GLOBAL BENCHMARKING SURVEY 2020

Benchmarking the competitiveness of the global animal health industry

BRAZIL
AUSTRALIA
CANADA
CHINA
EUROPE
INDIA
JAPAN
MEXICO
RUSSIA
SOUTH AFRICA
USA

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Global Benchmarking Survey 2020
Report for BRAZIL

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 **second for Brazil**. It summarises the data from **8 Brazilian based international companies**, examines key trends and draws conclusions and recommendations.

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

Key Conclusions

Since mid-2019, the Ministry of Agriculture, Livestock and Supply (MAPA) has been undergoing consecutive changes by its coordinators and director, either for internal reasons or due to changes in the government. The former Department of Surveillance of Livestock Inputs - DFIP / MAPA was replaced by the General Coordination of Veterinary Medicines - CGMV / MAPA, which now reports to the Department of Animal Health - DSA / MAPA. Additionally, new people were assigned as Minister of Agriculture (MAPA), Secretary (SDA), Director (DSA), General Coordinator (CGMV) and Coordinator (CPV - Coordination of Veterinary Products), with subsequent new replacement of the CPV Coordinator in early 2020.

A new department called Department of Support and Technical Standards (DSN) was established in order to deal with the simplification and reduction of regulations as well as making the procedures clearer and processes less bureaucratic.

SINDAN, as a representative entity of the sector, has already met with all representatives of the regulatory body, either to present the views of the sector regarding the necessary actions and the history of discussions with the previous Ministry, and to understand the recent changes that occurred in MAPA.

It is noteworthy that the reduction of Federal Agricultural Auditors numbers in recent years, has led MAPA to invite SINDAN to participate in an agreement between the agency and the Eliseu Foundation – EMBRAPA (a public company linked to MAPA) for a procedure for reducing the list of initial registration processes and changing the registration of products pending evaluation. Unfortunately, this proposed procedure was not approved by CONJUR (Brazil Government Legal Council).

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

Innovation in Brazil is negatively impacted by the regulatory scenario mainly due to the deficiency of the regulatory framework and lack of protection of intellectual property (patents or commercial data).

Added to this, the regulatory complexity, with norms that complement themselves but are not clear about requested procedures by MAPA, leads to inspectors having an individual interpretation and making divergent requests, providing an uncertain regulatory framework. Furthermore, the lack of legislation about specific types of products is a hurdle to de-bureaucratize the registration process taking into account a risk analysis.

Moreover, the increasing need of defensive R&D investment reduces resources for innovation. The length of time for evaluation of veterinary product dossiers and unpredictability, results in innovative products taking longer to be available for the Brazilian market and discourages their development by local industry.

Despite of having a shorter licensing time, but not reduced enough, biological products are not included in SIPEAGRO (electronic system for pharmaceutical product registration), making the whole process more time consuming for registration and meeting the health authority's needs.

It is important to note that MAPA recognizes that hurdle and has published an Ordinance about prioritization the evaluation for innovations (Ordinance nº 72 – June 2, 2017), determining that an innovative product assessment is prioritized if it meets certain conditions. There is also a normative instruction (Normative Instruction nº 23, December 22, 2016) that de-bureaucratizes the process for simple register changes.

Section C - Commercialisation of existing product

Due to the introduction of the electronic system for pharmaceutical product registration (SIPEAGRO), MAPA initiated a re-analysis process of all existing registered products due to their inclusion into the system, requesting studies updates, which leads to a delay in evaluation and renewals.

A MAPA Official Letter (Official Letter nº97, February 20, 2020) provided orientation for inspectors and industry concerned about their inclusion in SIPEAGRO. At this moment, those existing licenses would not be re-evaluated except for antimicrobials that must be fully updated. Obviously, the dossier can be re-evaluated at any time and an update request can be expected.

Therefore, publication of regulations or alignment of more restrictive requests by MAPA causes a large increase in costs on defensive R&D, which will be further addressed below.

Section D - Regulatory predictability and quality

Between 2015 and 2020, the backlog to evaluate product applications has increased due to decreasing number of MAPA inspectors and more time-consuming evaluations within not clear and deficient legislations allowing additional requests and no predictability for the process. Consequently, the length of time for process review increased to a four- or five-years for pharmaceutical products registration and two- or three-years for biological products registration.

In February, a legislation (Ordinance nº43, February 21, 2020) defined that product registration processes have 720 days to be evaluated or it will be tacitly approved. As the coming into force of Decree (Decree nº 10.178, December 18, 2019) to establish procedures for tacit approval for public acts, had been delayed to September 1st, 2020, industry will have the predictability of 720 days for products registration process filed only after this date.

SINDAN is working to clarify and maintain the chronology and legality for clearing the backlog, now product applications must be evaluated within 720 days after the legislation is in force, before the evaluation of new product applications.

Section E - Regulatory trends

As indicated above, to solve unpredictability government and MAPA published the tacit approval legislation providing two years period for the approval of veterinary products dossiers. Regarding regulatory complexity, government published Decree nº10.139, November 28, 2019, to list and simplify legislation. In addition, MAPA announced the subject list of the 'regulatory agenda' (Ordinance nº 277, August 07, 2020), which includes antimicrobials, antiparasitics, simplified registration, pharmacovigilance, and biological products registration.

Through the answer to three public consultations concerning antimicrobials, antiparasitic and simplified registration for lower risks products, SINDAN is following up with MAPA for the next steps until publication.

ANVISA published a list of maximum residue limits (MRL) and procedures for the inclusion of molecules/MRLs (Normative Instruction nº 51, December 19, 2019 and RDC nº 328, December 19,2019), basically based on *Codex*, however MAPA must define the attributes and deadlines to applicability of this legislation in veterinary product dossiers, which has not occurred yet.

It is worth noting that biological products will be inserted by industry into SIPEAGRO in the coming years as soon as the system is adapted to it.

Section F - Hopes and expectations for the next 5 years

Key trends

- Publication of regulations concerning antimicrobials, antiparasitic and simplified registration.
- Pharmacovigilance discussions and public consultation.
- Biological products legislation to be updated.

Most Helpful trends

- Definition about addressing the backlog and evaluation of new product dossiers.
- Tacit approval and predictability of process approval.
- Simplified registration according to lower risk products analyses.

Most unhelpful trends

- Antimicrobial and antiparasitic legislation that could lead to an increase in costs with defensive R&D to maintain products in the market.
- ANVISA definition about MRLs could be an unhelpful trend if the industry carried out studies considering other agency MRLs.

Changes still wanted

- Thus, SINDAN understands that important steps had been taken to reduce the backlog, de-bureaucratization, and predictability regarding the veterinary products marketing authorization, however it is important to update and publish clear regulations, according to science, internationally harmonized, and providing security for innovation and investments in the sector.

Section G - Regulatory cooperation and special product categories

- Industry understands that two special categories, products for aquaculture and minor species, are very important to be regulated. SINDAN had already proposed a legislation for minor species.
- Regulatory harmonization with European Union and United States is desired.

Summary and recommendations

In order to reduce the processes backlog, some actions were taken:

1) new regulation for the priority evaluation of innovative products registration (Ordinance 72/2017),

2) some new legislations were published:

a) Notice No. 1/2019: Regulates the withdrawal of initial registration processes by the industry itself.

b) Ordinance No. 43/2020: establishes deadlines for tacit approval of public act releases by SDA/MAPA.

c) Letter 97/2020: Informative Letter regarding submission of product processes already registered in SIPEAGRO determining minimum documents for inclusion and, at this time, evaluations only for antimicrobial products.

The impact of these regulations will be observed in the coming years.

Key recommendations

- Push hard to get backlog analysed and reduced to processes submitted only in the last two years.
- Continue effort to bring more efficient regulatory procedures.
- Pursue the regulation update in order to clarify and harmonize with international legislation.
- Lead discussions about pharmacovigilance.

2. Introduction and background

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

The survey originally benchmarked the European and USA regulatory systems but has since evolved and grown to include 11 countries in the 2020 survey (see box 1).

This report is the **second for Brazil**. It summarizes the data from **8 Brazilian-based international companies** and draws comparisons with the other key markets surveyed.

Box 1

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

With the cooperation and involvement of the HealthforAnimals member national associations, the survey is run every 5 years. 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 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** 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 organize 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 Brazil

In Brazil SINDAN collected filled questionnaires from **eight member companies** during September and December 2019, and **five** of these companies participated in workshop teleconferences on January 29 and May 27 of 2020.

Six of these are multi-national companies (MNC) and are also members of the global industry trade association HealthforAnimals.

For more information on the SINDAN membership please visit: http://www.sindan.org.br/associe-se/

1. *Agroceres Multimix*
2. *Bayer Animal Health (MNC)*
3. *Boehringer Ingelheim (MNC)*
4. *Ceva (MNC)*
5. *Delaval LTDA*
6. *Elanco (MNC)*
7. *MSD Animal Health (MNC)*
8. *Vetoquinol (MNC)*

4. The findings for BRAZIL

Section A – FINANCIAL DATA

Global context

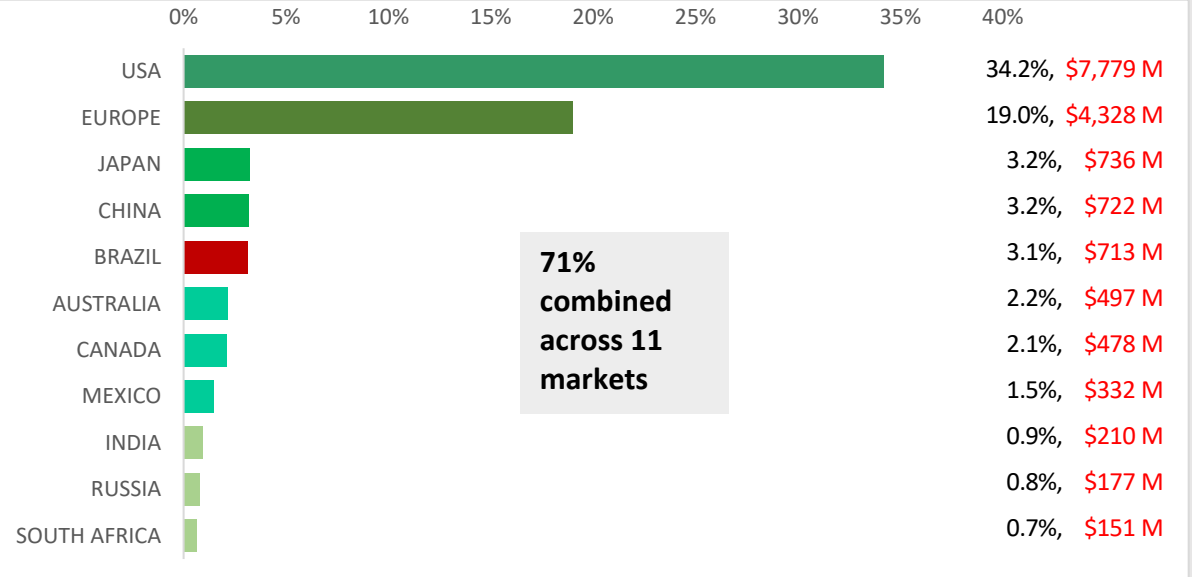
The financial data covers the 2018 full financial year. All data is presented in US dollars ($).

The GBS2020 Part 1 report on financial data is published separately. 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.

In 2018 the global animal health market was estimated to be worth $45.8 billion[1]. The 10 HealthforAnimals company members held over 50% of that market with a combined revenue of $22.7 billion, and an average of $2,274 million, of which 7% was invested in research and development.

The 11 benchmarked markets accounted for 71% of HealthforAnimals companies' global revenues (Figure 1), with Brazil representing 3.1% of that revenue.

Figure 1: Revenue distribution of HealthforAnimals companies across 11 markets in 2018



Overall, the multi-international 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 principal animal segments was 51% for companion animals and 49% for major food animal species.

