GLOBAL BENCHMARKING SURVEY 2020

Benchmarking the competitiveness of the global animal health industry

JAPAN

AUSTRALIA
BRAZIL
CANADA
CHINA
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Global Benchmarking Survey 2020
Report for JAPAN

1. Executive summary

The HealthforAnimals Global Benchmarking Survey is run every 5 years and has now grown to include 12 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, to continue to commercialize existing products and be competitive.

This report is the fourth for Japan. It summarizes the data from **13 local Japanese companies and 6 international companies**, examines key trends, provides analysis, conclusions and recommendations.

Data was collected through questionnaires in Q4 2019, which was aggregated and summarized to either allow discussion in a subsequent workshop or to be put into context through the knowledge and expertise of the trade association secretariat.

Key Conclusions

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. Japan is the third largest market, after USA and Europe, 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 multinational companies spent an average of 7% of their revenue on R&D (range 2% to 9.4%), which is consistent with previous surveys, while the local companies spent an average of 5.4% (range 2.4% to 6%). While the majority of the multinational companies had a mixed business between pharmaceuticals and biological products, the local companies were typically entirely focussed on either one or the other.

Section B - Impact of regulations on innovation

Since the 2011 survey there has been a trend for companies to move towards a more neutral opinion on the impact of the Japanese regulatory environment on ability to innovate (from 18% neutral in 2011 to 44% neutral in 2015 and 53% neutral in 2020. In 2011 a minority (18%) took a very negative view, but in 2015 and 2020 the overall outlook has been balanced (majority neutral, and equal numbers of negative and positive views).

The small size of market segments is the biggest factor having a negative impact on innovation. Other significant factors include a lack of skilled staff, the Japanese regulatory framework (particularly post-approval defensive research costs), and lack of availability of financial resources.

Regulations can also improve competitiveness in a number of ways, often revolving around safety and public trust (for example: public reassurance about product safety, improved product quality and prevention of dangerous products from entering the market) but also by facilitating business (creating a stable business environment and enabling faster product launches).

In addition 2 other factors were highlighted as very high in importance for companies: the improved acceptance of data generated abroad for New Animal Drug Applications (NADA) and national subsidies.

Increases in development time and costs as well as a perception of uncertainty and unpredictability are all highly important, negative effects of regulation in the Japanese animal health industry. Increased uncertainty around GMP rules and increased costs associated with AMR and GCP are highlighted. The cost of food-producing animal products showed, by far, the greatest increase.

Coupled with this are increased post-authorisation costs, such as the expense required for re-examinations, and especially for post-marketing surveillance. This appears to have caused a major increase in mandatory defensive R&D costs, overturning the large reduction reported in 2015.

With the small market sizes and high cost of product development, supporting incentives to invest become very important. The data protection provisions are generally seen as an incentive, although the provisions of 2 years for the subsequent addition of indications attracted a number of negative responses (e.g. 21% negative for pharmaceuticals).

Section C - Commercialisation of Existing Products

In Japan, the small market size has consistently remained the top obstacle to the exploiting of existing products. Pressure from competitors and the regulatory framework for maintenance or extension of licenses have remained in the top 4 obstacles since 2006. The most notable change in this survey is the increased importance of the lack of skilled staff.

Several companies commented that veterinarians' use of human drugs for companion animals in Japan and off-label use were also disincentives to further development of existing products.

Intellectual property protection is seen as helpful towards the ability to commercialize existing products, as are the trio of good practices of GLP, GMP and GCP. Less helpful are the increasing requirements for environmental safety and antimicrobial resistance data. The most unhelpful areas included variations, Post Marketing Surveillance , Import Regulations and Packaging/Labelling Modification Rules.

Section D - Regulatory predictability and quality

Generally the regulatory system in Japan is seen as good quality and based on the best available science. The expertise of the scientists responsible for the evaluation of new products was highly evaluated. Some doubts, however, exist around the “sub-committee system”, the caliber of the scientific assessors and the international standing.

The regulatory systems in Japan are also generally regarded as efficient, timely, transparent and predicable. The regulatory authorities are normally seen as prompt and helpful, although some areas nearly half of the respondents evaluated that this was not always the case.

Section E - Regulatory trends

Beneficial changes that have occurred in regulatory frameworks since the previous survey in 2015 include: the waiving of batch safety tests and potency tests in accordance with the VICH guidelines; the introduction of the synthetic long peptide (SLP) system for vaccines; the increased acceptance of overseas data; and the change from a sequential review process across regulatory bodies to ta parallel review process.

However some expected changes have not occurred in regulatory frameworks including: clarification of policy on the injection site residues; complying with the standard assessment periods for marketing authorisation applications; reduction of documents to be submitted for change applications and re-examination applications; and guidance on the application of the VICH pharmacovigilance guidelines.

The regulatory changes since 2015 that have given you the most problems include: the too detailed requirements for the SLP system for vaccines; the complicated application procedure for the preparation of antimicrobial substances for animals; and requirements to submit electronic files.

Section F - Hopes and expectations for the next 5 years

There have been several changes in regulatory approach since the previous survey in 2015, and the large majority of these have been appreciated as helpful or very helpful. The most helpful were the omission of batch safety tests for vaccines; the batch evaluation of adjuvants and additives for vaccines and the ability to submit data on clinical trials after application for approval has been submitted. A small number of companies experienced difficulties with the introduction of some other changes (e.g. restructuring regulations for veterinary medical devices and in vitro diagnostics).

The change that companies still want to see is greater international regulatory convergence, particularly with the USA and EU (including further promotion of VICH activities), particularly in the following areas: MRLs, replacing post-marketing surveillance by pharmacovigilance, acceptance of quality/GMP inspection results from trusted authorities, a notification system for in-vitro diagnostics, the mandatory priority use by veterinarians of authorised veterinary antibacterial products before human medicines and acceleration of the GMO approval procedure.

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 fourth for Japan. It summarizes the data from **13 local Japanese companies and 6 HealthforAnimals member companies based in Japan**, examines key trends, provides analysis, conclusions and recommendations.

The survey originally benchmarked the European 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 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 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 question is reproduced at the beginning of each question 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 Japan

In Japan, JVPA (Japan Veterinary Products Association) collected filled questionnaires from total of 19 companies. The breakdown of these 19 companies is the Japanese branch of **6 HealthforAnimals members** and **13 Japanese local companies**. Regarding section A, HealthforAnimals sent the questionnaires to **13 local companies** during October 2019. Of those 13 local companies polled, 5 provided responses for this report. In contrast to the other countries, no workshop was held for Japan. The aggregated answers were compiled by JVPA and subsequent synthesis and findings were incorporated into this report.

For more information on the Japan Veterinary Products Association membership please visit: http://www.jvpa.jp

4. The findings for JAPAN

Section A – FINANCIAL DATA

Global context

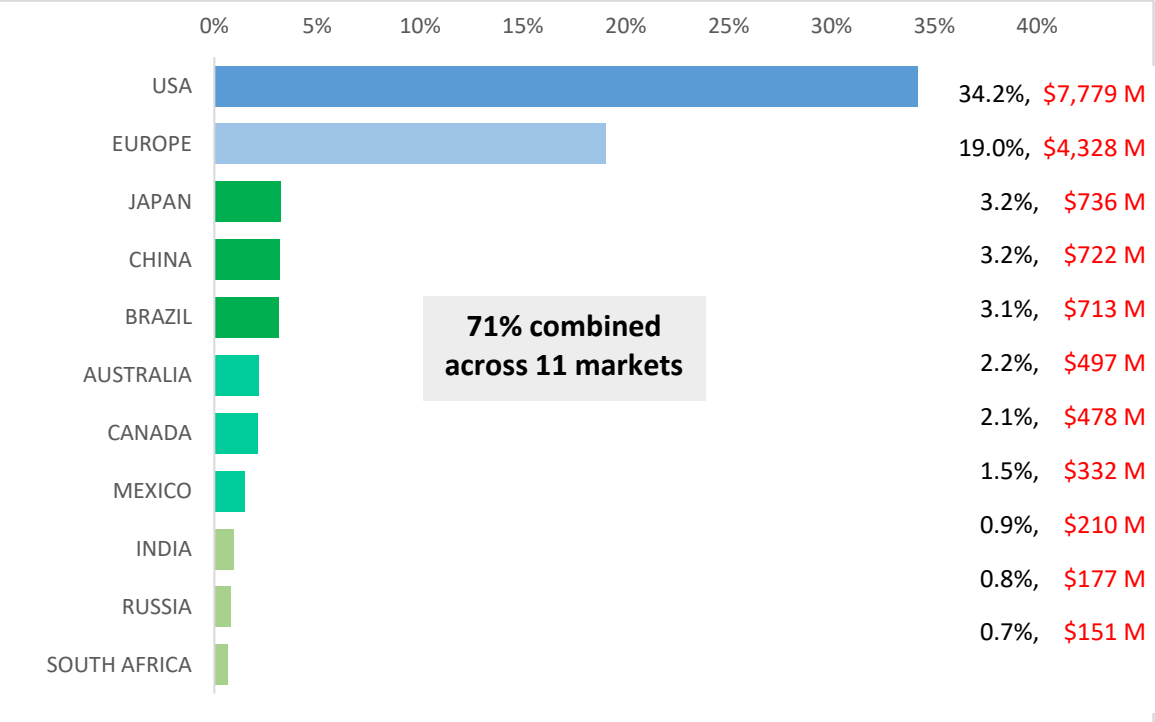
The financial data covers the 2018 full financial year. All data is presented in US dollars ($).

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 **Japan representing 3.2% of that revenue**.

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



Overall, top 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%). Companion animals 51% and major food species 49%.

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

Local context

The local companies spent an average of 5.4% of their revenue on R&D (range 2.4% to 6%) and had a greater tendency to specialise in both product category and animal category:

- while the majority of the multinational companies had a mixed business between pharmaceuticals and biological products, the local companies were typically entirely focussed on either one or the other.
- while the majority of the multinational companies had a mixed business between livestock and companion animal products, the local companies were typically more focussed on livestock (and several were entirely focussed on livestock).

