) depending on the product category.

Time to gain registration: Pharmaceuticals



Time to gain registration: Biologicals



Major food animals Companion animals Minor species

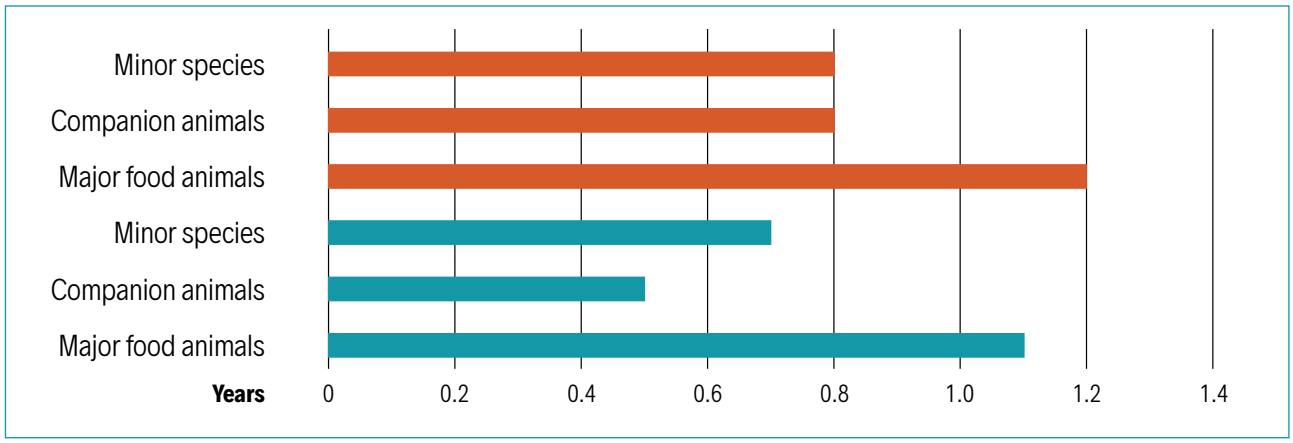
Shorter registration step?

- Experienced companies are improving their dossiers
- An increase in the use of the EMA scientific advice procedure
- Increase in the transparency of the process and an improved understanding of what is expected – the body of regulatory guidance continues to grow
- But also fewer new compounds being registered

Time to develop a major new product continues to increase

For the product development phase, in all product categories, an 'increase' (0.5 to 2 years) or 'little change' (up to 0.5 years) is reported in the length of time it takes to develop a major new product.

Average change in time to develop new products since 2015 (in years)



Biologicals Pharmaceuticals

Trends in time to develop major new products

Trend: Product development time continues to increase, but the rate of increase is slowing down, as judged by data covering a 30-year period.

Time: More time is now spent on human safety and user risk assessments, and more data is generally needed for environmental risk assessments.

IP protection: The steady increase in product development time means that the effective protection by a patent is reduced, placing more emphasis on the MA protection of technical documentation.

Cost: For all categories of products, none of the respondents reported that the cost of developing a major new product in the EU (from initial research to approval) had reduced compared to 2015.

Impact of EU regulations on ability to innovate

Top 4 most helpful areas of regulation

1. Centralised Procedure
2. Protection of Intellectual Property – patents
3. Mutual Recognition and Decentralised Procedure
4. Protection of Intellectual Property – marketing authorisation data

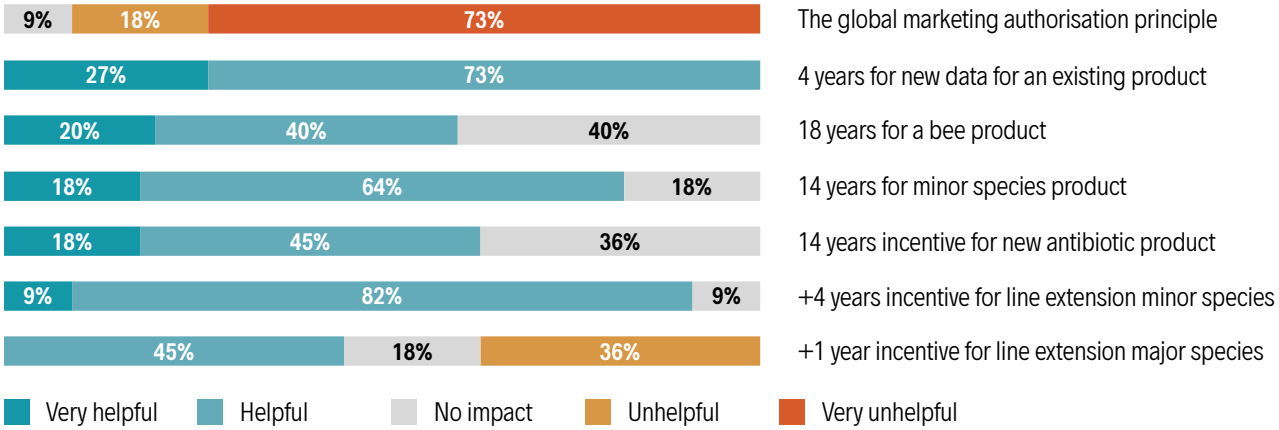
Top 4 most unhelpful areas of regulation