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

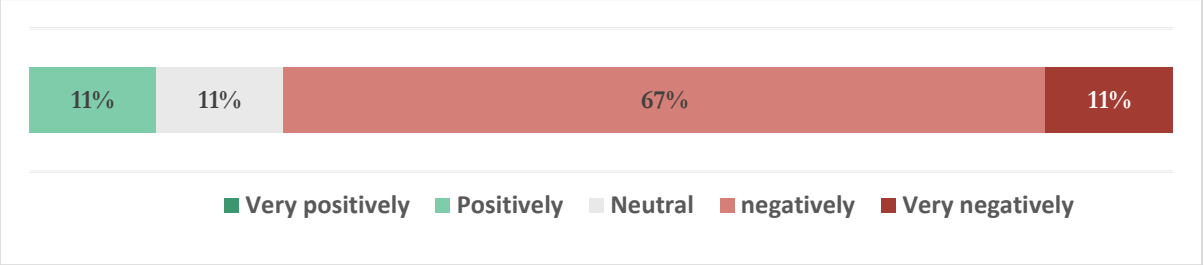
Section B – IMPACT OF REGULATIONS ON INNOVATION

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

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

Most respondents have a negative view of the Brazilian regulatory environment and find that it is not conducive to innovation.

Figure 2: Impact of the Brazilian regulatory environment on ability to innovate



Innovation in Brazil is negatively impacted by the regulatory scenario due mainly to the deficiency of the regulatory framework, lack of protection of intellectual property (patents or commercial data) and lack of or few mechanisms of technology transfer between academia and business.

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?

The overall ranking of the factors relevant to innovation are shown in Table 1. Unclear regulatory requirements and increased regulatory requirements (including MRLs) are the biggest challenges for companies looking to place veterinary medicinal products on the Brazilian market. Inadequate intellectual property protection is also a significant barrier for bringing new products to the market.

Table 1: Ranking of factors relevant to innovation

Factors relevant to innovation	Importance: Average ranking score
The Brazilian regulatory framework	1.4
Other: Increase Regulatory requirements / MRL and others	2
Inadequate intellectual property protection (for patents or commercial data)	3.4
Poor technology transfer mechanisms between academia and business	4.8
Closure of the US and/or other geographic markets for certain products	5.0
Lack of access to specialist biotechnology companies	5.1
Negative consumer attitudes	5.4
Small size of market segments	5.9
Lack of availability of financial resources	6.4
Lack of skilled staff	7.3
Internal company organisational or cultural barriers	8.6

3. Impact of regulations on competitiveness

Have Government Regulations in Brazil HELPED to improve the competitiveness of your business in any of the following ways?

All respondents ranked the factors individually and the average ranking scores for each factor is given in Table 2. The 2 most helpful factors where Regulations have helped competitiveness are:

a) they have prevented the entrance of dangerous products into the market and
b) redirected resources to innovation.

However, regulations have also helped to improved access to other geographic markets, have triggered innovation in new production processes and have allowed the development of new market segments.

Table 2: Impacts of regulations on Business Competitiveness

Factors relevant to innovation	Importance Average ranking score
Prevented dangerous products entering the market	3.4
Helped redirect resources to innovation	4.9
Improved access to other geographic markets	5.5
Triggered innovation in new production processes	5.6
Created new market segments	5.7
Provided a stable business environment	5.9
Improved product quality	6.1
Protected investments in innovation	6.1
Reassured the public about the safety of animal health products	6.6
Provided confidence to invest (added to certainty and predictability)	7.7
Speeded up time-to-market	7.9

4. Effects of regulations on business

Do government regulations in Brazil have any of the following effects on your business?

Despite the positive effects mentioned above, the regulations in Brazil also negatively influence the business as it creates some uncertainty and unpredictability, increases costs and development timelines and redirects resources to a defensive R&D.

Table 3: Impacts of regulations on business

Factors relevant to innovation	Importance Average ranking score
Create significant uncertainty or unpredictability	2.4
Increase costs of development	3.4
Increase development time	3.8
Re-direct resources into defensive R&D	4.0
Limit the use of innovative marketing methods	5.5
Reduce access to new ideas, particularly in biotechnology	5.5
Divert management time	5.8
Close markets for specific products	6.3
Reduce cash flows from existing products	6.6
Restrict collaborative R&D ventures	7.4

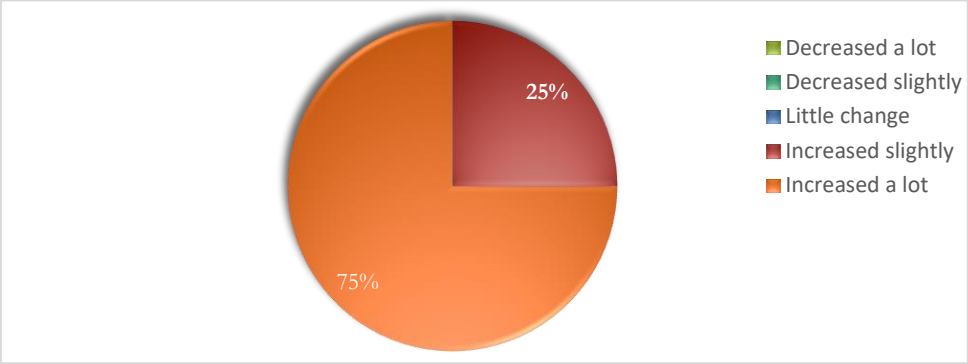
5. Expenditure on mandatory defensive R&D

Which of the following statements best indicates how your expenditure on MANDATORY DEFENSIVE R&D in Brazil has changed since 2015?

Mandatory defensive R&D (MDR&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).

The respondents were unanimous in their responses that Mandatory Defensive R&D spending has increased. Three-fourths described the increases as major (Figure 3).

Figure 3: Companies' perception of the burden of mandatory defensive R&D spending since 2015



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

The factors causing the change in expenditure on mandatory defensive R&D are reported in Table 4.

Due to the introduction of the electronic system for product registration, the re-assessment of existing registered products due to their inclusion into the system, and publication of regulations or alignment of more restrictive requests by MAPA, there was a large increase in costs on mandatory defensive R&D. No factors causing a decrease on mandatory defensive R&D are reported.

Table 4: Factors causing an increase in expenditure on mandatory defensive R&D

Factors causing an increase in expenditure on mandatory defensive R&D
• An increase of time to approval was caused by the **implementation of SIPEAGRO that forces all companies to upload products dossiers to the system**. Thus, all products are being evaluated again and, in addition, we have a decrease on the number of official analysts and, sometimes, they are asking for divergent demands from regulation or with a different interpretation, as an example we have the recurrent requirement for local efficacy studies (with local isolates for antimicrobials and parasiticides). This is preventing predictability of regulatory environment and adding unnecessary costs to dossiers. • **New regulations, or a misunderstanding of existing ones**, requiring new studies, were implemented but without a clear deadline that allows to carry out these studies and upgrade the dossiers. Furthermore, pharmacovigilance data is not being accepted to renew market authorization of old products. Moreover, companies are facing situations like development of tests with an approved protocol by one inspector that later was rejected by another one at the time of final dossier review.

7. TIME to gain registration for a major new product in BRAZIL

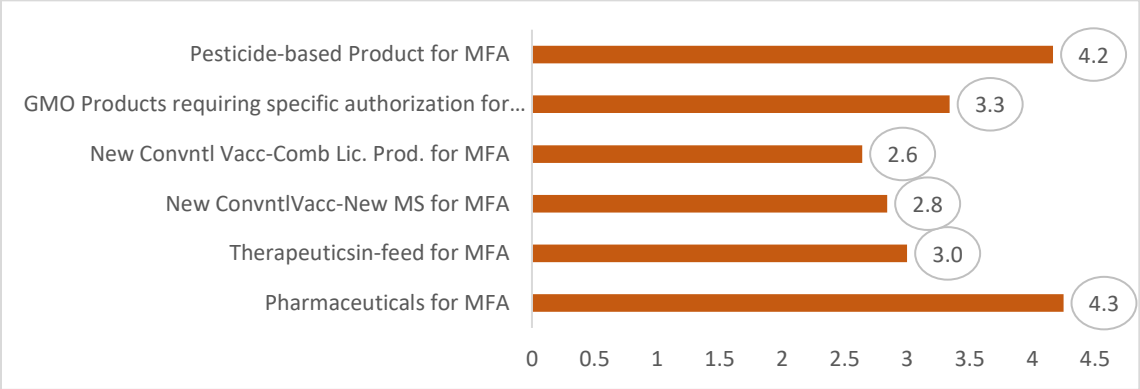
Please state the AVERAGE LENGTH OF TIME it takes you to gain registration for a major new product in BRAZIL, from submission of the marketing authorisation dossier to first-market product approval.

This question looks at the product registration step (the product development phase is covered in the next question). Companies were asked to provide their product registration times for 12 different product categories. The average product registration times are shown in Figure 4.

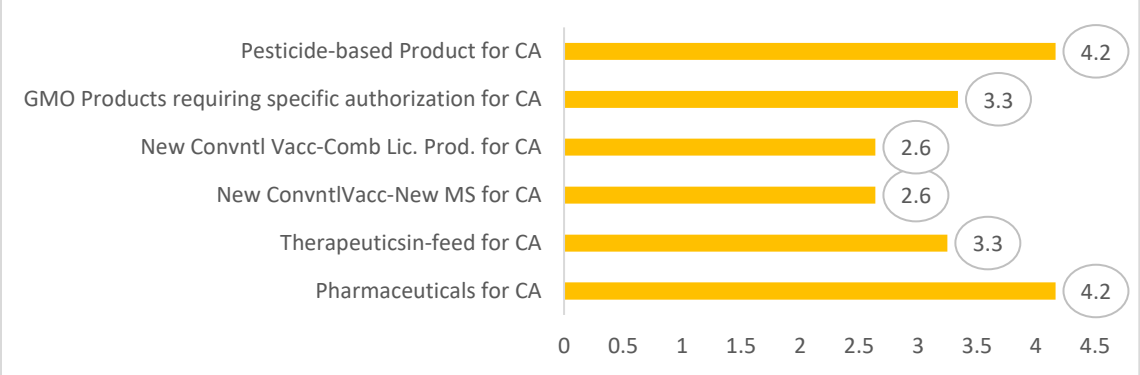
In Brazil, the processes are divided according to whether the product is a Pharmaceutical or a Biological, no matter if for production animals, companion animals or smaller species. The average time for the evaluation of pharmaceutical products is around three to five years and for biological products between two and three years.

Figure 4: Time (years) to gain registration of a major new product in Brazil

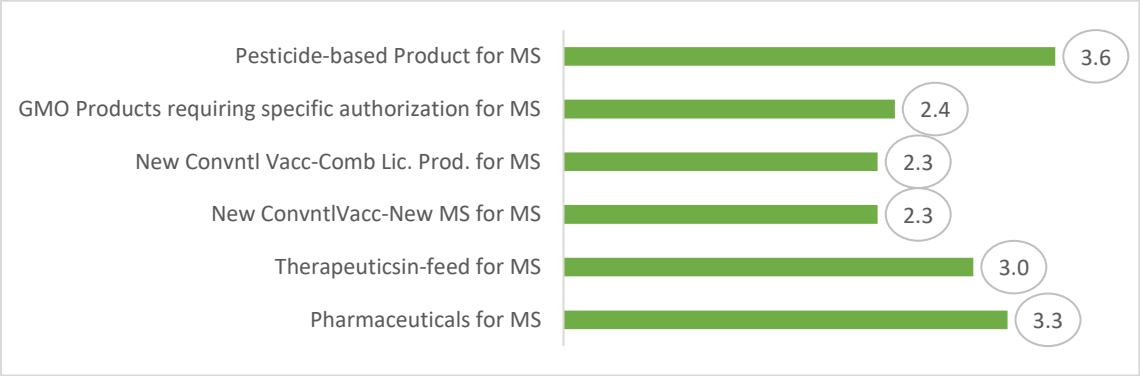
a) For Major Food Animal products



b) For Companion Animal products



c) For Minor Species



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

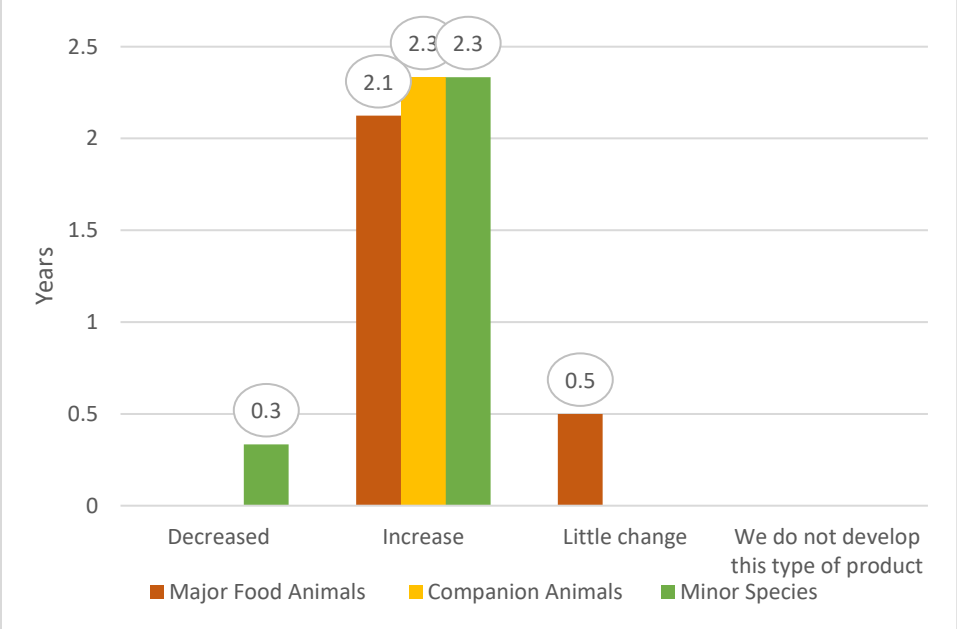
Have REGULATORY FACTORS caused a change in the AVERAGE LENGTH OF TIME it takes you to develop a major new PHARMACEUTICAL product in Brazil (from initial research to final market authorisation), compared to 2015?