Section B – IMPACT OF REGULATIONS ON INNOVATION

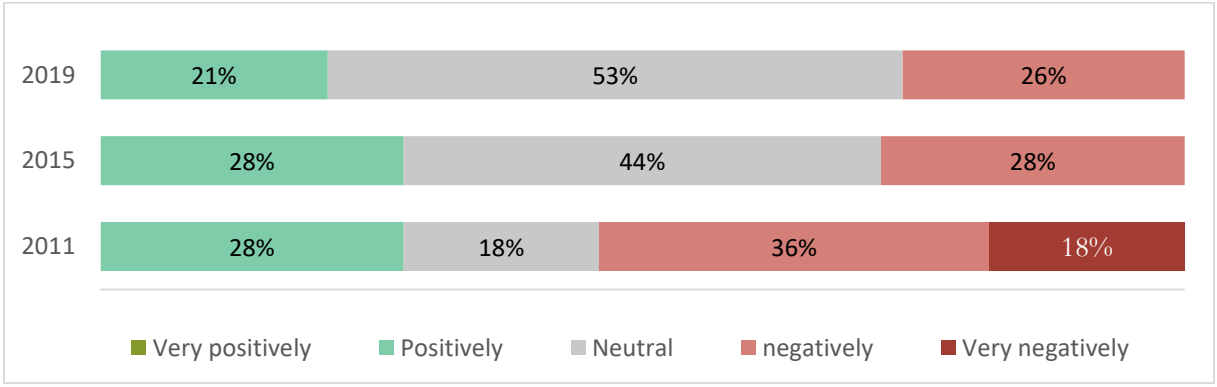
1. Impact of the Japan regulatory environment on ability to innovate

How much positive or negative impact does the regulatory environment in Japan have on the company's ability to innovate?

In 2019, there was no extreme response (very positive or very negative) to the Japanese regulatory environment. More than half (53%) answered that they were neutral and nearly a quarter (21%) viewed the regulatory environment as positive, indicating that more than 74% of the respondents were almost satisfied. However, it cannot be ignored that a quarter of respondents (26%) answered in the negative.

The changes in views between the last three surveys shows a gradual evolution to a more positive outlook. Nevertheless, more detailed discussions revealed that the opinions are still mixed.

Figure 2: Impact of the Japan regulatory environment on ability to innovate (2011 – 2019)



In the 2011 Global Benchmarking Survey (GBS) report for Japan, more than 50% of companies considered Japan's regulatory environment to be negative or extremely negative, but a significant percentage (28%) of companies considered it positive.

In the 2015 GBS report for Japan, there are no companies that have extremely negative opinions on Japan's regulatory environment, and the number of companies who feel negative is greatly reduced. This may be due to the effects of various deregulation policies issued by the Japanese government.

In this 2020 GBS report, more than half said they were neutral, and it was thought that the impact of the current regulatory environment was not a barrier to investment. The government has taken further deregulation measures to increase agricultural competitiveness since 2016, and the impact is likely to be limiting the number of companies with a negative impression. However, some say that deregulation measures are not effective, which may have reduced positive opinions.

2. Factors relevant to innovation in the animal health industry

Below is a list of potential FACTORS RELEVANT TO INNOVATION in the animal health industry in Japan. Which of these, if any, are significant for innovation in the company you belong to?

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 range of sentiments behind the ranking choices can be seen in Figure 3. The factors listed under the open option "Other" are listed in Table 2 with their individual rankings.

Small size of market segments is the highest ranked factor, by a margin, having the most negative impact on innovation. The next factors having the most impact on innovation are lack of skilled staff, the Japanese regulatory framework, and lack of availability of financial resources.

Many Japanese companies have been in business for over 40 to 50 years. One of the reasons for the lack of skilled staff may be due to the retirement of many skilled staff and the lack of transfer of skills and know-how to new generations.

Among the regulatory frameworks for veterinary medicine in Japan, what companies want to reduce the most may be post-approval defensive research costs. In Japan, the drug surveillance system is about to be introduced in accordance with the VICH guidelines, so it is thought that there may be fears of overlapping with Japan's own re-examination system and re-valuation system.

Table 1: Ranking of factors relevant to innovation

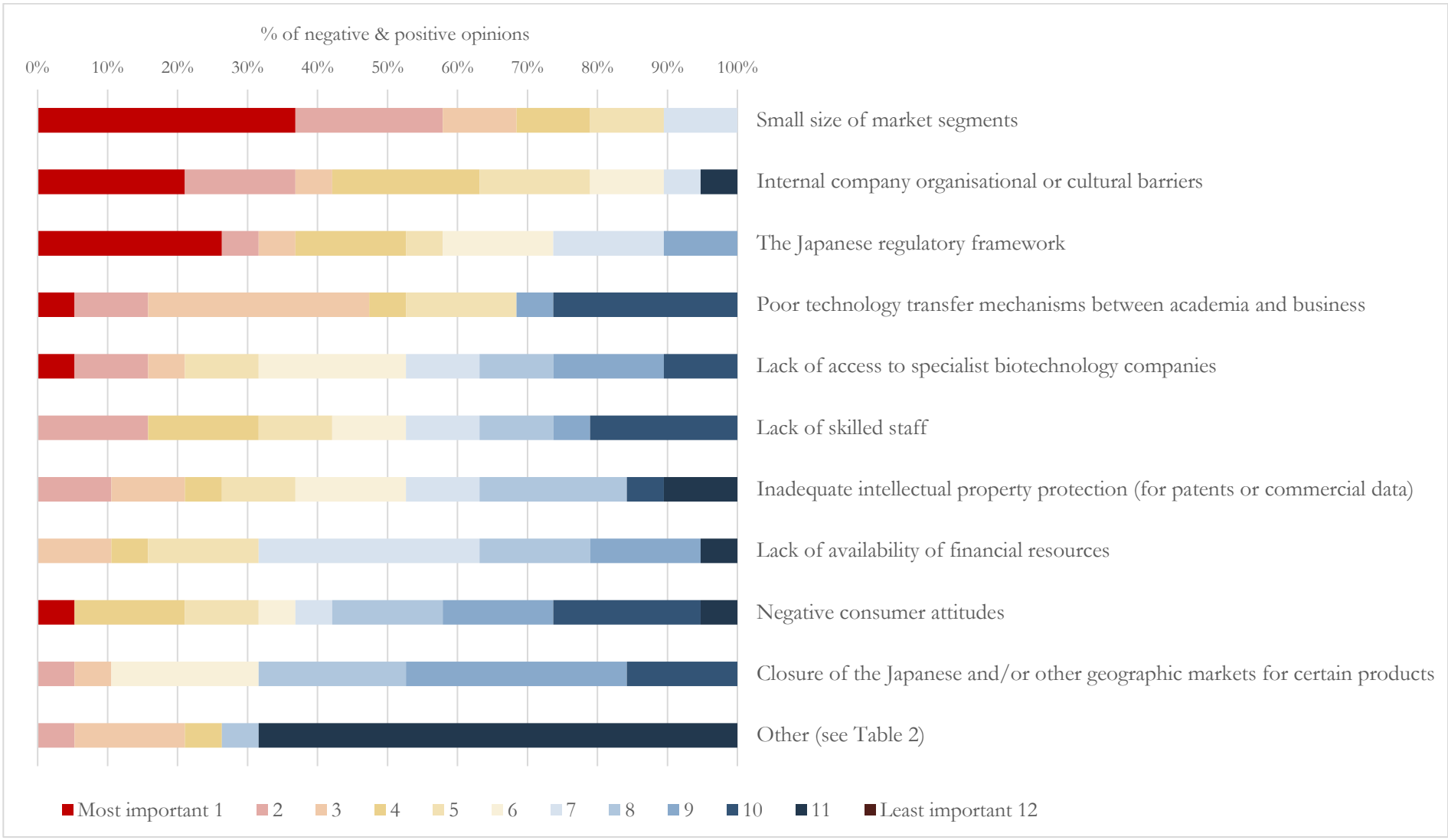
Factors relevant to innovation Ranked in order of negative impact	Average ranking score
Small size of market segments	2,8
Lack of skilled staff	3,9
The Japanese regulatory framework	4,4
Lack of availability of financial resources	5,3
Negative consumer attitudes	6,3
Internal company organizational or cultural barriers	6,3
Closure of the Japanese and/or other geographic markets for certain products	6,3
Lack of access to specialist biotechnology companies	6,8
Inadequate intellectual property protection (for patents or commercial data)	7,3
Poor technology transfer mechanisms between academia and business	7,6
Other	See Table 2

The highly ranked “Other” relevant factors reported in Table 2 highlight issues caused by lack of the time management of the review period(<1year) in Japanese authority, relatively short data protection periods for the line extension to other species, the long lead-time to approve manufacturing and the importance of PIC/GMP.

Table 2: Other factors reported relevant to innovation

Other factors reported	Average Ranking Score
Lack of time management of review period (< 1 year) in Japanese authorities	2
Relatively short data protection period, for the line extension to the other species	3
The regulatory framework is positive, but it takes time to approve manufacturing.	3
Importance of PICS/GMP	3
Insufficient measures to distinguish between livestock animals and companion animals.	4
Relatively high market maturity.	8
Few innovative ventures in veterinary products	11
Lack of language skills.	11

Figure 3: Ranking of factors relevant to innovation for companies



3. Regulations that have improved competitiveness

Have government regulations in Japan HELPED to improve the competitiveness of the company in any of the following ways?

As seen in Figure 4, there are numerous factors that companies viewed as being helpful contributions towards their competitiveness: public reassurance about the safety of animal health products, improved product quality, contributing to a stable business environment, faster product launches to the market and the prevention of dangerous products from entering the market. All save two (stable business environment and faster product launches) revolve around safety and public trust. These, when coupled with the strategic business factors (stable environment and faster product launches) are likely explanations for Japan's situation as an attractive market for animal health businesses.

In addition to the list provided to the respondents in the survey, there were several 'Other' options mentioned as seen in Table 3 below. Two of these responses ranked very high in importance for companies: the improved acceptance of global data for New Animal Drug Applications (NADA) and national subsidies.