1. Retrospective application of environmental safety regulations
2. Manufacturing – duplicated GMP Inspections
3. EMA policy on access to documents
4. Good laboratory practice when applied to clinical studies

Is EU legislation on protection of technical documentation an incentive?

Regulation (EU) 2019/6 contains improved provisions for the protection of technical documentation; these are seen as either helpful or very helpful (see Figure below), with two exceptions:

1. High dissatisfaction is expressed that the "global marketing authorisation concept" is retained
2. Dissatisfaction is expressed that the +1 year was retained for a line extension to a major species, when experience shows this is not an incentive



Stimulation of innovation for biologicals

Recommendation: focus on faster approval times for new vaccine technologies and diagnostic methods

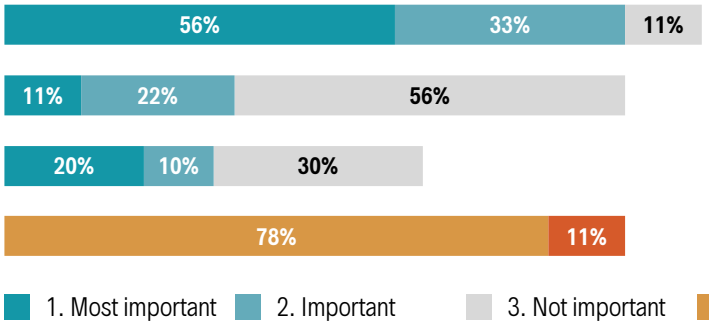
Vaccine platform technologies could bring significant improvements to the vaccine development process

Must be managed by well-trained assessors

Requirements and regulatory approach should be clearly defined

Training of assessors and access to suitable/sufficient experts within the EU regulatory network is key

Focus points to promote innovation in biologics



Faster approval times for new vaccine technologies or diagnostic methods

More focus/activity on approving in vitro testing to replace in vivo methods (where appropriate)

More flexibility on requirements of Conditional Licensing (or similar regulatory practices)

More flexibility on requirements concerning the production and use of autogenous biologics

The top most important factors relevant to the commercialisation of existing products

1. Regulatory framework for maintenance/extension of licenses
2. Pressure from competitors (including parallel imports and generics)
3. Small size of market segments; the market for veterinary medicines is highly fragmented
4. Negative consumer attitudes
5. Inadequate protection of intellectual property for innovation to existing products (more than 5 years old)

Differences in SPCs are important

Impact of regulation on ability to commercialise existing products

In the views of the surveyed companies, the top 4 most helpful and most unhelpful factors are:

Top 4 most helpful

1. Centralised Procedure Licence Maintenance
2. Incentives for line extensions
3. Good Manufacturing Practice in general
4. MRP/DCP Licence maintenance

Top 4 most unhelpful

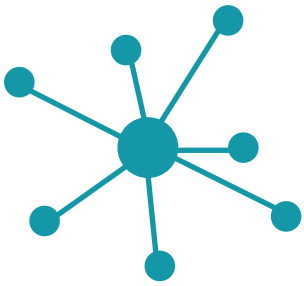
1. Environmental safety regulations
2. Variations Regulation – manufacturing changes
3. Disease resistance regulations
4. Packaging/labelling modification rules

Predictability of EU regulatory procedures

- The Centralised Procedure is regarded as predictable with good regulatory quality
- The Decentralised and Mutual Recognition Procedures do not always deliver these attributes

Predictability of a regulatory system – ability to predict the successful outcome of a registration process if the requirements are satisfied – can have a large influence on a company's willingness to invest.