This question looks at the total product development time.

Regarding the change in the meantime for product development, there was a trend of increase of this period compared to 2015. There will be differences between the dossiers of the different companies and analyses carried out by the different Federal Inspectors, but on average the addition was two years for registration processes of pharmaceutical products for all three segments: minor species, companion animals and major food animals.

This fact can be explained by the small team of Federal Agricultural Auditors (AFFA) available for evaluation of products and requests for information or request for new studies by AFFA in disagreement with current regulations.

Figure 5: Impact of Regulations on TIME to develop a major new PHARMACEUTICAL product

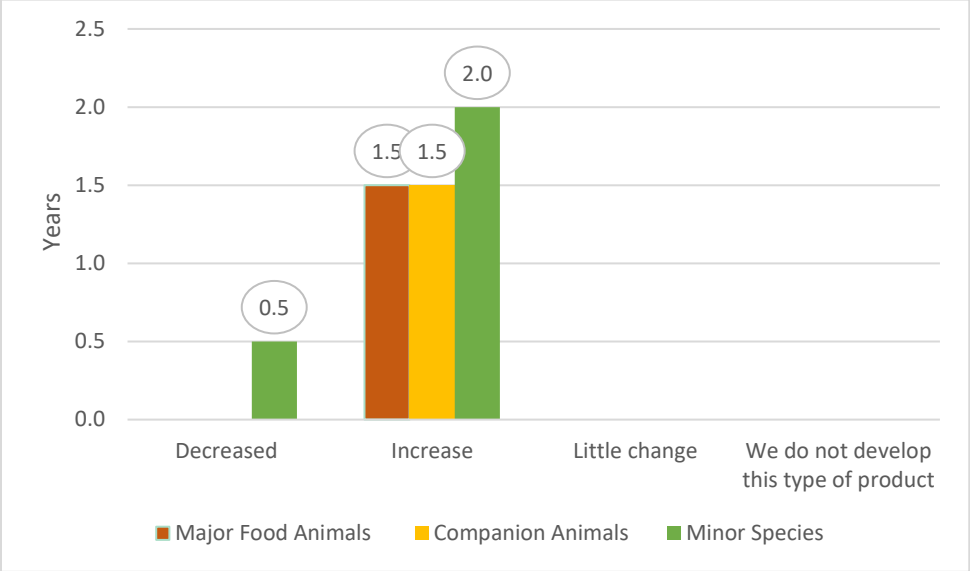


9. Impact of Regulations on TIME to develop a major new BIOLOGICAL product

Have REGULATORY FACTORS caused a change in the AVERAGE LENGTH OF TIME it takes you to develop a major new BIOLOGICAL product in Brazil (from initial research to final market authorisation), compared to 2015?

Considering biological products, a major stability of the evaluation of products can be observed, and the trend of increase in total development time and approval of a product registration increased by approximately one year in comparison from 2015 to 2020. For the process of evaluation of biological products, the team of available AFFAs had been maintained, managing to evaluate the products with a more satisfactory speed and without generating pending issues in disagreement with the current legislation.

Figure 6: Impact of Regulations on TIME to develop a major new BIOLOGICAL product since 2015

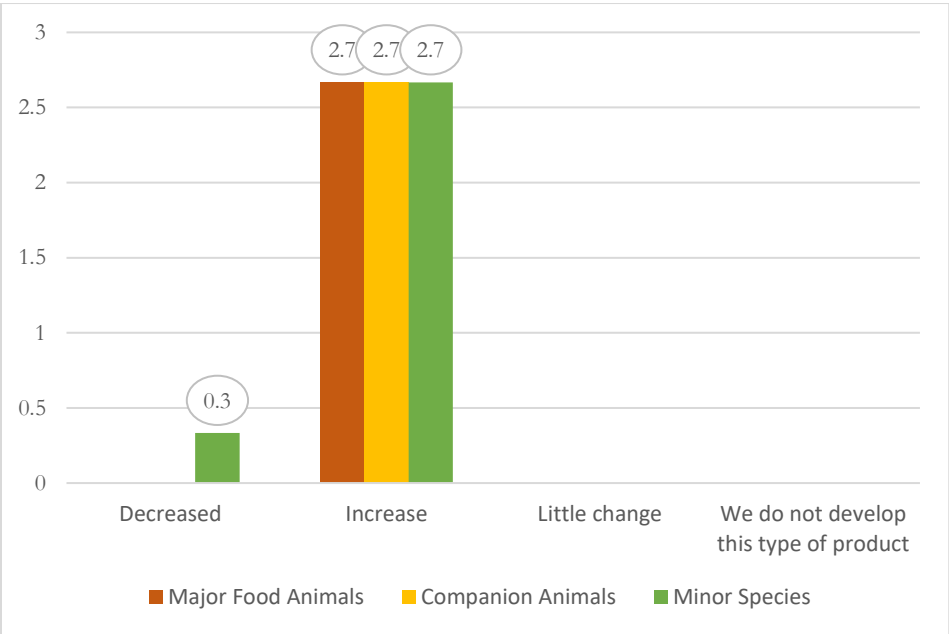


10. Impact of Regulations on TIME to develop a major new PESTICIDAL product

Thinking about the AVERAGE LENGTH OF TIME it takes you to develop a major new PESTICIDAL product in Brazil (from initial research to final market authorisation), compared to 2011, have REGULATORY FACTORS caused this time to change? Please make separate estimates for major livestock species, companion animals and minor species.

Processes for the registration of pesticide products showed a trend of increasing the deadlines until their final marketing authorization of just under three years for all three market segments.

Figure 7: Change in time to develop a major new PESTICIDAL product



11. Impact of Regulations on COST to develop a major new PHARMACEUTICAL product

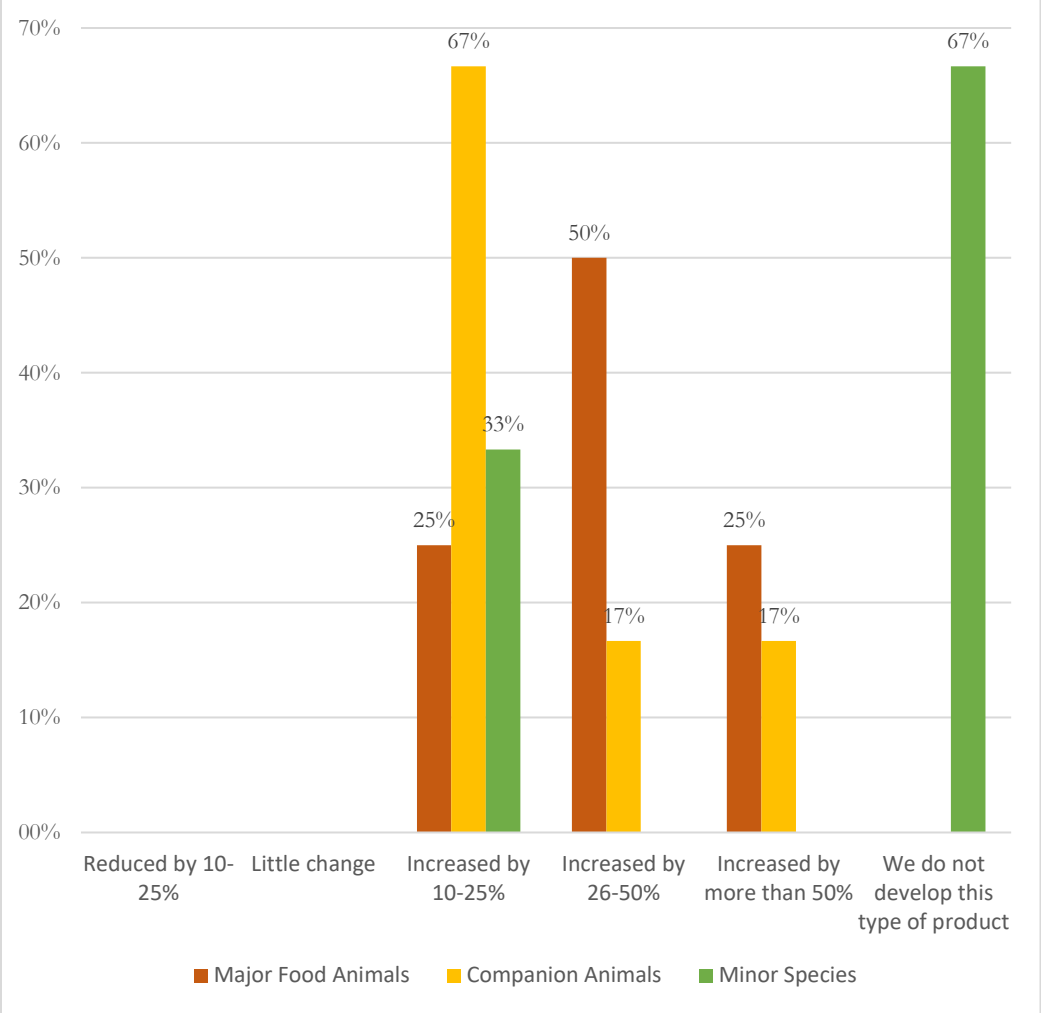
Thinking about the AVERAGE COST of developing a major new PHARMACEUTICAL product in Brazil (from initial research to final market authorisation) for all possible species and indications for that product, compared to 2015, have REGULATORY FACTORS caused this cost to change in real terms? Make separate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

Changes in Regulations can have an impact on the time it takes to develop a product.

In general terms, for half of the companies the increase in development and availability costs for pharmaceutical products for production animals was between 26 and 50%. For a quarter of the companies the increase was greater than 50% and for the other quarter between 10 and 25%.

For companion animals, the increase observed by companies was mostly lower, with two-thirds of the companies considering an increase between 10 and 25%, a sixth between 26 and 50% and a sixth greater than 50%. Considering pharmaceutical products for smaller species, we observed an increase between 10 and 25%, considering the information of a single company.