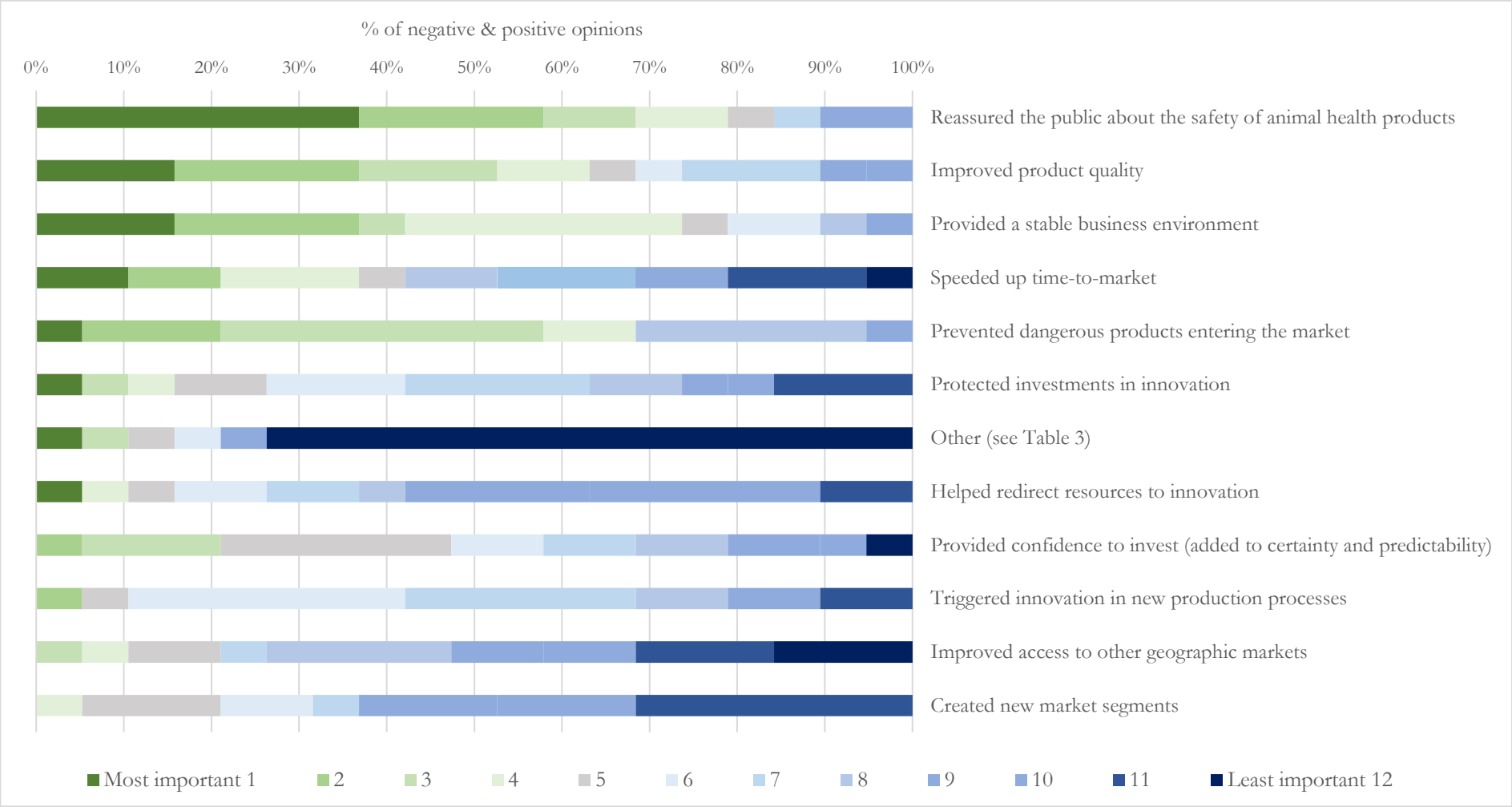
During the last few years, JMAFF has started accepting data generated abroad as part of the Japanese MA application, first for pharmaceuticals and later for biologicals. This has reduced both the time to dossier submission, as well as the costs for development for imported product to the Japanese market.

Table 3: Other factors reported relevant to company competitiveness

Factors	Rank
Improved acceptance of global data for NADA	1
National subsidies	3
Human resource development	5
Improved support system for application consultation	6
Human capital investment has increased, including for GCP	10*

*two respondents mentioned this and both ranked it 10

Figure 4: Ways in which government regulations have helped to improve company competitiveness



4. Other effects of regulations

Do government regulations in JAPAN have any of the following effects on your company?

While the companies surveyed outlined numerous factors where regulation has positively influenced their competitiveness, there still are many factors that affect the industry negatively. As seen in Figure 6, increases in development time and costs as well as a perception of uncertainty and unpredictability are all highly important, negative effects of regulation in the Japanese animal health industry. Loss of management time and of cash flows are also important.

Table 4: Other factors reported where regulations affect business

Other Factors affected by Regulations	Rank
Understanding of law concerning the conservation and sustainable use of biological diversity through regulations on the use of Living Modified Organisms	1
Human capital investment including GCP has increased	1
There is no specialized training for regulatory review	2
Costs of re-examination system for 6 years and resistance monitoring of FQs as long as products in the market	2
Relatively short data protection period, in particular for the line extension to the other species	5
It is basically a paper-based application process.	11

5. Expenditure on mandatory defensive R&D

Which of the following statements best indicates how the company's expenditure on MANDATORY DEFENSIVE R&D in Japan has changed since 2015?

After marked **decreases** in the time frame from 2011 to 2015, more than 70% of companies surveyed answered that expenditures in mandatory defensive R&D had increased since the last survey. The biggest factor contributing to the increase was the expense required for re-examination, especially for post-marketing surveillance. In Japan, many companies outsource their work to outside organizations.

Figure 5: Changes in expenditure on mandatory defensive R&D since 2006

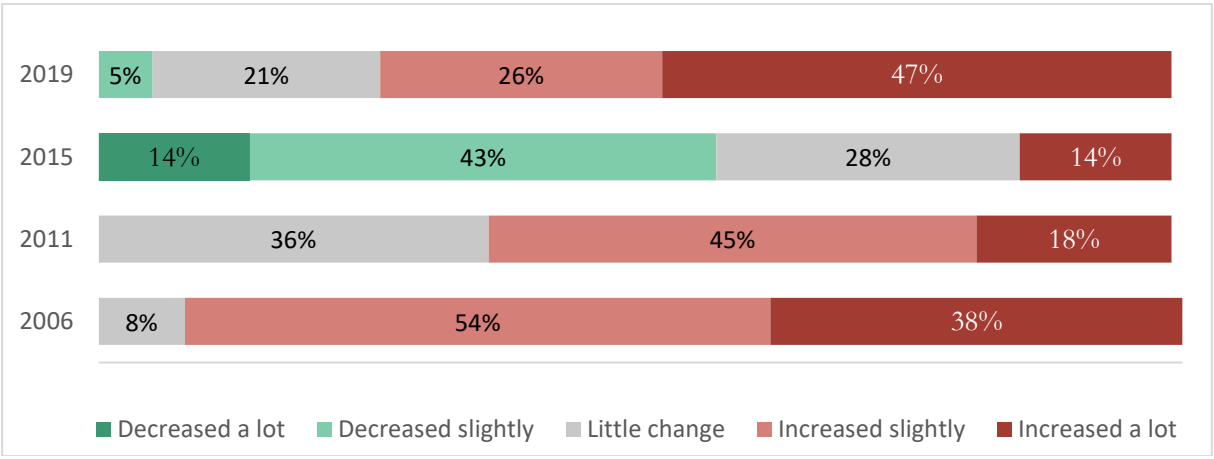
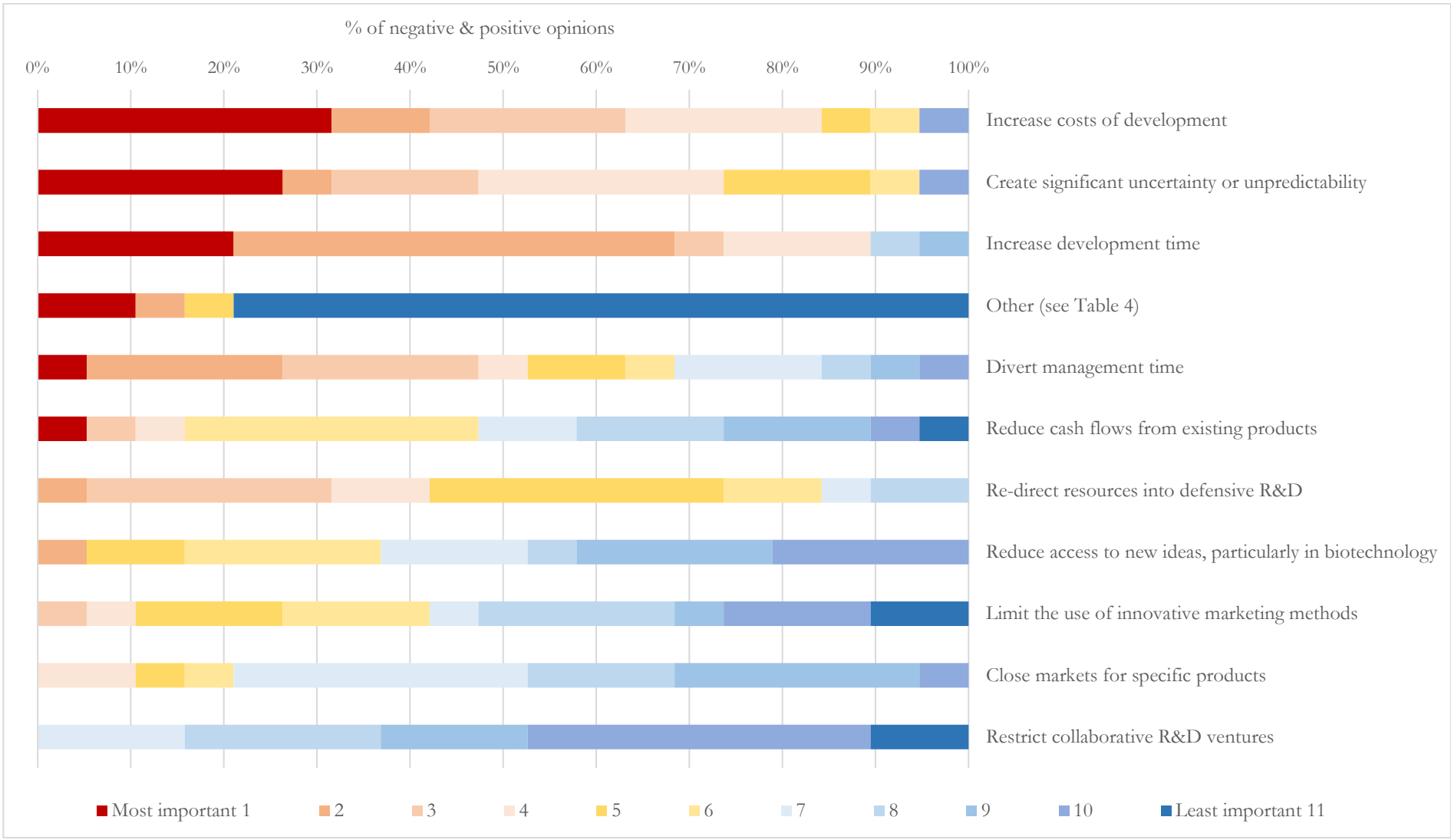


Figure 6: Effects of government regulations on business



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

A common theme within the factors causing an increase in expenditure on mandatory defensive R&D has been the implementation of increased requirements for post marketing surveillance (pharmacovigilance). The increase in the cost of studies to address antimicrobial resistance is also mentioned several times.

The total responses for changes in mandatory defensive R&D included:

DECREASE:

- Application for special approval for human medicines that have been used in dogs and cats as veterinary medicines.
- Since many of their products are relatively old, their proportion within the overall product portfolio is decreasing year by year.