Centralised Procedure



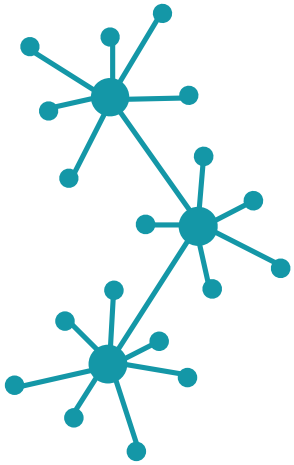
- Important for innovation
- Obtaining a single decision valid across all EU markets
- Access to the best regulatory expertise within the EU

BUT

The missing factor is open discussion at different steps of product development – i.e. a more informal discussion on dossier content and product development strategy.

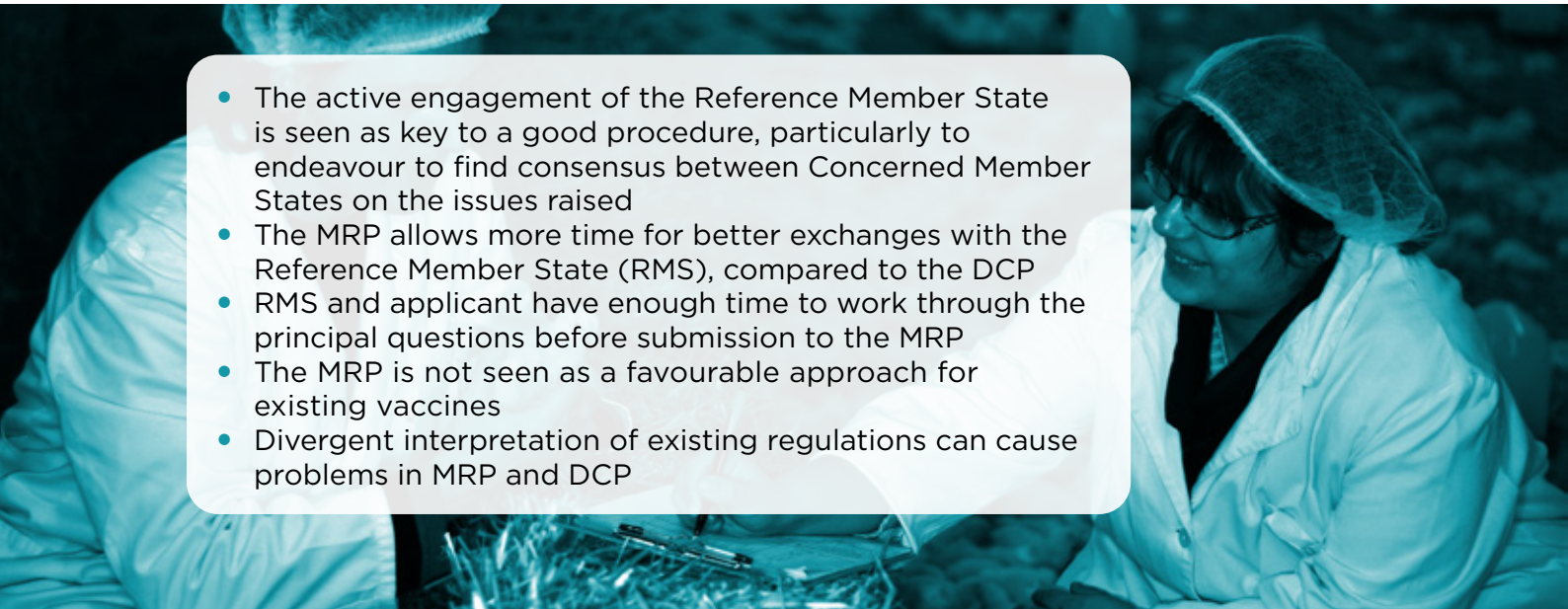
Companies fear there will be even less open dialogue following the European Ombudsman recent challenges to the EMA's procedures for interacting with applicants.