Figure 8: Change in cost to develop a major new PHARMACEUTICAL product

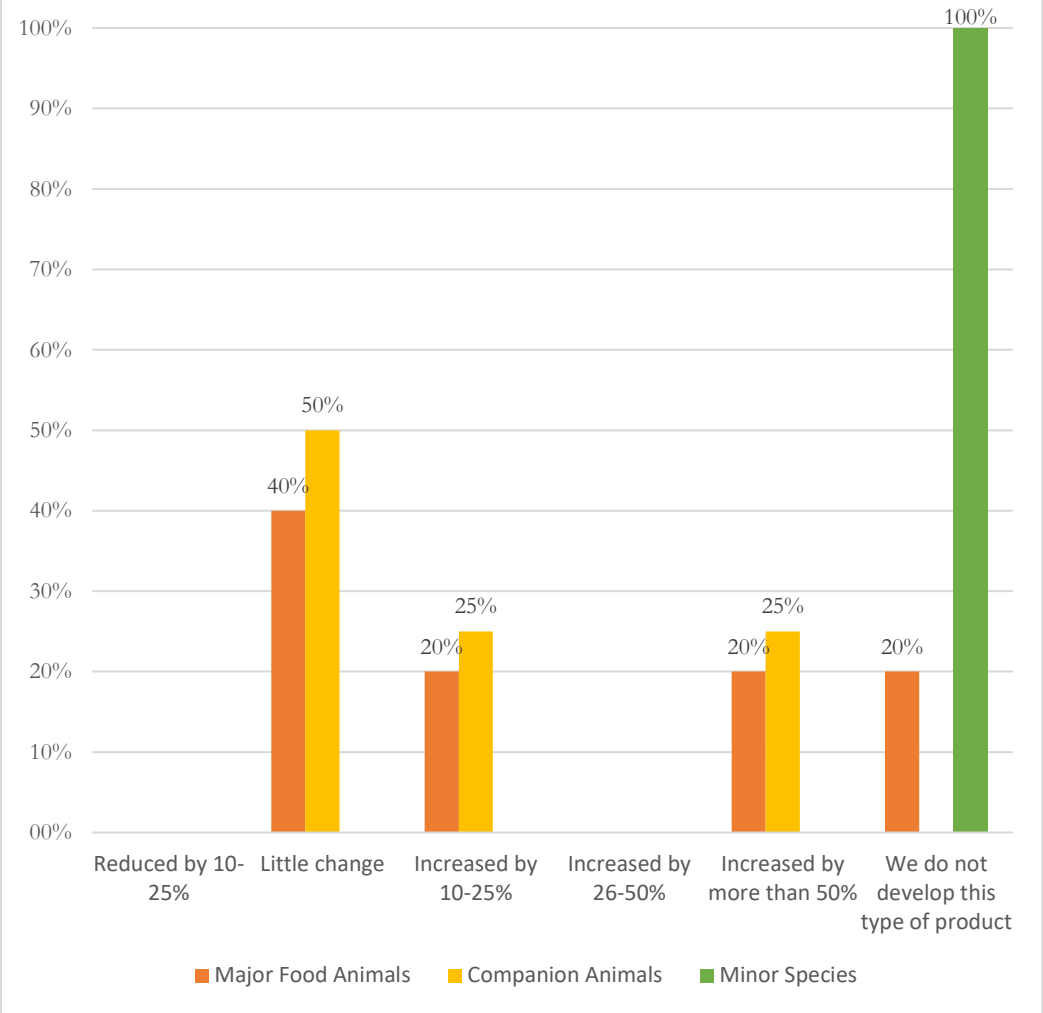


12. Impact of Regulations on COST to develop a major new BIOLOGICAL product

Thinking about the AVERAGE COST of developing a major new BIOLOGICAL product in BRAZIL (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.

For biological products, no company reported data regarding smaller species. For both production animals and companion animals, half of the companies that develop products intended for them believe that there has been a small change in the average cost of developing a new biological product in Brazil. A quarter of companies reported an increase of 10 to 25% and a quarter an increase of more than 50%.

Figure 9: Change in cost to develop new BIOLOGICAL product

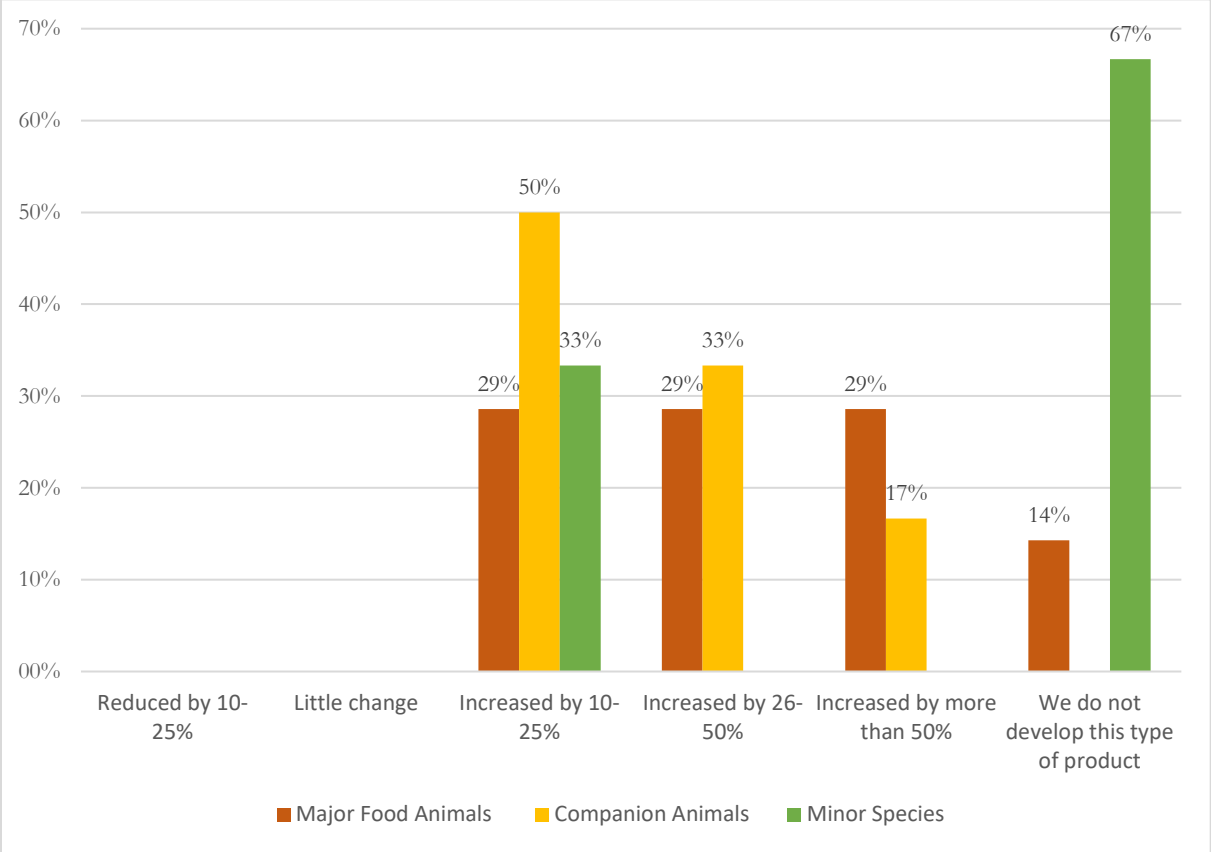


13. Impact of Regulations on COST to develop a major new PESTICIDAL product

Thinking about the AVERAGE COST of developing a major new PESTICIDAL product in BRAZIL (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.

For the average cost of developing pesticide products, according to the surveyed companies, there was an increase of 10 to 25% for one third of companies, from 26 to 50% to another third and greater than 50% for the others. For pet animals, half of the companies considered an increase of 10 to 25% in the cost of developing pesticide products, a third reported an increase of 26 to 50% and a sixth, an increase greater than 50%. The only company that reported data for smaller species considers a 10 to 25% increase in the cost of developing pesticide products for these species.

Figure 10: Change in Cost to develop new PESTICIDAL product

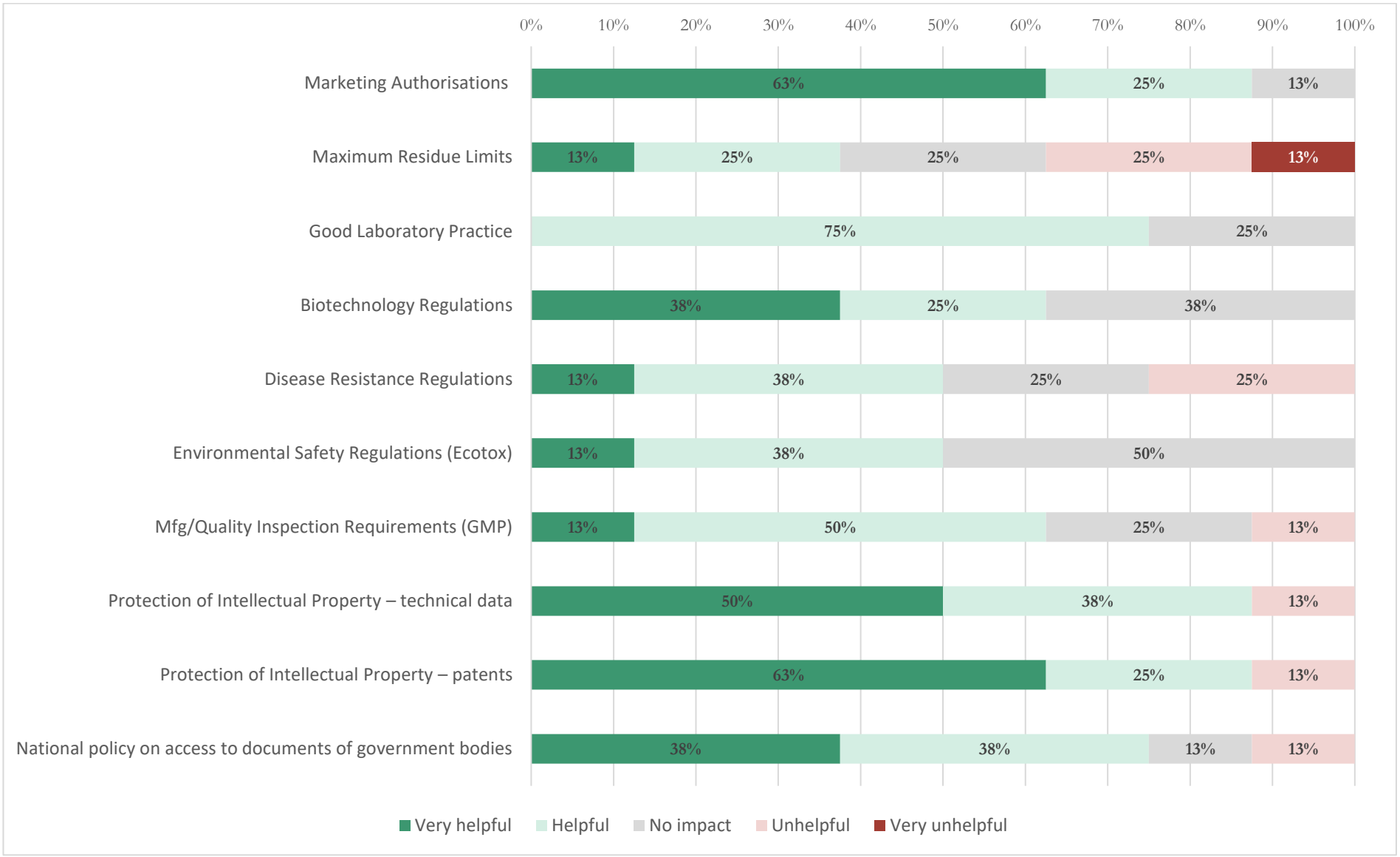


14. Regulations' impact on innovation

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

The ability to innovate successfully is mainly impacted, and greatly helped, by a regulation of product licensing and protection of intellectual property whether technical data or patents. Areas such as Good Laboratory Practices, Biotechnology Regulation, Resistant Disease Regulation, Environmental Safety Regulations, Quality Inspection Requirements and National Government Agency Document Access Policy helped in the ability to innovate. Only the Area of Maximum Residue Limits was considered as without overall impact on the ability to innovate.