INCREASE:

- More innovative activities, i.e., launches of new VMPs as well as line extensions (e.g. new indications), more resources are required for post marketing surveillance (PMS). In addition, the external costs when outsourcing the PMS, for efficacy, to CRO are increasing.
- Increase of expenditure are caused by post marketing activities, e.g. re-examination costs (PMS) of new products, resistance monitoring costs of fluoroquinolones. PMS costs have become higher over the last 6 years. Resistance monitoring costs are born if the products in Japanese markets.
- Due to the increase of new products and introduction of outsourcing.
- Post marketing surveillance requires the similar level of quality with the pre-approval field clinical studies. That increased the cost for the direct CRO costs as well as the monitoring and managing costs internally.
- Frequently, effectiveness studies are outsourced to CROs. In addition, we often outsource safety surveys for preparations for dogs and cats.
- For the evaluation of effectiveness in post-marketing surveillance, the same standards as those at the time of development have been required. (In the past, the focus was rather on safety.)
- Increased cost of resistant bacteria monitoring due to colistin being designated as second-line drug.
- Conduct clinical trials based on GPSP
- Implementation of literature search based on GVP (increase in human and time)
- In the use-results survey for special approval applications for human-use drugs that have been used in dogs and cats as veterinary drugs, evaluation criteria equivalent to those of GCP are required, resulting in a burden on development
- Outsourcing such as post-marketing surveillance
- Unexpected costs for re-examination
- Secure personnel necessary for the creation and management of documents such as GPSP
- Internal operation of post-marketing surveillance

7. COST of developing a major new product

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

53% of companies reported that Major Food Animals showed, by far, the greatest change (increase) in cost to develop new products while Companion Animals and Minor Species showed small reductions and little change or increase. As with many other markets, products for Minor Species are not developed by a quarter of Japanese companies.

Figure 7: Changes in COST of developing a major new product since 2015

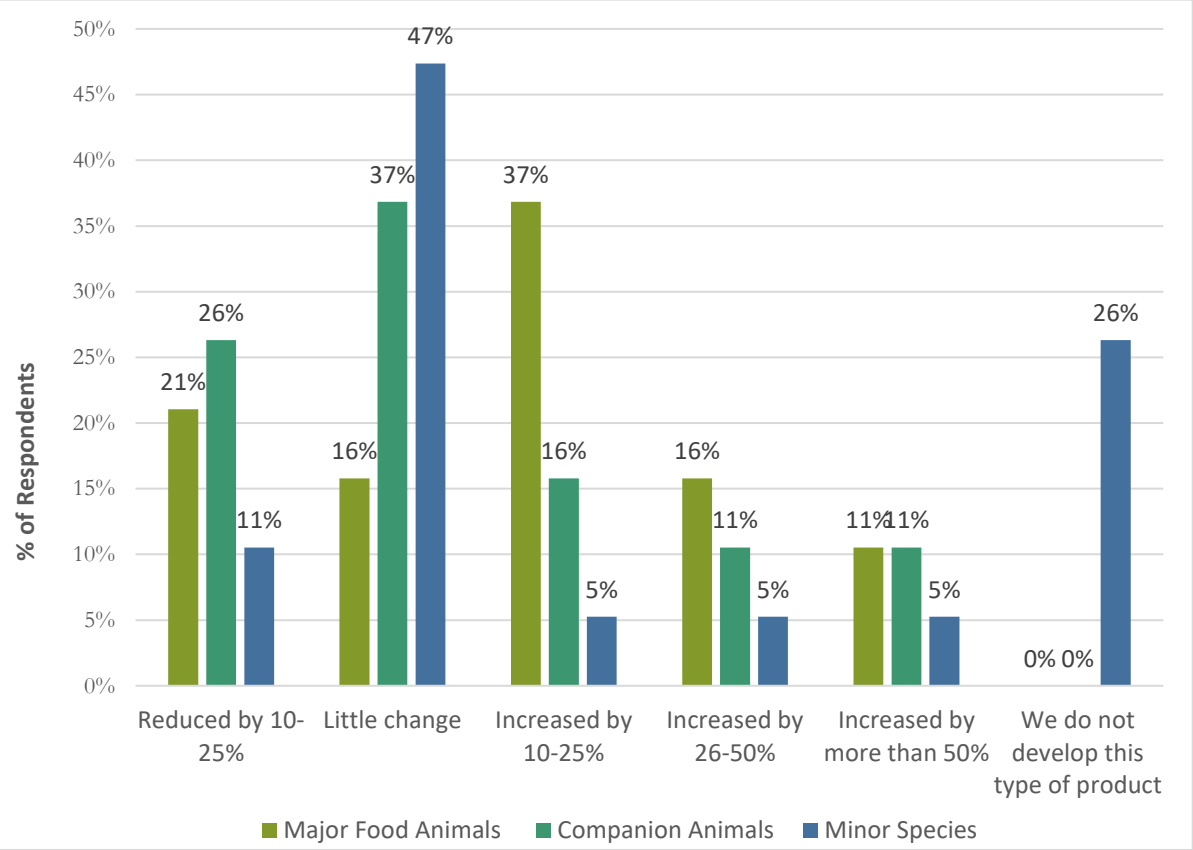


Figure 8: Changes in COST of developing a major new product since 2011-2019 – Major Food Animals

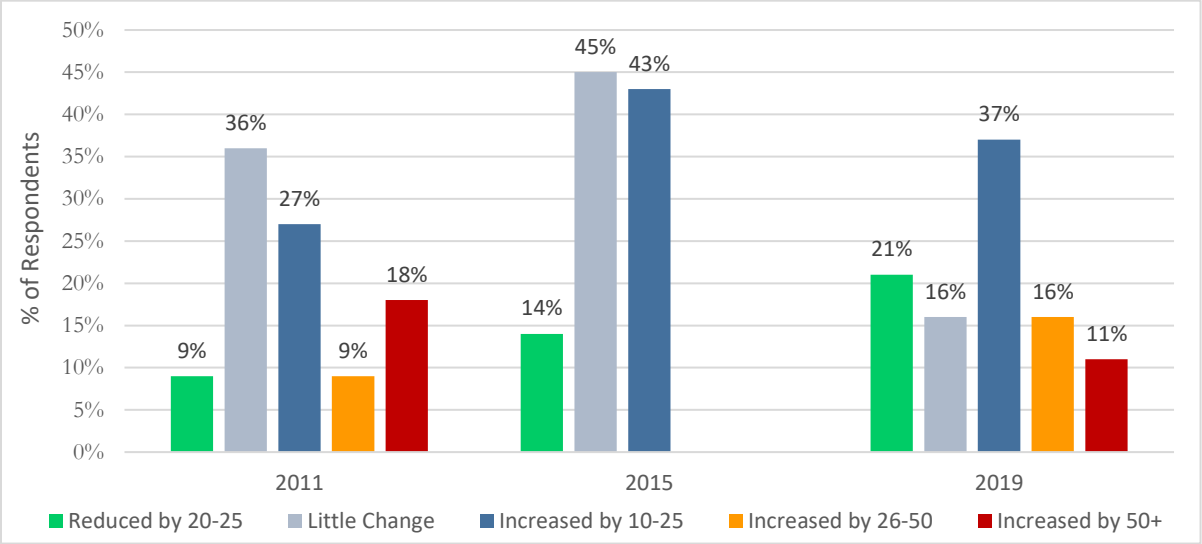


Figure 9: Changes in COST of developing a major new product since 2011-2019 – Companion **Animals**

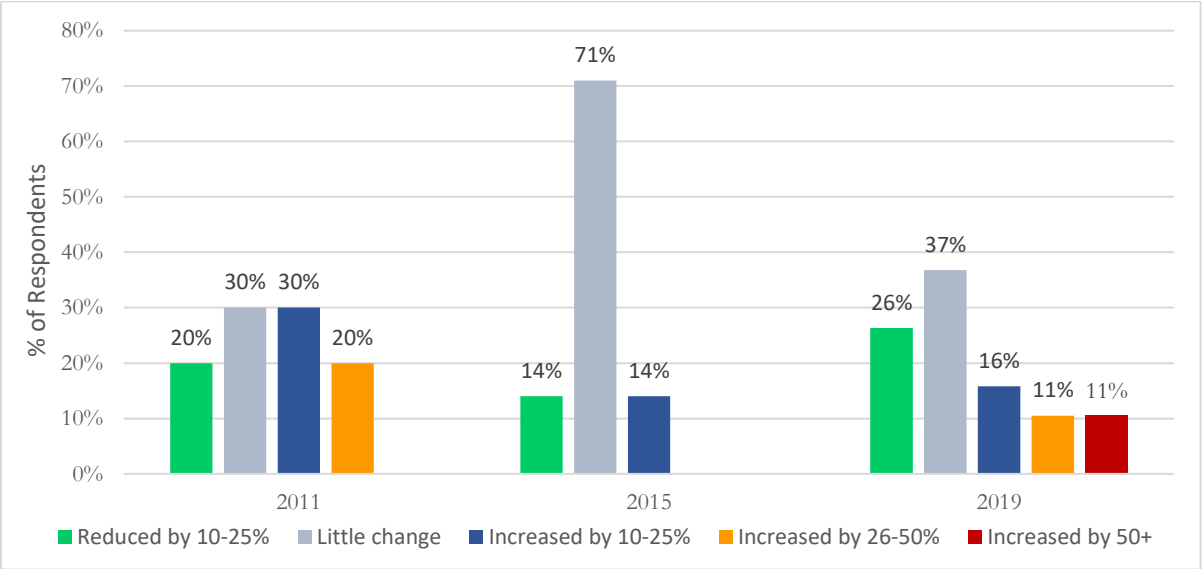
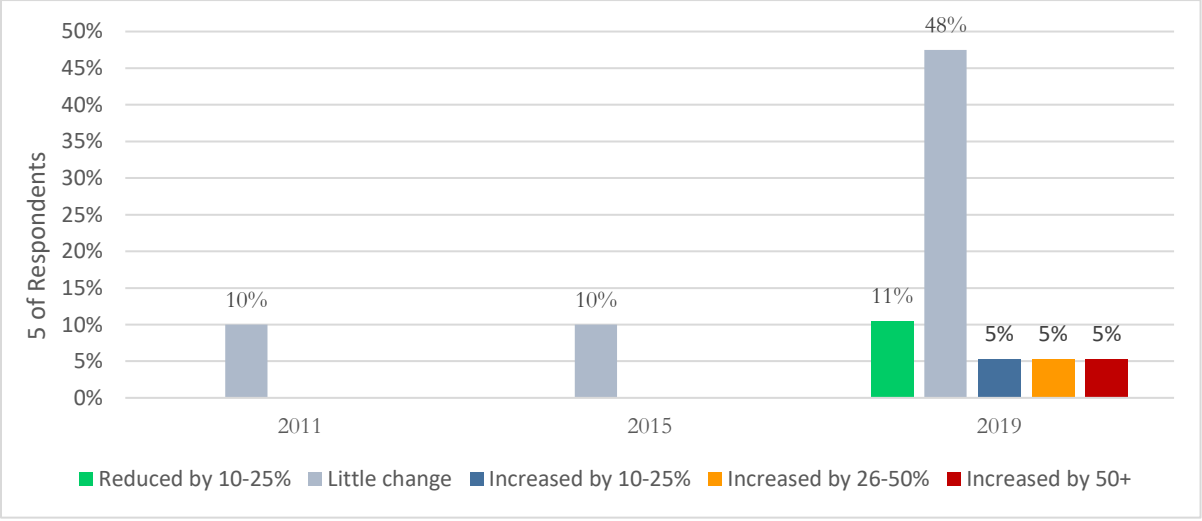