Decentralised and Mutual Recognition Procedures



- Unpredictability of post-submission steps and additional national requirements
- Effort required to address the different concerned member states
- Agreeing the national packaging can be complex, e.g. for multilingual packs
- Time it takes the different member states to issue the marketing authorisation

→ **This all creates a feeling of 'more work and more rush'**



- The active engagement of the Reference Member State is seen as key to a good procedure, particularly to endeavour to find consensus between Concerned Member States on the issues raised
- The MRP allows more time for better exchanges with the Reference Member State (RMS), compared to the DCP
- 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
- Divergent interpretation of existing regulations can cause problems in MRP and DCP

Recent beneficial changes to EU regulatory frameworks

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 guidelines 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 (in vitro assay allowance, animal safety/toxicity testing, harmonisation and improved guidance on viral purity requirements).

Recent changes to EU regulatory frameworks causing the most problems

- Increased environmental safety requirements
- New or revised guidelines and lack of clarity of assessment process for biotech products
- Policies relating to the development of antibiotic resistance
- Pharmacovigilance new periodic reporting and assessment timelines
- GMP inspections of active pharmaceutical ingredient manufacturers
- Disproportionate level of fees for variations affecting multiple (or all) products in a manufacturer's portfolio
- Recent increase in administrative burden (issues with the new electronic-application form and BREXIT, disharmonised country rules on reporting out of stock situations

Impact of EU regulatory frameworks on major business decisions

The top 4 decisions taken by the companies surveyed 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)

Expected impacts of recent trends or changes in EU regulatory approach

In the views of the surveyed companies, the top 4 most helpful and most unhelpful trends are:

Top 4 helpful trends 2019

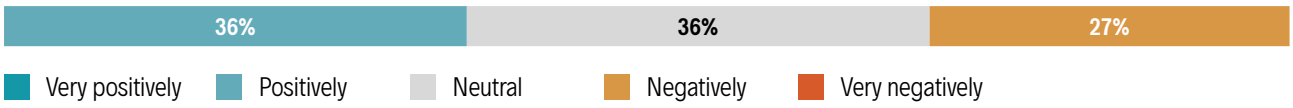
1. Move from zero-risk to benefit-risk assessment approach
2. Increased use of work sharing to deal with variations
3. Move towards greater use of electronic submission
4. Acceptance of international standards for maximum residue limits

Top 4 unhelpful trends 2019

1. Increasing transparency and data disclosure (access to documents policies)
2. Continued use of the Global Marketing Authorisation concept
3. Increasing requirements for post-marketing surveillance & pharmacovigilance
4. Trend to wider participation of other interested parties in the regulatory process

Expected impacts of the new veterinary medicinal product Regulation

The surveyed companies took the following views regarding the expected impacts of the new veterinary medicinal product Regulation (EU) 2019/6:



Positive outcomes of the new Regulation (EU) 2019/6

- Opening up of the scope of the centralised procedure
- Innovation on existing products rewarded
- Increased clarity on biological product requirements
- Inclusion of vaccine platform technology
- The multi-strain dossier approach
- Grouped variations, work-sharing, no renewals, no sunset clause

Negative outcomes of the new Regulation (EU) 2019/6

- Too many uncertainties from high number of implementing measures
- Unknown impact of new processes: pharmacovigilance signal management, summary of product characteristics (SPC) harmonisation procedure and new variations procedure
- No clear decrease in existing expensive data requirements, of which some contribute little to improved safety
- Increased uncertainty especially towards antimicrobials
- Insufficient reduction in administrative burdens
- Requirements for environmental studies and hazard-based approaches

Opportunities

The unprecedented number of implementing and delegated acts present the possibility to improve the outcome, particularly for reduction in administrative burdens and encouraging innovation.

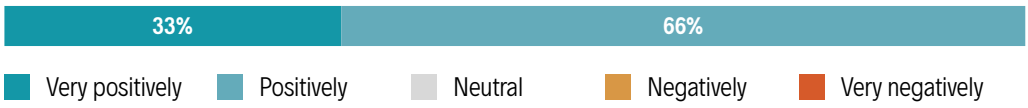
The following will be key: efficient procedures for SPC harmonisation, variations and database management; antibiotic and endectocide product life cycle management and new technology assessments.

Long–term changes still wanted in EU regulatory approach

- 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 (EU, USA…) and more mutual recognition in scientific assessment and inspections

How does regulatory cooperation impact ability to innovate?

- Industry appreciates that their regulatory authorities engage in cooperation with other entities
- There is unanimity among the surveyed companies that international regulatory cooperation has a positive or very positive impact on ability to innovate (see below):



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animalhealth europe
THE VOICE OF THE ANIMAL MEDICINES INDUSTRY

Health for Animals
global animal health association