Figure 11: Regulatory impacts on innovation



15. New product development

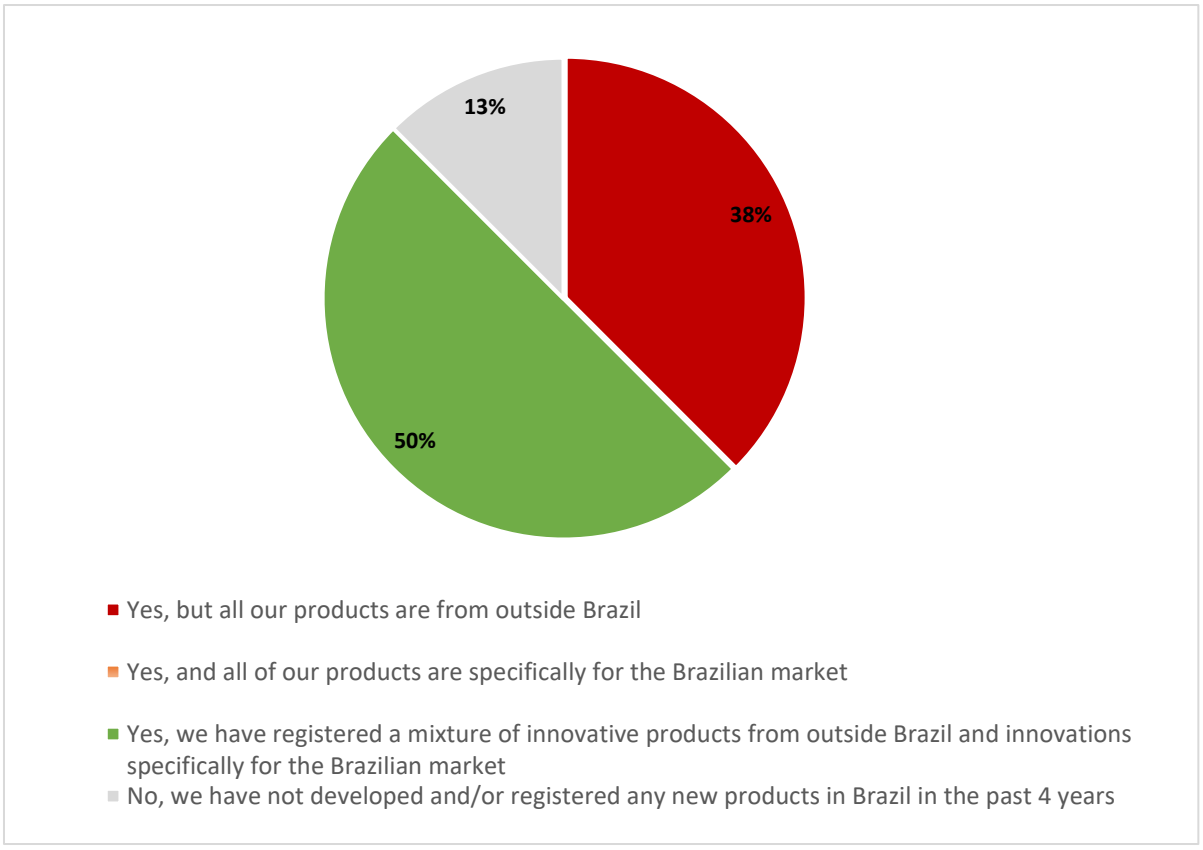
Have you developed and gained approval for any products new to the Brazilian market in the past 4 years?

This question examines not just whether companies have introduced new products onto the market in Brazil, but also the origin of those products. The respondents are mainly multi-national companies (75%) and a minority of local companies (25%).

The multi-national companies will have an opportunity to bring products onto the Brazilian market that have already been developed for other primary markets (typically other markets in the Americas and EU). Therefore, the question provided 3 options covering whether the products came from outside Brazil or were developed specifically for the Brazilian market.

The question yielded responses as follows i(Figure 12): 1 company had not launched a new product during the last 4 years; 3 companies had launched products all coming from outside Brazil; and 4 companies had launched a mixture of new products from outside Brazil and new products developed specifically for the Brazilian market. None of the companies had launched products developed specifically for the Brazilian market.

Figure 12: New product development



Section C - COMMERCIALIZATION OF EXISTING PRODUCT

1. Commercialization factors for exploiting EXISTING PRODUCTS

Below is a list of potential FACTORS RELEVANT TO THE COMMERCIALIZATION OF EXISTING PRODUCTS in the animal health industry in Brazil. Which of these, if any, are significant for the exploitation of your existing products?

The respondents were asked to rank, from 1 to 12, a list of factors relevant to the commercialization of existing products in the animal health industry in Brazil.

The outcome of the ranking of the factors is shown in Figure 13. The factor that was ranked as important by all the companies was the regulatory framework for the maintenance/extension of licenses in Brazil; in fact, a majority of the companies (63%) ranked it as the top-most important factor.

Other highly ranked factors included competition pressure, inadequate protection of intellectual property, availability of illegal veterinary drugs, and legal restrictions on notices, labels, trademarks and communications.

The lowest raked factors include the small size of market segments, lack of skilled staff and demand volatility in certain market segments.

2. Impact of regulation on successful commercialization

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

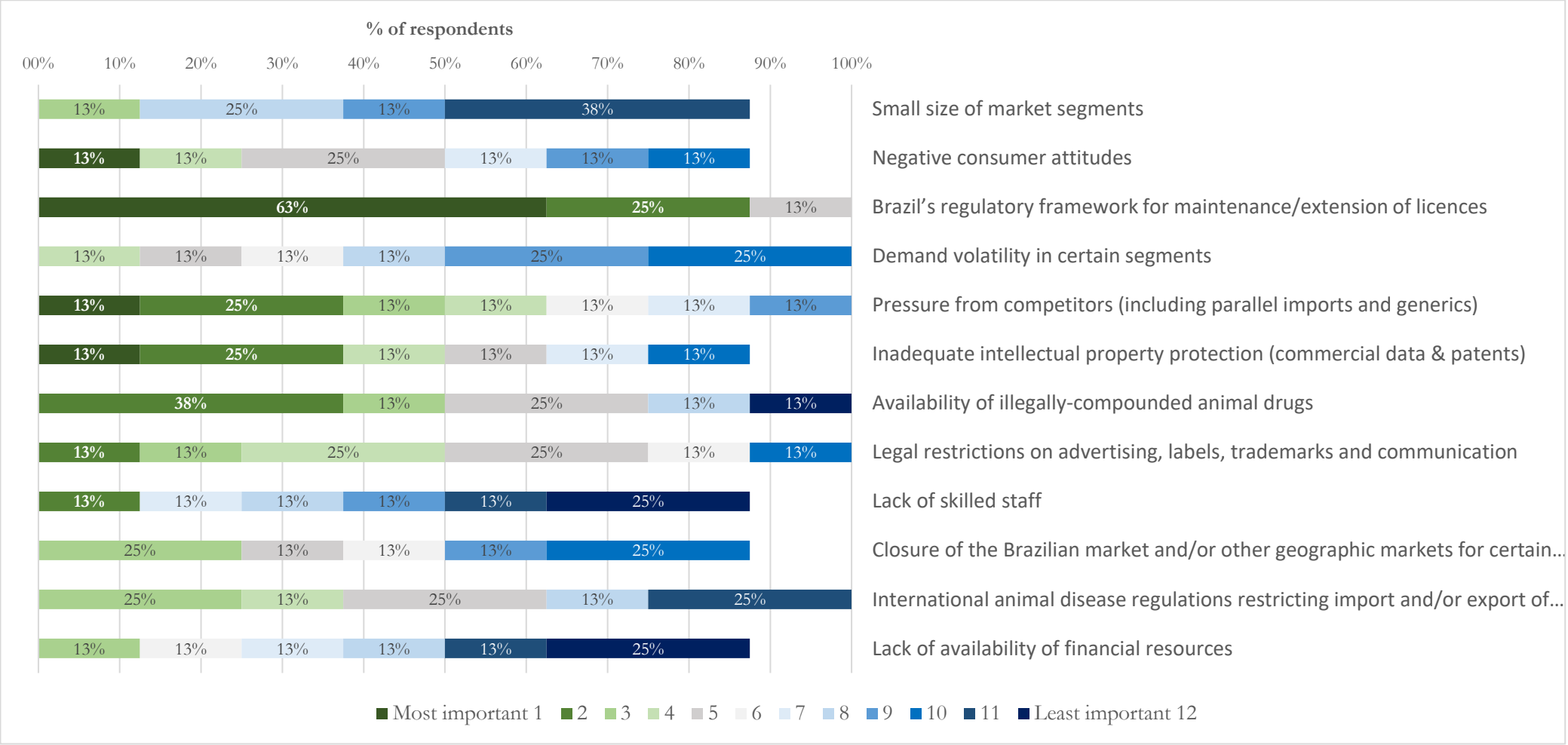
The regulations that were overall helpful were the License Maintenance Process, maximum residue limit regulations, the implementation of international regulations and standards and the safety data requirements. Several companies regarded Good Manufacturing Practice as helpful, but none ranked GMP as very helpful.

However, 25% of companies regarded the License Maintenance Process and the import regulations as unhelpful.

3. Conclusion and key recommendations for section C

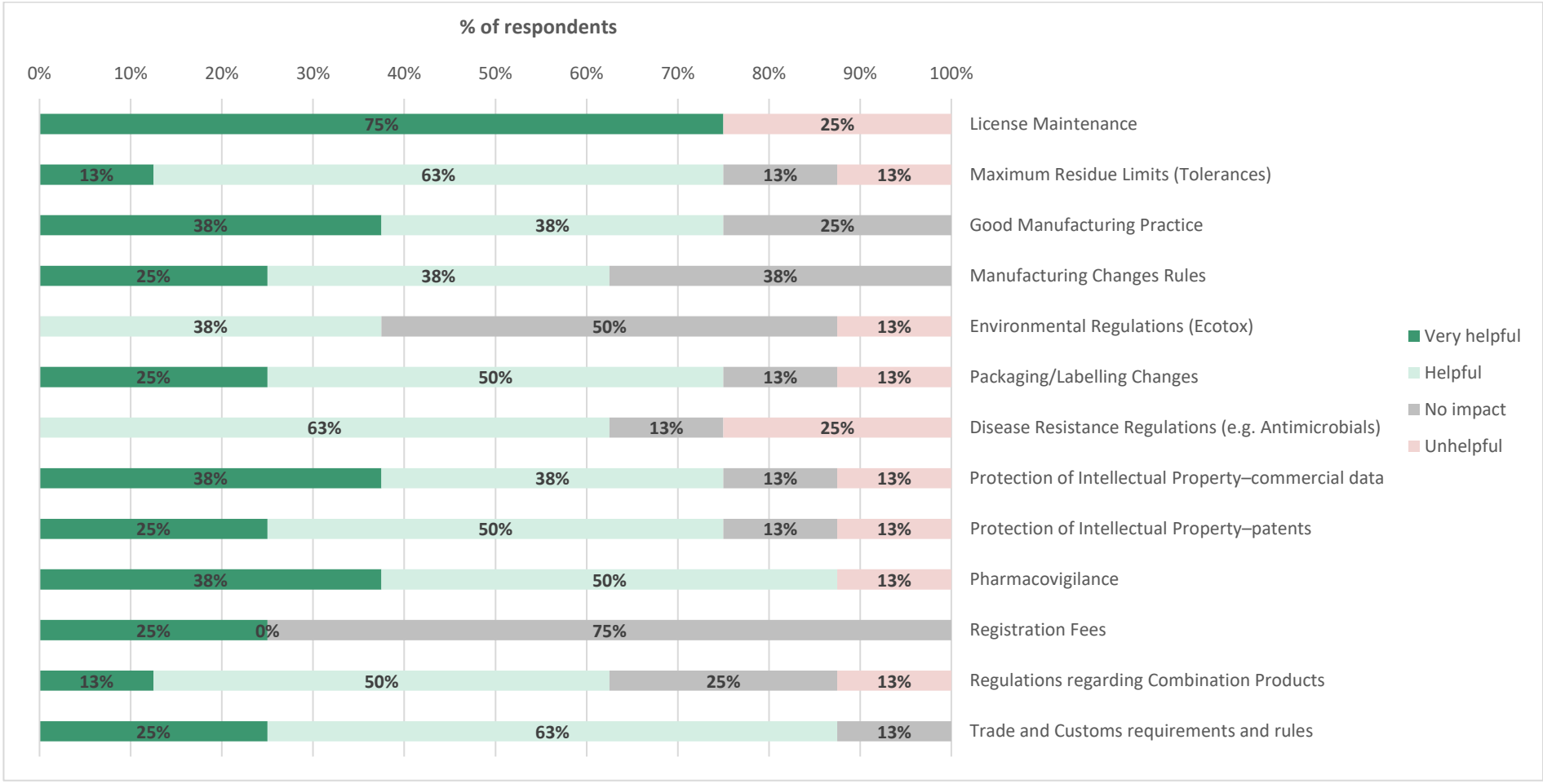
The ability to successfully market existing products is impacted, and greatly helped, by a regulation for the maintenance of licenses; other helpful regulations included Maximum Residue Limits, Good Manufacturing Practices, Changes in Manufacturing Rules, Changes in Labeling and Packaging, Regulations of Resistant Diseases, Protection of Intellectual Property - whether commercial data or patents -, Pharmacovigilance, Regulations regarding Combined Products and Rules and Requirements on Marketing and Customization. Both environmental regulations and registrations fees were considered as issues that do not have a significant impact.

Figure 13: Ranking of all factors relevant to the exploitation of existing products



N.B. Gaps in the data to reach 100% of respondents are due to some companies not ranking certain factors

Figure 14: Ranking of factors impacting commercialization



Section D - REGULATORY PREDICTABILITY & QUALITY

1. Predictability and quality of regulatory procedures in Brazil

(a) Does the regulatory procedure in Brazil as currently managed provide you with the regulatory predictability that you need and the regulatory quality you expect? (b) If not, please tell us what the top issues are and what might be done about them (your proposed solutions moving forward).