Figure 10: Changes in COST of developing a major new product since 2011-2019 –Minor Species



8. Data protection/market exclusivity periods

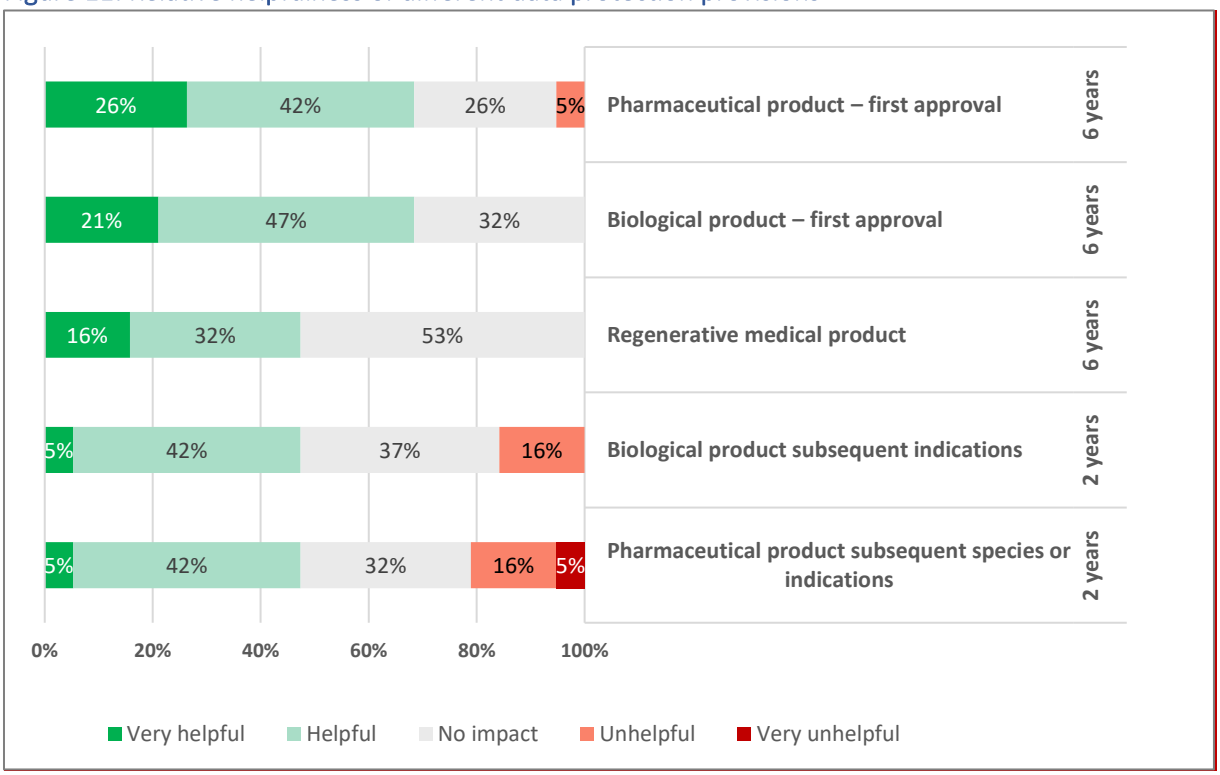
Considering the length of data protection (market exclusivity) given for different product types (or categories), to what extent do you consider it to be an incentive?

A summary of the different data protection provisions is listed in Table 5. The opinions of the companies whether these data protection provisions are seen as an incentive are summarized in Figure 11. Most helpful were the data protection provisions of 6 years for first approvals of biological, pharmaceutical products and the regenerative medical products. However the data protection provisions of 2 years for the subsequent addition of indications, while attracting 47% positive comments, also attracted a greater proportion of negative responses (e.g. 21% for pharmaceuticals).

Table 5: Data protection provisions

Type of Product	***Years Protected***
Pharmaceutical product – first approval	6 years
Pharmaceutical product subsequent species or indications	2 years
Biological product – first approval	6 years
Biological product subsequent indications	2 years
Regenerative medical product	6 years

Figure 11: Relative helpfulness of different data protection provisions



Section C - COMMERCIALISATION OF EXISTING PRODUCT

1. Obstacles to exploiting EXISTING PRODUCTS

Below is a list of potential OBSTACLES TO THE EXPLOITATION OF EXISTING PRODUCTS in the animal health industry in Japan. Which of these, if any, are significant obstacles to the exploitation of your company's existing products?

The overall ranking of the potential factors relevant to the commercialisation of existing products is shown in Figure 12, ranked from most important at the top, to least important at the bottom. The topmost important factors relevant to the exploitation of existing products, and their rankings in previous surveys, are:

Table 6: Ranking obstacles to exploiting EXISTING PRODUCTS

2019	2015	2011	2006
1. Small size of market segments	1	1=	2
2. Pressure from competitors (including parallel imports and generics)	3	1=	2=
3. Japan's regulatory framework for maintenance/extension of licenses	4	3	1
4. Lack of skilled staff	8	7	5
5. Negative consumer attitudes	2	4	4

In Japan, the small market size has consistently remained the top obstacle to the exploiting of existing products since 2011. Pressure from competitors (including parallel imports and generics) and the regulatory framework for maintenance/extension of licenses have remained in the top 4 obstacles since 2006. The most notable change in 2019 is the increased importance of the lack of skilled staff.

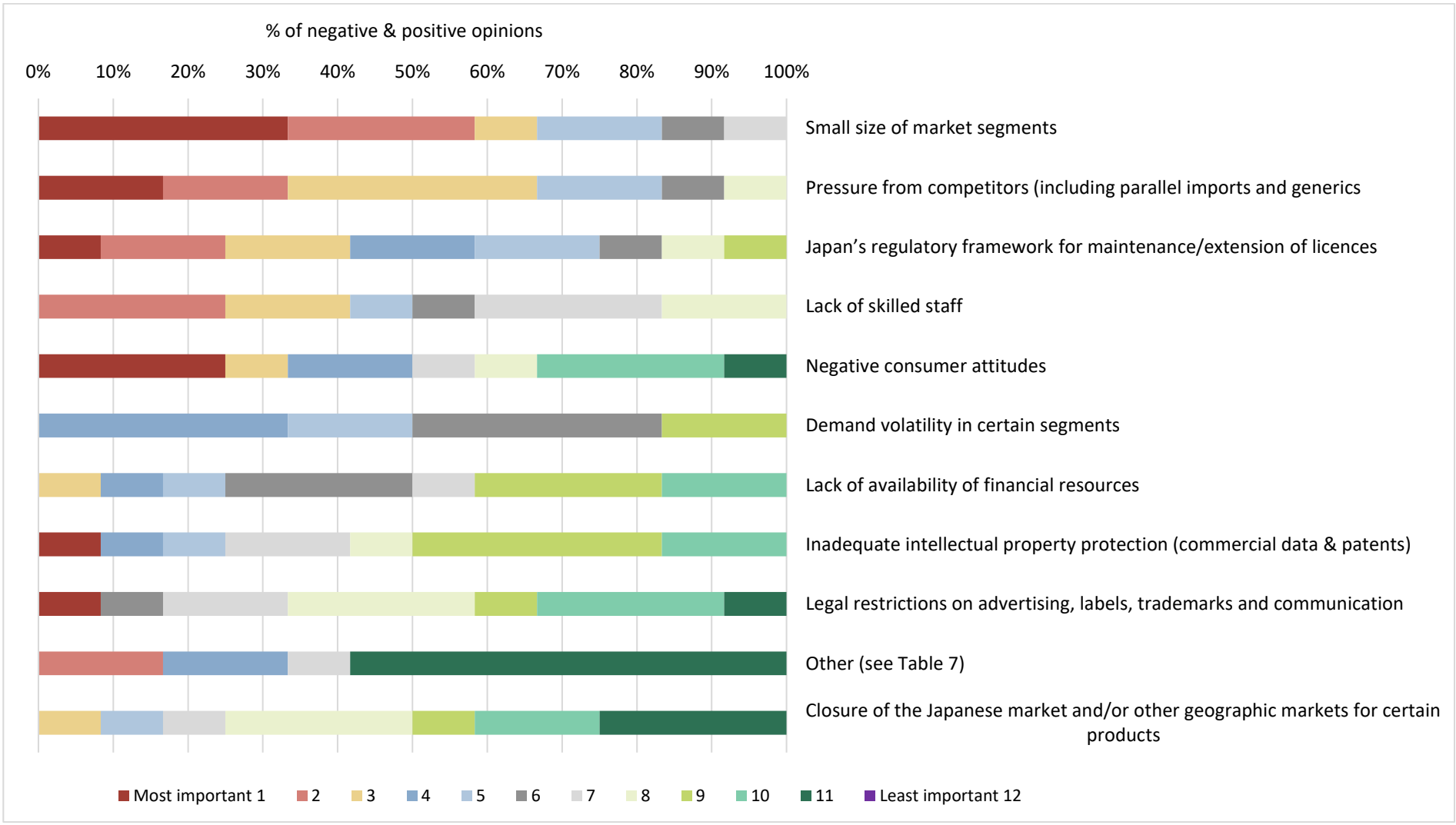
It cannot be denied that since the BSE outbreak in 2001, consumers continue to have a negative attitude toward veterinary medicine, especially for use in food animals, with a particularly high impact in the 2015 survey. In that sense, expanding the product line is a major challenge for companies, as there is a risk of costs required to maintain approval (e.g. new safety studies). Other obstacles are shown in Table 7.

Several companies commented that veterinarians' use of human drugs for companion animals in Japan and off-label use were obstacles to development. In addition, the existence of an examination system after approval such as re-examination and reassessment is also an obstacle.

Table 7: OTHER obstacles to exploiting EXISTING PRODUCTS

Factors	Rank
Off label use of human drugs in companion animal space or lack of cascade system in Japan	2
Importance of the disease against target animals	3
Since comparative tests cannot be performed on products that are not on the market or discontinued, it is difficult to develop existing products.	4
Re-evaluation system based on new knowledge.	4
Leveling off unauthorized use by veterinarians and producers.	5
Slander from other companies	7

Figure 12: Ranking obstacles to exploiting EXISTING PRODUCTS



2. Impact of regulation on ability to commercialize EXISTING PRODUCTS

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

Figure 13 shows how the regulations in Japan affect the sales of existing products, in order from the most helpful to the least helpful.

Helpful aspects:

Intellectual property protection-patents were the most helpful outcome and there was no opinion that it was unhelpful. The majority also thought the protection of commercial data was also highly evaluated.

On balance, the quality standards embedded in the trio of Good Laboratory Practice, Good Manufacturing Practice and Good Clinical Practice were seen as helpful, as were the consumer safety standards of Maximum Residue Limits and pharmacovigilance rules.

Mixed responses

The following government regulations received a more mixed assessment: Environmental Regulations (Ecotox), Antibiotic Resistance Regulations, Safety & Risk Assessment (FSC) and Licence Maintenance (J-MAFF).

For one of these a small minority (11%) regarded it as very unhelpful (Antibiotic Resistance Regulations)

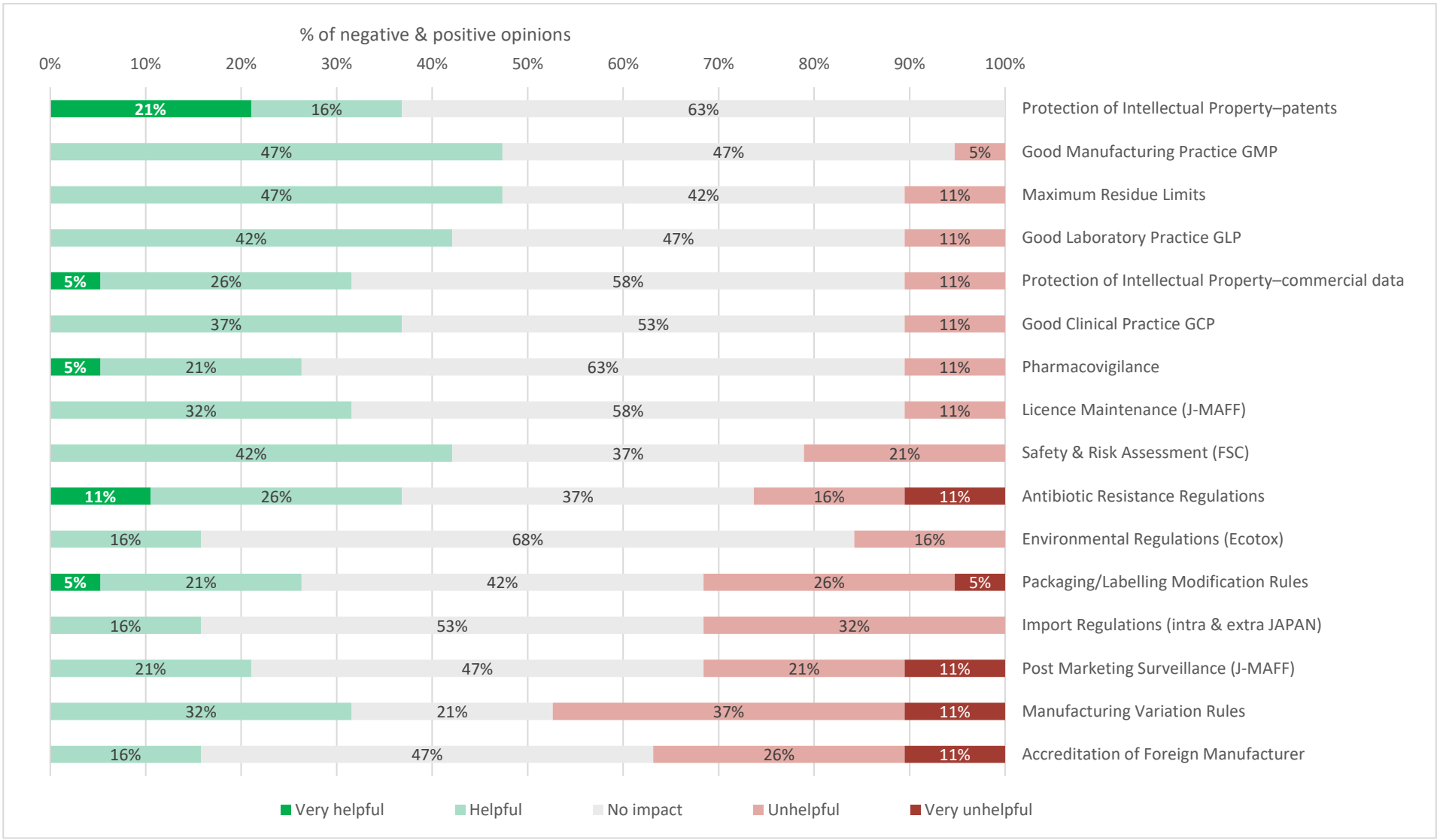
Unhelpful aspects:

The following government regulations were, on balance, less appreciated: Accreditation of Foreign Manufacturer, Manufacturing Variation Rules, Post Marketing Surveillance (J-MAFF), Import Regulations (intra & extra JAPAN) and Packaging/Labelling Modification Rules.

For three of these a minority (11%) regarded Accreditation of Foreign Manufacturer, Manufacturing Variation Rules, Post Marketing Surveillance (J-MAFF), as very unhelpful.

In the free text box to add ‘Other’ regulations, the ‘Fineness of license division’ was mentioned as ‘Very unhelpful’.

Figure 13: Impact of regulation on ability to commercialize EXISTING PRODUCTS



Section D - REGULATORY PREDICTABILITY & QUALITY

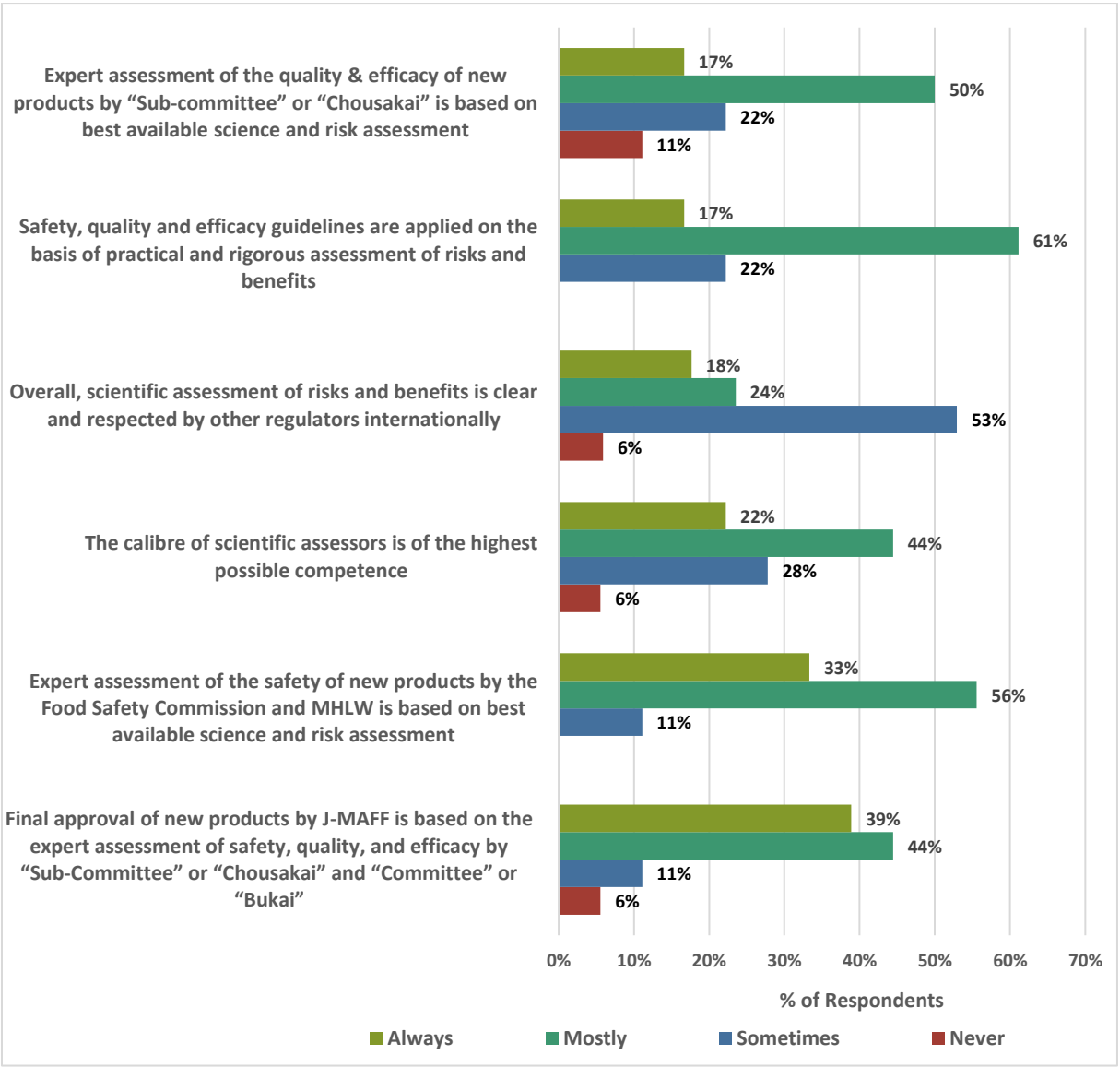
1. Procedures for approving NEW products (Scientific & Process Bases)

Please consider the current J-MAFF process for approving new products. To what extent does the process meet the following criteria?

Generally the regulatory system in Japan is seen as good quality and based on the best available science. Some doubts, however, exist around the "sub-committee system", the caliber of the scientific assessors and the international standing (Figure 14).