Companies understand that it is rarely possible to predict MAPA's actions and that only a few times MAPA´s actions present the expected regulatory quality. In relation to ANVISA, a mixed picture is presented, with an evenly split view among companies that ANVISA delivers regulatory predictability and regulatory quality either mostly, sometimes or never.

Figure 15: Regulatory predictability under MAPA and ANVISA

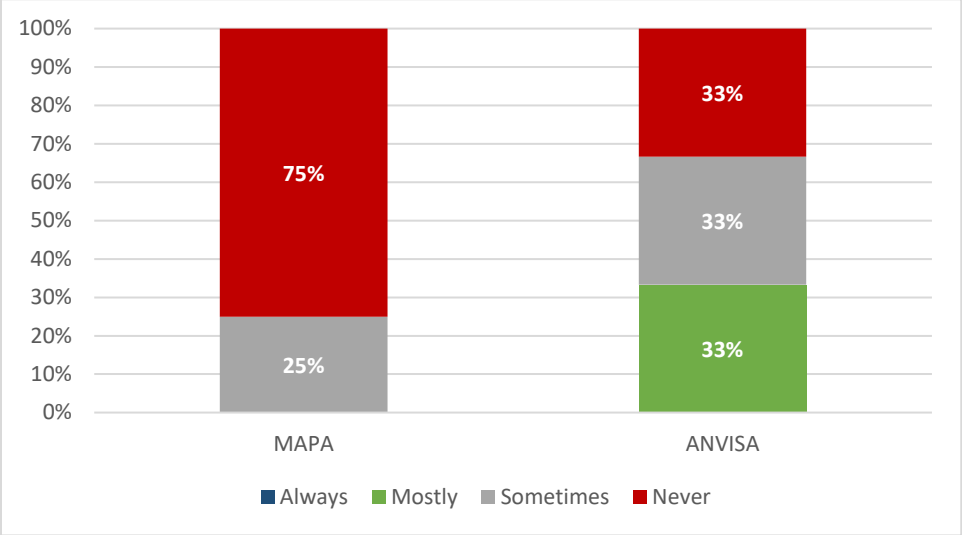
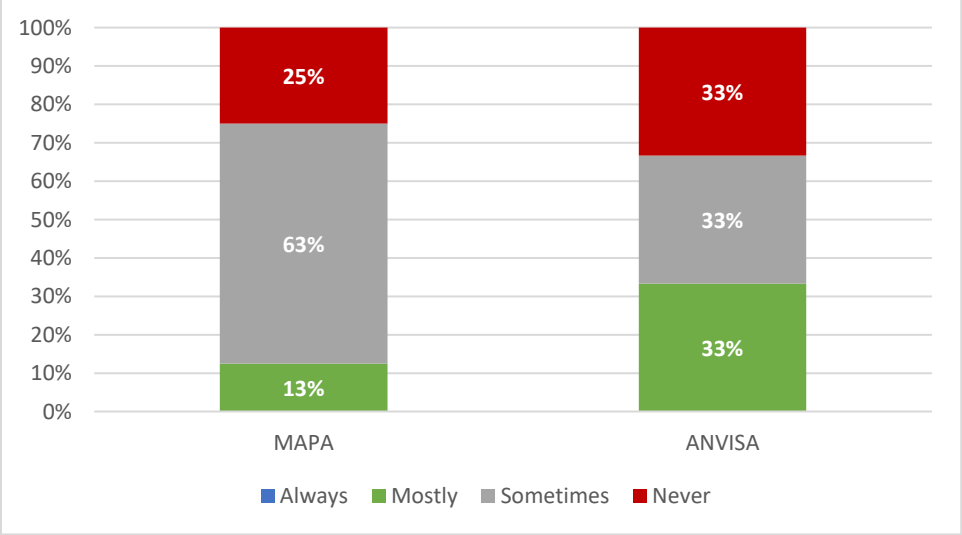


Figure 16: Regulatory quality under MAPA and ANVISA



What the top issues are and what might be done about them

MAPA

- With the current legislation, **MAPA needs to standardize the interpretation of the inspectors** (assessors) and application of law allowing a harmonized and predictable process. For well-established products, MAPA should accept pharmacovigilance data and determine achievable deadlines to update studies, considering all the applicable variations.
- An **improvement** of the **legislation** can be made **by determining the specificities to each type of product**, reducing the number of official letters and converging documents (Decree, Normative etc.) to allow a constant updating and a better regulatory quality.
- It would be rational and productive that the **regulatory inspectors take part of the new product project since its early development** (consultations, approval of protocols etc.) so each step approved by one inspector, would be valid for any other in further review. That could speed up the final product evaluation and approval.

The **use of guides** that, in convergence with the current legislation and official auditors, could improve the regulatory predictability and quality.

ANVISA:

- ANVISA is already moving towards better segmentation of its Resolutions, such as parent legislation and ordinances as "guides", which helps with updates. In addition, it already comes with a model for updating legislation, mainly GMP aligned with ICH and WHO, which helps to maintain the regulatory quality of Brazil as an industry, facing the world.
- **Lack of knowledge of the animal health sector and publication of MRL regulation** can have a negative financial impact and reduces the availability of veterinary medicinal products.
- The **pressure on antimicrobial resistance in animal health products**, without proper risk analysis and targeted as the main sector responsible for antimicrobial resistance, could result in a reduction of available veterinary medicinal products.

2. Procedures for registering NEW products

Consider the current Coordination of Veterinary Products *(CVP) process for approving new products. To what extent does the process meet the following criteria?*

Considering the scientific basis of the product registration process, specialized evaluations are sometimes performed based on science, based on risk analysis and based on consistent application and interpretation of regulatory guides (Figures 17 and 18).

Final approval of new products is sometimes based on expert evaluation on safety, quality and efficacy. As well as sometimes pre-registration inspection and validations are carried out promptly and efficiently and the knowledge of pre-registration inspectors and quality and manufacturing validations are of the highest possible competence.

Safety, quality and efficacy guides are sometimes applied based on a practical and rigorous assessment of risks and benefits in a clear and respected manner by other regulators internationally.

Related to the processes of registration of products in MAPA, these do not follow predictable, efficient or transparent standards; in addition, the official body does not proactively inform new or unexpected regulatory standards and their potential impacts.

Pre-registration validations and inspections sometimes follow the same standards for all companies, as does the administrative process. Regulatory authorities sometimes handle submissions quickly, actively, with useful interactions, and promptly.

Figure 17: New Product Registration Criteria – Scientific Basis

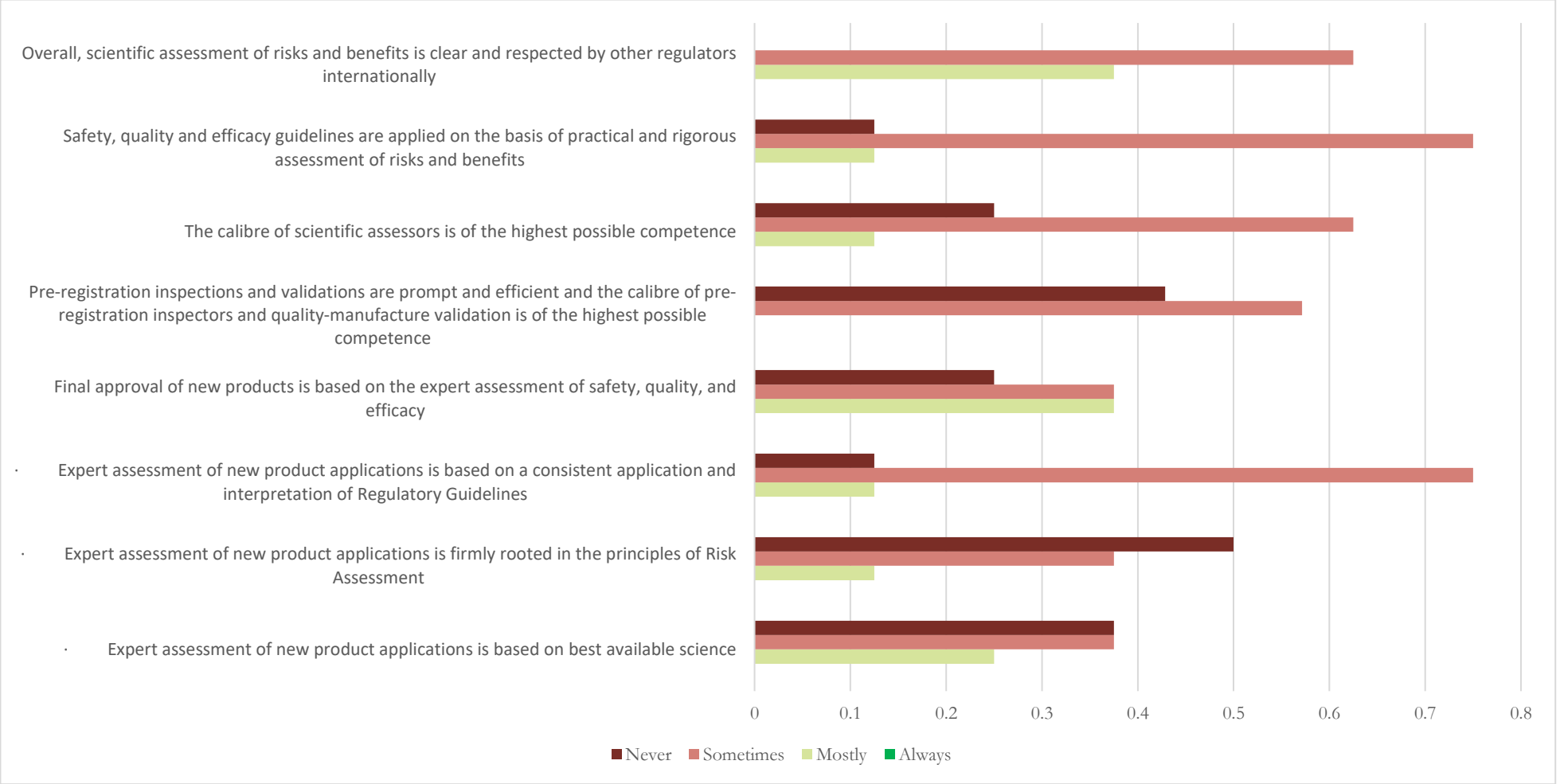
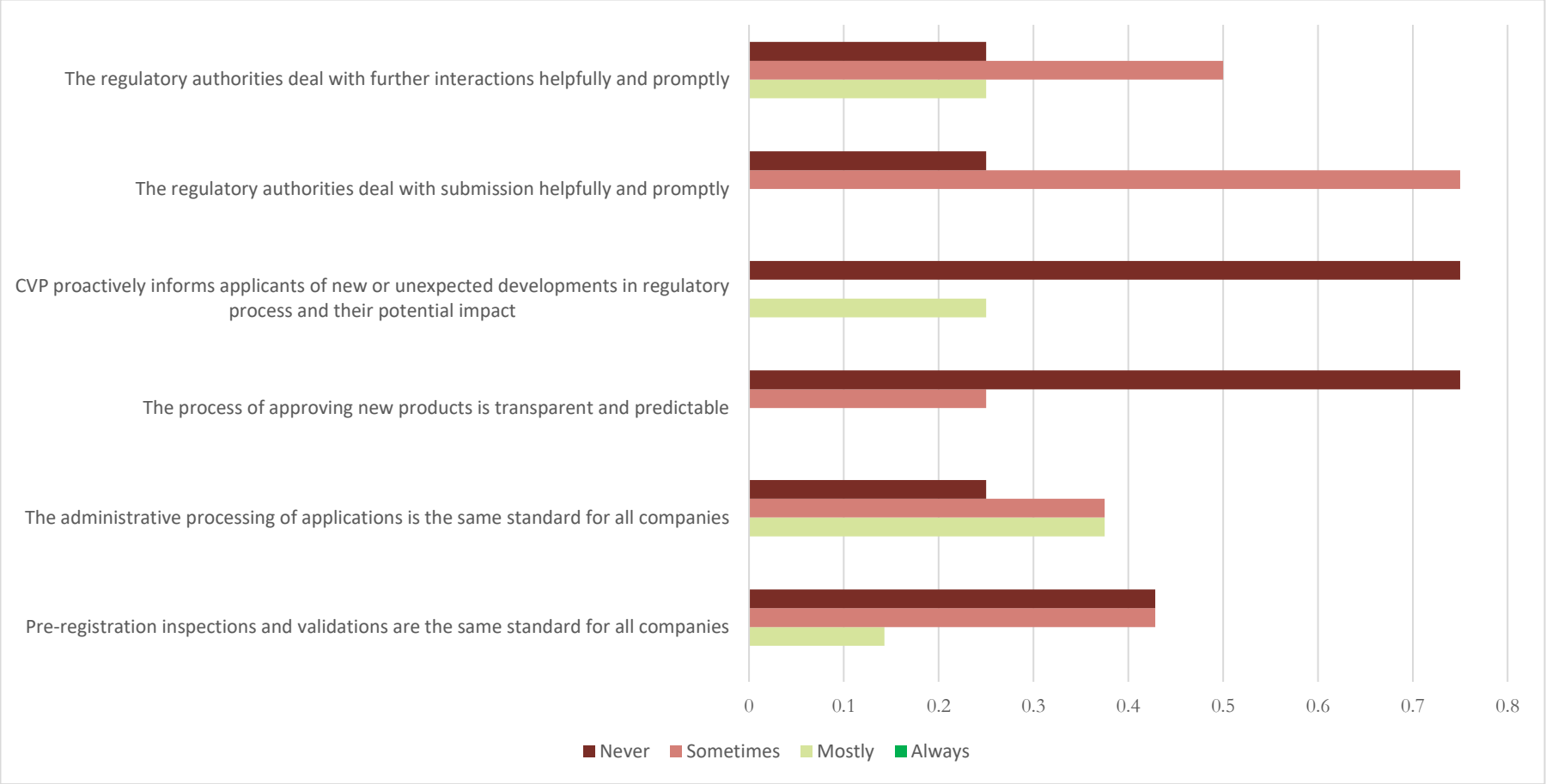