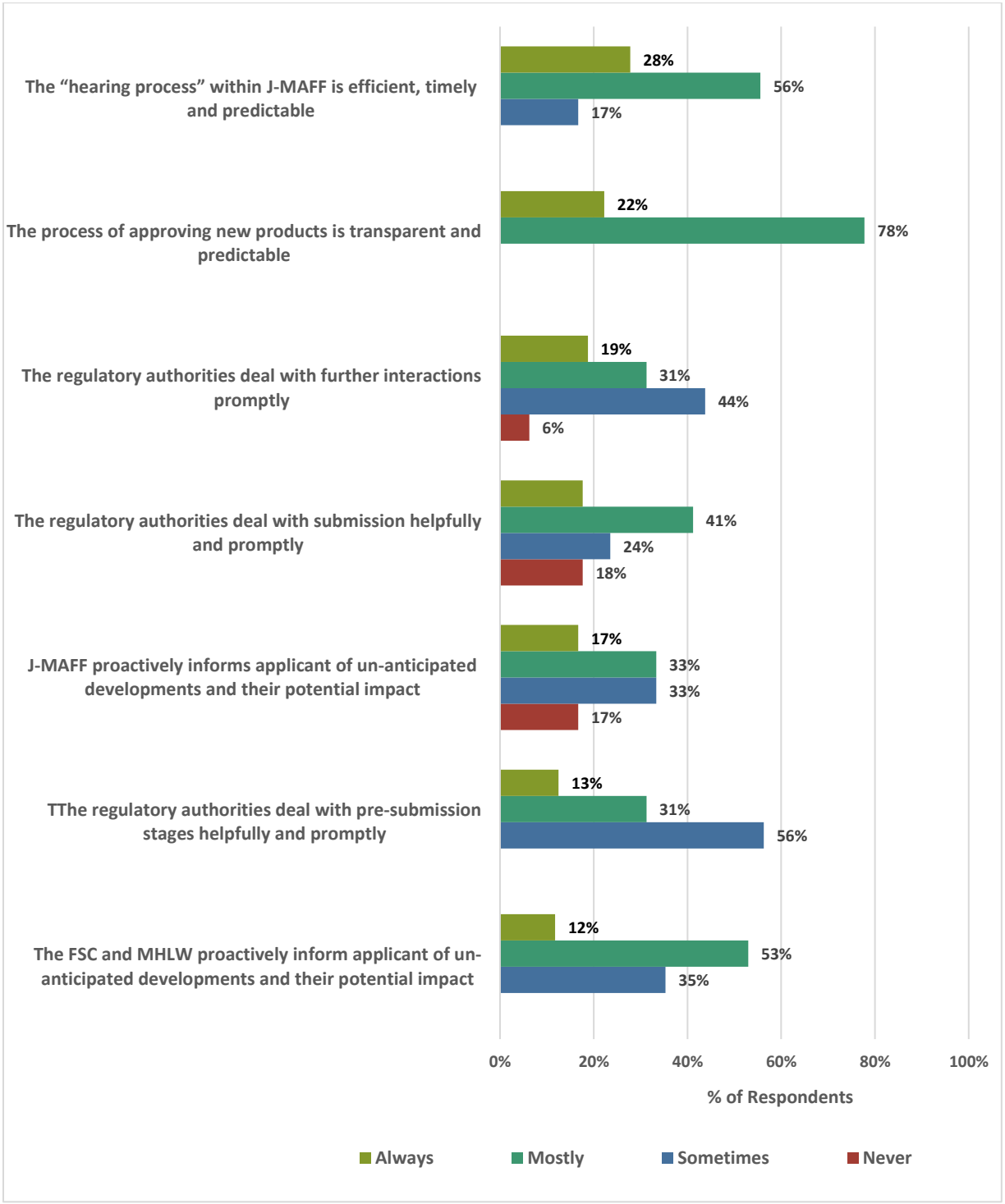
Regarding the approval procedure of new products, it is considered that the examination by advisory bodies such as research committees and subcommittees and the evaluation by the Food Safety Commission are conducted scientifically, but the international evaluation was not high. This is probably because there are not many original Japanese products that have expanded into Western countries. On the other hand, it is considered that Japanese vaccines are well respected when they are registered in other Asian countries.

Figure 14: Criteria related to NEW product approval procedures (Scientific Basis)



On a process basis (Figure 15), the regulatory systems in Japan are generally regarded as efficient, timely, transparent and predicable. The regulatory authorities are normally seen as prompt and helpful, although in 2 or 3 areas nearly half of the respondents evaluated that this was not always the case (e.g. 50% reported there was not always prompt responses with submissions and with later interactions, such as notification of the status of an approval procedure).

Figure 15: Criteria related to NEW product *approval* procedures (Process Basis)



2. Procedures for evaluating NEW products

Please consider the scientific basis of the current J-MHLW & FSC procedure for evaluating new products. To what extent does the process meet the following criteria?

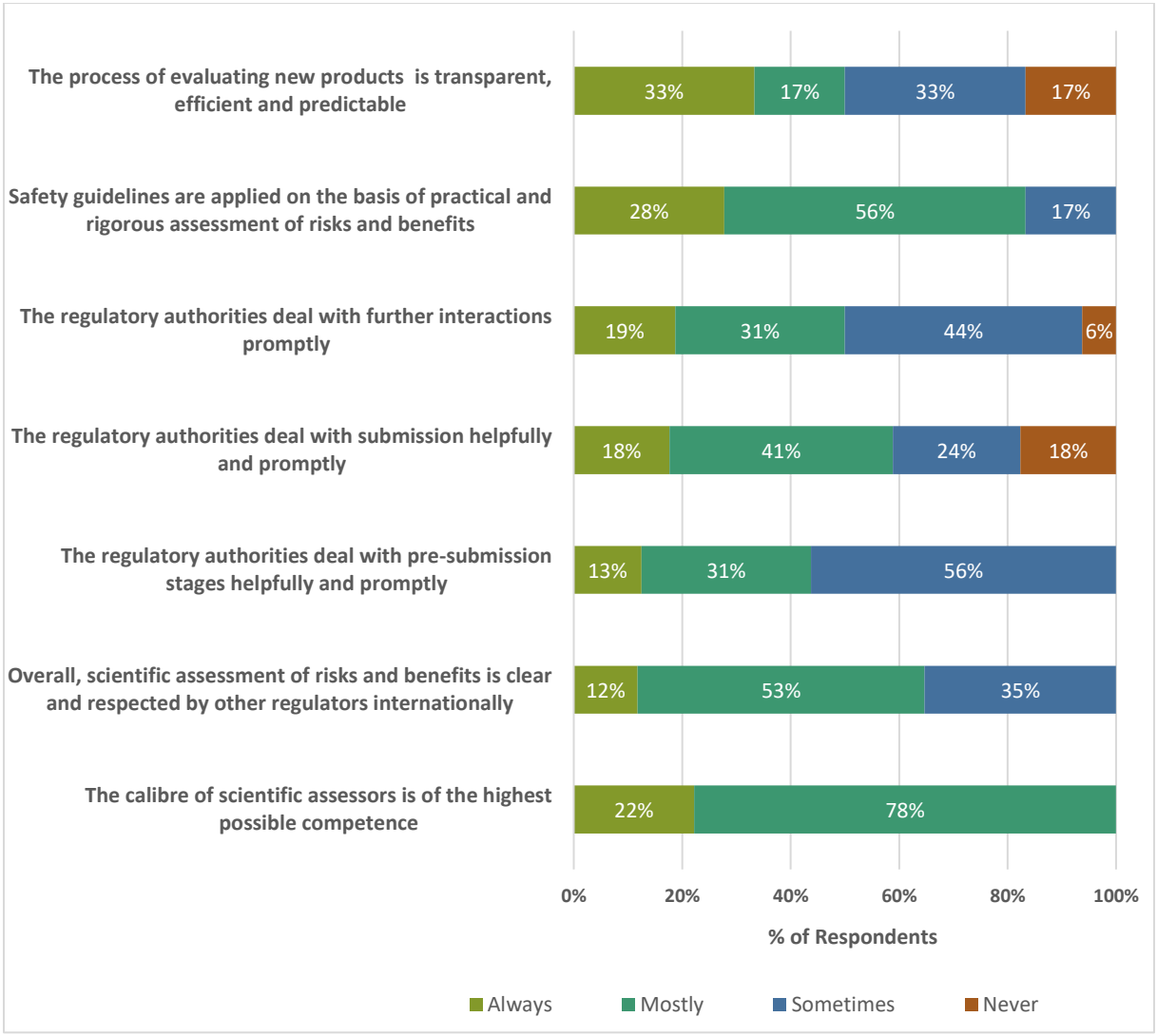
In Japan, since the outbreak of BSE, the Ministry of Health, Labour and Welfare (MHLW) and the Food Safety Commission (FSC), in addition to the Ministry of Agriculture, Forestry and Fisheries (MAFF), have been required to conduct safety assessments of new drugs used for food animals prior to marketing. The results of the questionnaire on the expertise of the safety assessment conducted by MHLW and FSC are shown in Figure 16.

The expertise of the scientists responsible for the evaluation was highly evaluated (nearly 100%).

International evaluations of the usefulness of the safety guidelines and the risk assessments performed were also highly evaluated by 60-80% of the companies.

About half (48%) rated the transparency and promptness of the regulatory assessment process as consistent, while more than half appeared dissatisfied with the response at the pre-submission stage and further interaction at the assessment stage.

Figure 16: Criteria related to NEW product *evaluation* procedures (Scientific Basis)



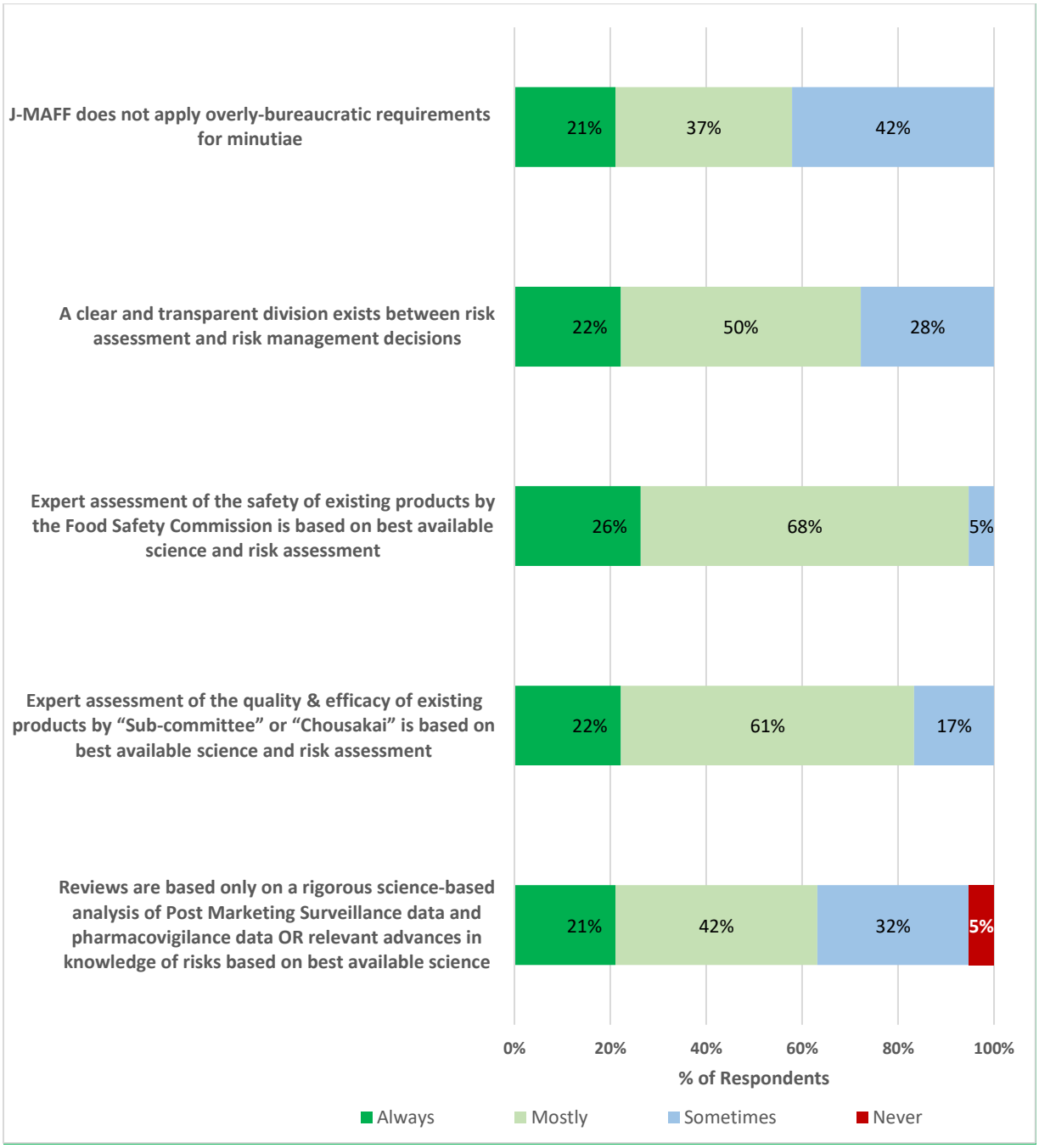
3. Procedures for maintaining EXISTING products on the market

Please consider the current J-MAFF re-examination and re-evaluation requirements for maintaining existing products on the market. To what extent does the process meet the following criteria?

The results of the re-examination and re-evaluation in Japan are shown in Figure 17.

More than 80% gave high marks to the evaluation conducted by the Research Committee and the FSC. However, as in other sections of this report, the area of post-marketing surveillance or pharmacovigilance attracted the most criticism, although this still remained a minority view and the majority of respondents were positive.

Figure 17: Criteria related to NEW product *evaluation* procedures (Scientific Basis)



Section E - REGULATORY TRENDS

1. Recent beneficial changes to the regulatory frameworks in Japan

What beneficial changes have occurred in regulatory frameworks SINCE 2015?

Regarding vaccines, the following two points were found to be beneficial.

(1) Deregulation, which enables the waiving of batch safety tests and potency tests in accordance with the enforcement of VICH GL50R and GL55, was highly appreciated from the viewpoint of animal welfare.
(2) It was also appreciated that the limited use period for vaccines was shortened by the collective evaluation process for vaccine additives.

Another minority opinion was that it was good to introduce the synthetic long peptide (SLP) system for vaccines and to show precedents on the manufacturing method of applications.

Regarding clinical trials for pharmaceuticals at the time of application, it was most appreciated that:

(1) it became possible to accept overseas data and that it was possible to conduct clinical trials after application for authorisation; and,
(2) the introduction of a system in which the reviews by the MAFF, the MHLW, and the FSC were carried out simultaneously was also highly anticipated.

There was some support for the conversion of human medicines to companion animals.

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

What expected changes have NOT occurred in regulatory frameworks SINCE 2015 in spite of promises of change?

The following items were pointed out as desired changes in the regulatory framework that were not implemented.

- Regulation/policy on the injection site residues is still unclear

- Complying with the standard assessment period for product applications for authorisation

- Reduction of review period involving MAFF, MHLW and FSC

- Reduction of documents to be submitted for change application and re-examination application

- Notification system for in vitro diagnostics for infectious diseases

- Guidance on VICH pharmacovigilance guidelines (VICH GL24 & 29)

- Reduction of data on diverted drugs (e.g. conversion of human medicines to companion animal medicines).

3. Problematic changes to the Japan regulatory frameworks

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

Several regulatory changes were noted as being problematic:

- SLP system for vaccines - the conversion of the system has been supported, but the requirements are too detailed which makes it difficult to implement
- Standard for the preparation of antimicrobial substances for animals has been abolished - the application procedure has become complicated
- Cancellation of designated feed additives for colistin has resulted in lost sales
- Requirement to submit an electronic file of the attached document has complicated the process
- It is difficult to obtain GCP-level results for the “Usage Survey” required for applying for diverted medicines.

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?

Figure 18 shows the response to the impact on business results of 10 trends or changes related to veterinary drugs in the past five years.

The top 5 most helpful changes are as follows:

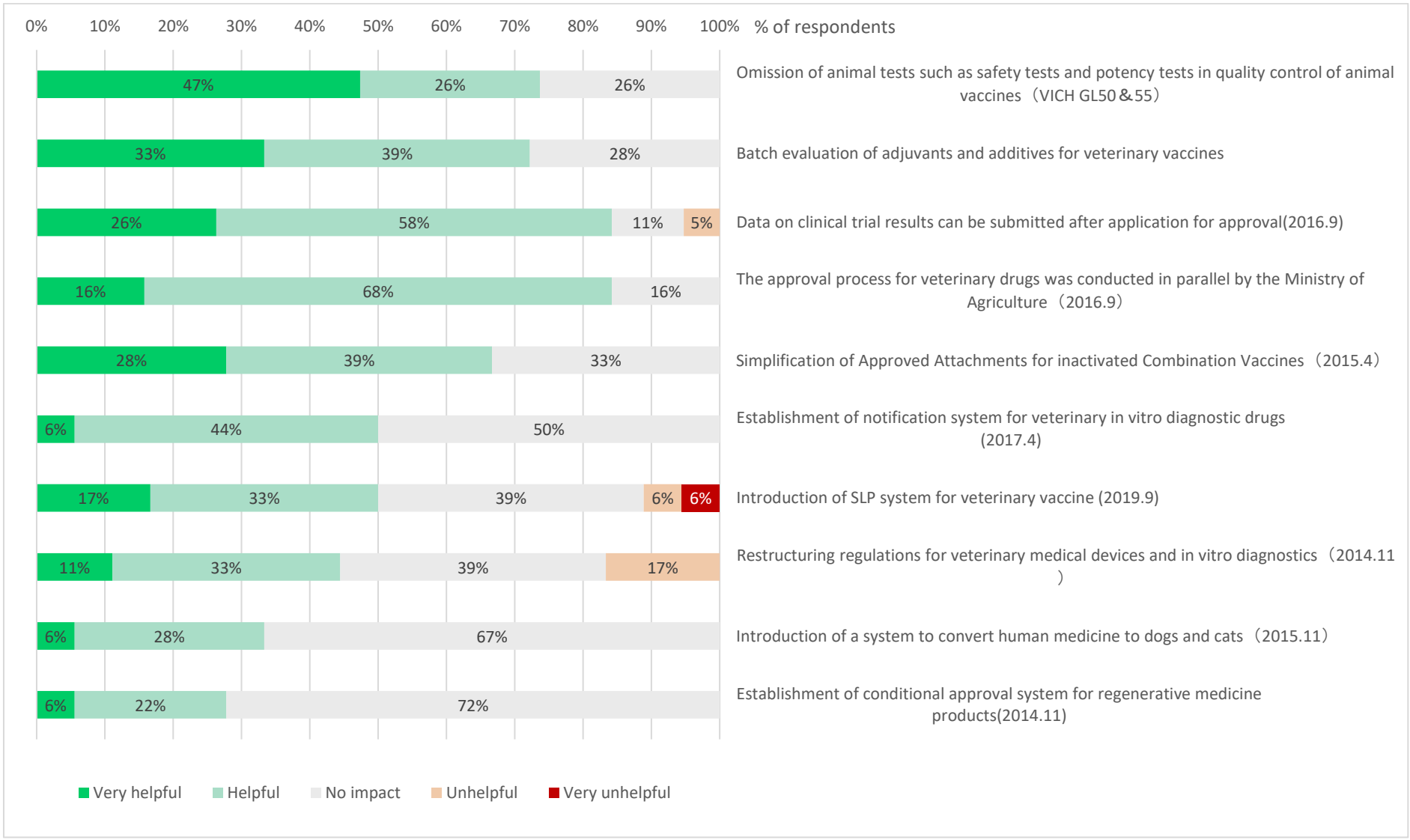
1. Omission of animal tests such as safety tests and potency tests in quality control of animal vaccines when the pre-conditions have been fulfilled (VICH GL50 & 55, April 2018)
2. Batch evaluation of adjuvants and additives for veterinary vaccines
3. Data on clinical trial results can be submitted after application for approval (September 2016)
4. The approval process for veterinary drugs was conducted in parallel by the MAFF, the FSC and the MHLW (September 2016)
5. Simplification of Approved Attachments for inactivated Combination Vaccines (2015.4）

The following changes were not considered helpful by a number of companies:

1. Restructuring regulations for veterinary medical devices and in vitro diagnostics (November 2014), with 17% of the companies finding this unhelpful
2. Introduction of SLP system for veterinary vaccines (September 2019) (some aspects being problematic as noted in the previous section)
3. Data on clinical trial results can be submitted after application for approval (September 2016)

The reason for the poor experience of a small number of companies with the points above, while the majority found these aspects helpful or very helpful, should be investigated.

Figure 18: Impacts of regulatory trends



2. Desired changes

What changes do you still want to see and why?

There were many requests from global companies that they would like the same regulations as in the EU / US in the following aspects:

- Conduct a food health impact assessment (e.g. MRLs) of new active ingredients before applying for a product approval
- Acceptance of evaluation results by EU / US
- Abolition of post-marketing surveillance and replacement by pharmacovigilance
- Permission for tar dyes approved for use in the EU / US
- For biologicals, it is desired to change the regulation from following the development process to performing a quality inspection after approval
- Abolition of safety / titer tests in quality monitoring
- Acceptance of quality/GMP inspection results from trusted authorities
- Elimination of efficacy studies in pre-application clinical trials
- Promote notification system for in-vitro diagnostic drugs
- Acceleration of examination for use of GMOs

Furthermore, there were the following requests:

- Further promotion of VICH activities
- Enable paid clinical trials
- Mandatory priority use of antibacterial substances for animals by veterinarians (cascade decision making for prescribing).

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 and to the JVPA secretariat for collating and interpreting the results. 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

AH	Animal Health
BSE	Bovine Spongiform Encephalopathy (aka Mad Cow Disease)
CA, CAP	Companion Animal[s], CA Product[s]
FSC	Food Safety Committee
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
CRO	Contract research organization
EU	European Union
GBS	Global Benchmarking Survey
GMO	Genetically modified organism
GPSP	Good Post-marketing Study Practice or Good Post-marketing Surveillance Practice
GVP	Good Veterinary Practice
J-MAFF	Japan's Ministry of Agriculture, Forestry and Fisheries
JVPA	Japan Veterinary Products Association
MHLW	Ministry of Health, Labour and Welfare
NADA	New Animal Drug Application
PMS	Post-Marketing Surveillance
R&D	Research and Development
SLP	Synthetic long peptide
VICH	Veterinary International Cooperation on Harmonization (of Technical Requirements for Registration of Veterinary Medicinal Products)

Report prepared by Koji Oishi of JVPA (Japan Veterinary Products Association) www.jvpa.jp 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

Health for Animals
global animal health association