Figure 18: New Product Registration Criteria – Process Basis



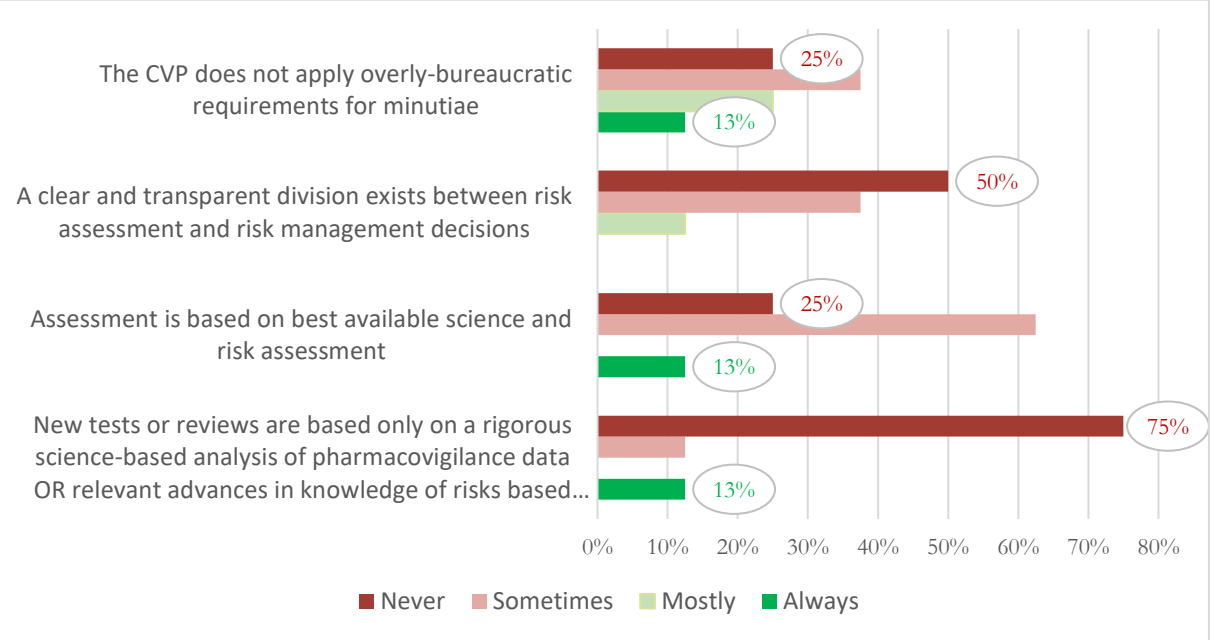
3. Procedures for maintaining EXISTING products on the market

Consider the current process for maintaining existing products on the market. To what extent does the process meet the following criteria?

The current process for maintaining existing products on the market received marginally less severe criticism that the processes for registration of new products, and each of the four criteria shown in Figure 19 received a positive score from one company.

However, the overall picture is negative, particularly for the criteria concerning the scientific basis of new tests of reviews applied to existing products, and to a lesser extent to a transparent division between the risk assessment decisions and the risk management decisions.

Figure 19: Criteria for the process to maintain existing products on the market



4. Conclusion and key recommendations for section D

New tests or renewals are never based solely on rigorous, science-based analysis of pharmacovigilance data or relevant advances in risk knowledge based on the best of available science. Therefore, it is not possible to observe a clear and transparent division between decisions on risk assessment and risk management. The regulator sometimes does not apply excessively bureaucratic requirements for minutiae and the assessment is sometimes based on the best available science and risk assessment.

Section E - REGULATORY TRENDS

1. Recent beneficial changes to the regulatory frameworks in Brazil

What beneficial changes have occurred in regulatory frameworks SINCE 2015?

MAPA had implemented the SIPEAGRO, an electronic registration and tracking system that has the potential to improve speed and visibility to the product evaluation process. MAPA has also approved a fast-track process for innovative products and a provisional license for non-critical products, that has innovative products (the first one) and resulting in a reduced queue for other products.

A normative regulating post-registration changes was implemented determining when you can just notify MAPA about simple changes (variations) and continue to sell the product, thus, sharing responsibility between the regulatory authority and the company´.

In communication, MAPA is publishing two lists of products in order of evaluation (initial registration and post-registration changes). This allows some predictability about when your product will be evaluated, and it is updated every three months.

Allowing discussion between the Regulatory Authorities and Industry, a Normative Acts Monitoring System – SISMAN – was implemented. The system lists the subjects that the government is working on internally and the publishing of the texts of public consultations.

shortened the timelines to market authorization for these products, with the creation of a priority list of Expected changes that have NOT occurred in Brazil regulatory frameworks

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

The industry expected greater agility, speed and predictability in the registration processes of veterinary products, creating product categorizations for a more specific evaluation and according to their risk profile, reducing product evaluation time and the list of products pending evaluation.

Changes in legislation were expected from the simplification of the definition of veterinary products, through to the adjustment of the Decree to reflect the needs of categorization understood as important by the sector, reaching the publication of new regulations and reliable guides on:

- Pharmacovigilance - allowing its use for proof of safety and efficacy data
- Renewal of licenses and reduction of animal tests (3Rs)
- Protocol validation by the responsible authority - avoiding the refusal of such tests performed after previous design approval
- Regulation for adjuvant supplements
- Updated legislation for registration and marketing of antiparasitics
- Expansion of the scope of innovation
- Regulation of stability studies of biological products.

The most anticipated topic was the approval and start of the activities of the "Eliseu Foundation" for evaluation of the product backlog at MAPA. Unfortunately, despite all the efforts of SINDAN, the project was not approved by CONJUR – government legal counsel.

2. Problematic changes to the Brazil regulatory frameworks

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

The lack of trained assessors and their correct interpretation of the law, as it is, was the main regulatory point of impact, particularly for antiseptic products – treated in the same way and in the same normative instruction as antimicrobials – interpretation of studies "*in vivo*" versus *"in vitro"* and the mandatory use of national strains despite the legislation only states it as preferable; insertion of records and deficiency of the SIPEAGRO system, which had been presenting a number of problems; lack of transparency and agility with the evaluation of products; publication of regulations (IN51/2019 and RDC 328/2019) by ANVISA regarding the definition of MRL for veterinary products.

With the upload of the products onto the SIPEAGRO system, all products were evaluated again. There was a need to conduct new studies in order to update reports on the system and maintain the license of the products, mainly antimicrobials. For products with MRLs defined by ANVISA, which are different from those MRLs used previously, there are still doubts regarding the applicability and deadlines to get into compliance with MAPA in such matters. Also, there is a grey zone regarding existing products, that are without MRL defined by ANVISA, and products under assessment using MRLs different from what is defined. It is not clear how to proceed in those cases.

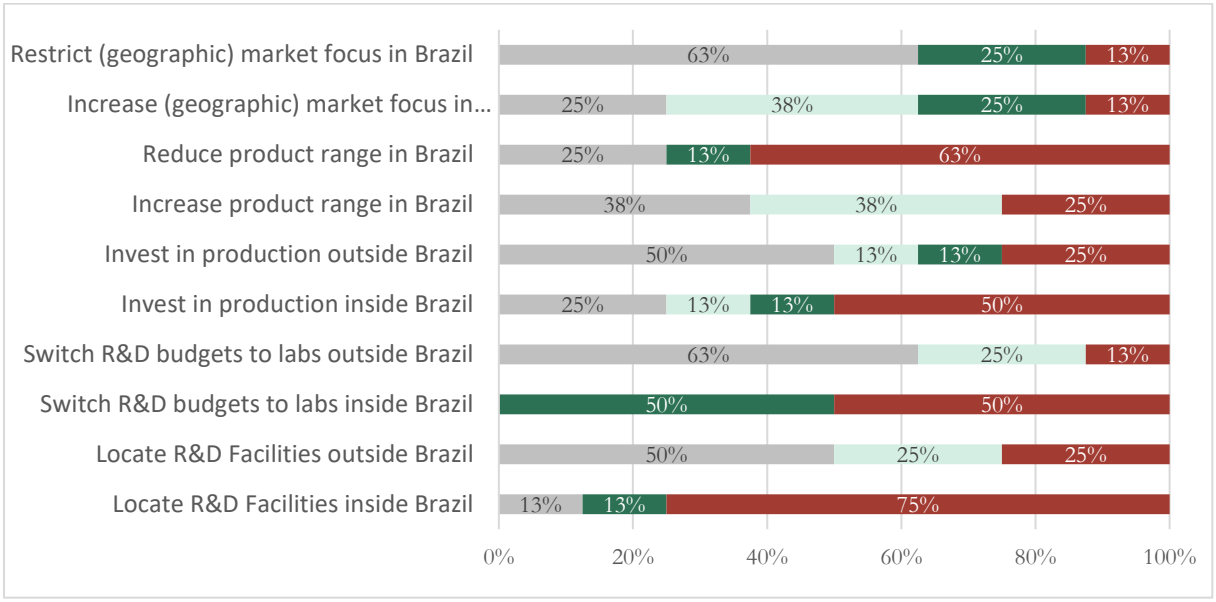
3. Business decisions as influenced by regulations

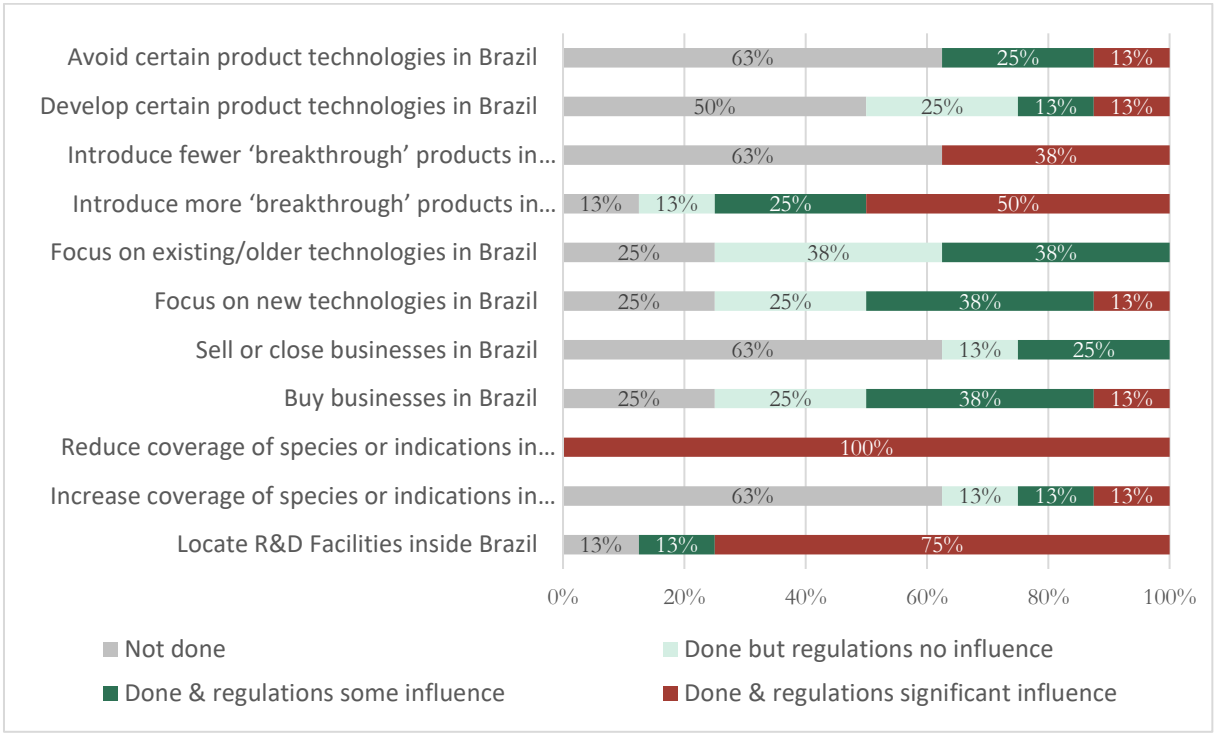
Have regulations played a major role in influencing you to take any of the following major decisions over the last five years?

The survey participants were presented with a list of typical major business decisions (as shown in Figures 20 and 21) and asked to what extent regulations influenced those decisions.

Business decisions most influenced by regulations included: reducing the coverage of species and indications (100% of companies); locate R&D facilities outside and inside Brazil (75% each way, which is an interesting result); reduce product range in Brazil (63%); introduce more 'break-through' products (50%); switch R&D budgets to labs inside Brazil (50%); and invest in production inside Brazil (50%). From this it is evident that regulations have had both positive and negative effects.

Figure 20: Business decisions as influenced by regulations





Section F - HOPES AND EXPECTATIONS FOR THE NEXT 5 YEARS

1. Changes in regulatory approach and their impact on the future

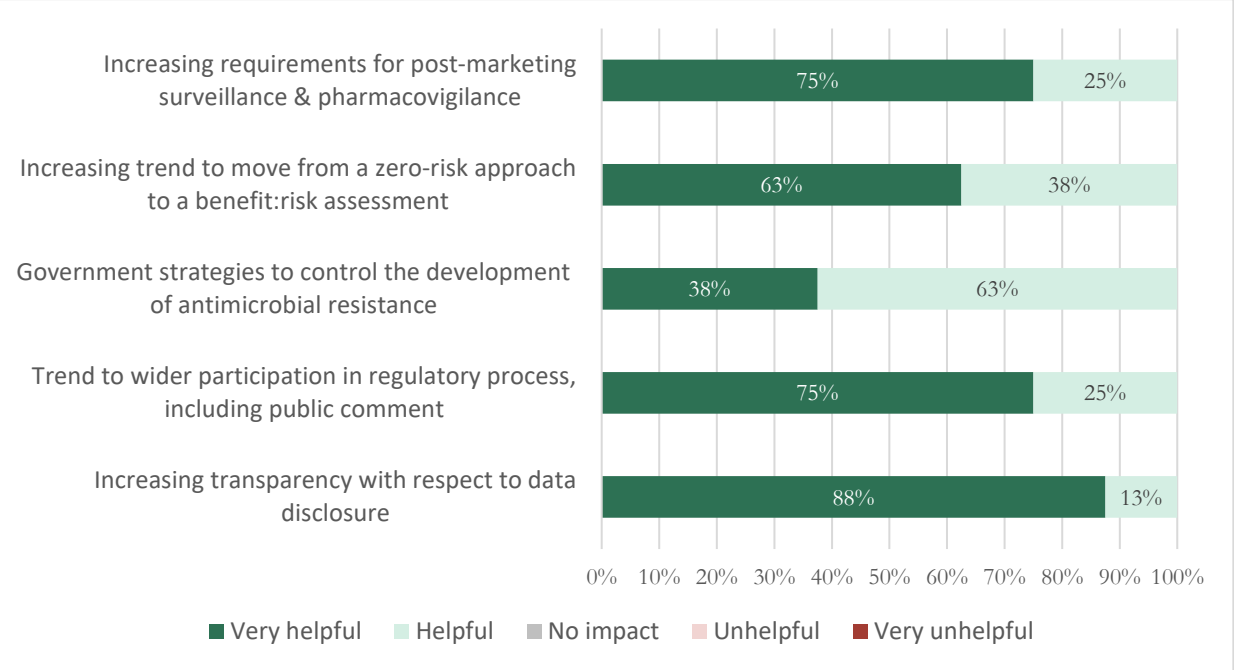
The following trends or changes in regulatory approach have been taking place recently and may well have an impact in future. What impacts do you expect these changes to have on your business in the next 5 years?

As discussed previously, greater transparency regarding data disclosure, greater participation in regulatory processes including public consultations, increasing tendency to replace the zero risk approach with a benefit risk assessment, increase in requirements for post-marketing surveillance and pharmacovigilance, increasing globalization of post-marketing surveillance data, acceptance of JECFA agreements for non-litigation molecule residues and electronic submission of processes are trends that would greatly help in the submission of dossiers according to legislation, agility of submission, monitoring of processes, monitoring of products in the market and use of this data registration renewal.

The prior discussion of legislation allows an alignment between multinational industries, national industries and the regulatory body, for harmonization with international legislation so that everyone has the same understanding on the various issues.

The government's strategy to control the development of antimicrobial resistance is useful but requires that actions be taken based on science and to avoid the reduction of tools available for the treatment and control of animal diseases.

Figure 21: Impacts of regulatory trends

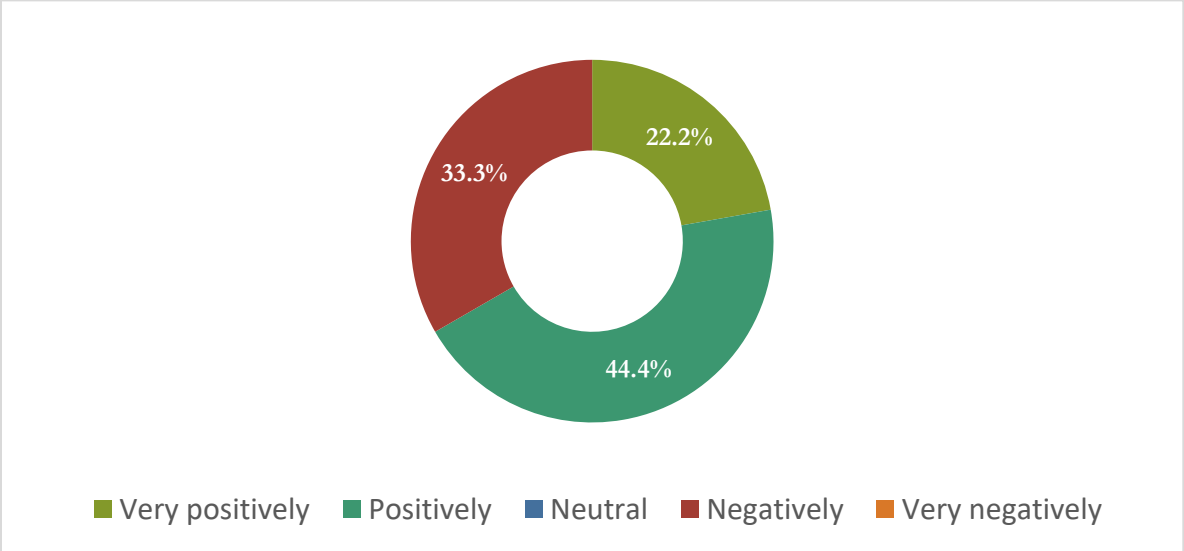


2. Impact of foreign regulatory decisions on innovation

Does the use of foreign regulatory decisions in the Brazilian review process impact your ability to innovate?

It is noteworthy that one of the companies has mentioned that some acceptances of international regulatory decisions are quickly made when it is more stringent than what is currently used, causing a negative impact on the industry and without previous discussion. However, when some international regulatory decision with potential for positive impact in the industry is made, it is not always accepted or requires a large period of discussion for acceptance.

Figure 22: Impacts of foreign regulatory decisions on innovation



3. Impacts of NEW VETERINARY PRODUCT regulations on business

What impacts do you expect the NEW VETERINARY PRODUCT REGULATIONS to have on your business and why?

- Categorization will place each product on the correct rule. If MAPA continues with the idea of automatic and simplified registration, these categories will help the regulatory environment.
- An easier access to MAPA is required for communication and trading based on the principles of risk analysis and data control.
- Make the regulation clearer and standardize the interpretation of the law by inspectors/assessors (training x uniformity x coherence) permitting agility, forecasting and transparency is urgent. Then, it would be possible to make more investment in innovation to increase the portfolio and/or expand indication of species.
- The use of Pharmacovigilance as a tool for monitoring marketed products, in order to update safety data in the information made available to the consumer, data related to the resistance to the use of certain products, MRL violations and other data on a much larger scale.
- Follow the FDA's regulatory model, where the regulatory body "participates" in the evolution of the project during the development phase (consultations, approval of protocols, etc.).
- Greater stability in the governmental structure is also expected since changes in management and reviewers/assessors significantly impact the evaluation of products.
- A higher cost to update the dossiers based on increases in regulatory requirements is expected.

4. Changes still wanted in Brazilian regulatory approach

What changes do you still want to see and why?

- Modernization of the regulatory framework, categorization, predictability of standards and dossier evaluation and clearer rules from the regulatory sector;
- Transparency of information (mainly regarding the product assessment queues) and agility;
- Responsibility shared between the regulatory authority and industries' technical experts in order to make the best technologies and products available to customers;
- Technical and careful analysis of the documents made available by the companies;
- Best scientific and risk assessment evaluation made available;
- Requesting new tests or reviews, based solely on a rigorous analysis of the science of pharmacovigilance data or relevant advances in knowledge of risks based on the best available science, and previous assessment of clinical studies protocols.
- Final approval of new products based on expert evaluation of safety, quality and effectiveness.
- Safety, quality and effectiveness guidelines applied based on a practical and rigorous assessment of risks and benefits.
- Public-private partnership for product evaluation (e.g. FEA - Eliseu Foundation).
- Significant reduction in product evaluation deadlines within MAPA, especially for new products.
- End of sending regulatory submissions in physical way (SEI system), maintaining only digital channels.

Section G - REGULATORY COOPERATION AND SPECIAL PRODUCT CATEGORIES

1. Regulatory trend for regional regulatory cooperation

(a) Does your regulatory authority engage in any forms of regulatory cooperation, such as joint reviews or parallel assessment, with another regulatory authority? (b) If yes, how do joint reviews or parallel assessment between Brazil and another country impact your ability to innovate?

Yes. MAPA engages in CAMEVET discussions for regional harmonization, despite a slow internalization of the CAMEVET guidelines.

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

The ability to innovate is not impacted (neutral) according to four companies. For two companies the ability to innovate is positively impacted and for the other two in a negative way.

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)?

There are currently no special categories of products in the Brazilian market. Nevertheless, two efforts are in progress:

- **Minor Species:** proposal submitted by SINDAN awaiting MAPA approval;
- **Veterinary products with automatic registration and simplified registration:** legislation under discussion between SINDAN and MAPA – public consultation.

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

AFFA	Federal Agricultural Auditors
ANVISA	Agência Nacional de Vigilância Sanitária/ National Health Surveillance Agency
CVP	Coordination of Veterinary Products
CGMV	General Coordination of Veterinary Medicines
DFIP	Department of Surveillance of Livestock Inputs
DSA	Department of Animal Health, MAPA S
DSN	Department of Support and Technical Standards
FEA	Eliseu Foundation
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MAPA	Ministério da Agricultura, Pecuária e Abastecimento / Ministry of Agriculture, Livestock and Supply
MRL	Maximum Residue Limit
SINDAN	Sindicato Nacional de Indústria de Produtos para Saúde Animal
SIPEAGRO	electronic system for pharmaceutical product registration

Report prepared by Luiz Monteiro of SINDAN (www.sindan.org.br) 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

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