GLOBAL BENCHMARKING SURVEY 2015

Benchmarking the competitiveness of the global animal health industry

Europe report

A report produced by

BioBridge®

for HealthforAnimals and IFAH-Europe

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HealthforAnimals
GLOBAL BENCHMARKING SURVEY
2015

Europe

Benchmarking the competitiveness of the animal health industry in Europe

A report by BioBridge Ltd
for HealthforAnimals and IFAH-Europe

BioBridge Ltd
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Available separately

1 The HealthforAnimals Global Benchmarking Survey 2015 – Europe Summary

For the purposes of this report 'Europe' is understood to mean the European Union.

13 international companies participated in the survey, of which 9 are MNCs (Multinational companies), and 11 of these participated in the interviews. Key findings were:

Innovation

- In 2015, the majority (69%) regarded the impact on innovation of the regulatory environment in the EU (European Union) as negative. This is a marked deterioration in opinions compared to 2011, when 36% were negative or very negative. Survey comments indicate the three most important factors are the restrictions on obtaining registrations for certain types of product, the regulatory framework itself and insufficient data protection. Specific areas identified as the major barriers included requirements for environmental risk assessments and requirements for antibiotics relating to resistance. Interviews point to uncertainties for NPD (New Product Development), largely arising from Europe's activities on antimicrobials, the uncertainties created during the period until the finalised new Regulation is adopted, and the lack of clarity on future data protection.
- The average R&D (Research & Development) spend in 2014 was 7.8% of global turnover (versus 7.7% in 2011 and 9.5% in 2006).
- The single biggest factor adversely impacting innovation, from the interviews, is the amount of money that needs to be spent on defending and maintaining products, and especially the costs of manufacturing, compliance and variations.

Regulatory landscape and dynamics

- Since 2011, the major change in the European regulatory landscape is the proposed new Veterinary Medicines Regulation. The on-line survey provided over 50 comments covering the positive effects companies hoped this would have (63%), the concerns they still had about its effectiveness and impact on the industry (31%), or 'wait-and-see', concerning the large number of implementing acts that will be needed, whose shape and content are unknown at present (6%).
- The positive comments were mainly about the promise of streamlined and harmonised processes and procedures and better alignment between Member States (84%), additional data protection (80%) and labels and packaging simplification (100%).
- The negative comments mainly concerned antimicrobials (100%), problems foreseen with SPC (Summary of product characteristics) harmonisation (75%), the maintenance of the current CP/DCP/MRP/national quadripartite system (Centralised Procedure, Decentralised Procedure and Mutual Recognition Procedure) and individual concerns over aspects such as distribution, generics, the cascade system and more intensive interpretation of requirements for environmental risk assessments.
- Expectations about the impact of changes on administrative burden for pharmacovigilance were rather balanced (57% positive but 43% negative).

Specifics for Europe

- Although the average spend on Mandatory Defensive R&D (MDR&D) for EU respondents appears to be slightly lower than the percentage of global R&D in 2011 (35%), this is still very high at 29%. And the average disguises the fact that the spread was 6%-50%, with 5 companies spending an average of 45% of total R&D budget. Over half the companies noted an increase since 2011 and no company has reported a decrease since 2006.
    - One commented that, though their percentage spend had declined, this was because they had taken an active decision not to defend certain older products because of the regulatory environment.
- The main factors given in the survey to explain the increase in MDR&D absolute costs were referrals and product reviews. Interviews revealed product referrals have become far more important as a cause of concern for respondents, sometimes going hand in hand with difficulties in SPC harmonisation and Member State disagreements with indications previously approved by other Member States.
- An increasing autonomy of national authorities has been seen in the national phases of procedures, leading to last-minute demands for changes in labelling, and delays in issuing approvals from 2 months to as long as 8 months.
- Distrust between MSs (Member States) over complete acceptance of rapporteur reports is still noted, with the risk that last-minute objections and requests for changes, such as to the wording of product information and packaging, delay the process.
- Improved management of variations has been welcomed, especially work-sharing and grouping; acceptance of e-submission, increasing evidence of a benefit:risk balance approach and acceptance of Codex Alimentarius's agreements on MRLs (Maximum Residue Levels)[1] are all considered to be positive.
- By contrast, retention of the 'global marketing authorisation concept'[2] is almost unanimously regarded as very unhelpful, as this seriously undermines data protection, and new data transparency initiatives which undermine commercially confidential data and involvement of more parties, including public comment, in the registration process are widely regarded as unhelpful.

Positive aspects identified by the GBS 2015 survey in Europe include:

- Good experiences with the work-sharing and grouping processes for variations.
- A general reduction in the cost of NPD projects[3] (with the exception of livestock biologicals) – see also 'Market factors' box on next page.
- Continued satisfaction with the Centralised Procedure, on the whole, and with the Decentralised Procedure to a lesser extent, but still much less satisfaction with the Mutual Recognition Procedure.
- A cautious welcome for many aspects of the proposed Veterinary Medicines Regulation, including the approaches to data protection, pharmacovigilance, labelling and variation simplification and the potential for a unified dossier.
- E-submissions.
- The approach of the EMA (European Medicines Agency) to assisting innovations and learning more about them from companies.

1 Articles 3 and 14.3(b) of Commission Regulation (EU) No 37/2010 on maximum residue limits

2 Article 5.1 of Directive 2001/82/EC as amended by Directive 2004/28/EC.

3 This requires more in-depth investigation to elucidate whether there has been a reduction in the actual costs of the elements of NPD, or whether companies are simply targeting lower-cost products (for example, in Europe there has been a significant switch towards generic products by companies that historically have focused more on new products).

Issues identified by the GBS 2015 survey in Europe include:

- The increasing percentage of respondents compared with 2011 regarding the regulatory environment as negative for innovation.
- Serious concern about the future of antimicrobials and antimicrobial innovation, because of the current climate about AMR (Antimicrobial Resistance) in Europe and the approach to antimicrobials in the proposed Veterinary Medicines Regulation.
- Continued concern about fragmentation of the market by species and uses that make a high proportion of products relatively low-sale, versus the costs involved in maintaining and defending those products and the disproportionate regulatory burdens.
- The continuing increase in time from start of research to approval for new products, especially for livestock products.
- The unanimous view that environmental risk assessment requirements have a very adverse impact on innovation and on the continuation of existing products.
- The continuously-increasing power of other stakeholders, including politicians, NGOs (non-governmental organisations), interest groups and food retailers and providers, that threatens to take the place of science-based regulation, and has done, in the case of antimicrobials at national level.
- The absence of a guaranteed unified outcome in the EU, in that national agencies still have their own interpretations of EU-agreed guidelines; and industry experience is that, even after the close of procedures, they impose their own demands on top of those agreed in the DCP and MRP. Some also run to their own timescales to issue authorisations, significantly increasing time-to-market.
- No overall reduction of administrative burden, just a re-distribution to different activities.
- The referrals process and the major impact on defensive R&D costs.
- The continuing difficulties with national language labelling and difficulties in the use of single-language packs for multiple country markets.
- Negative aspects of variations, including the sheer numbers needed for minor changes in products such as excipients, or for changes in suppliers.
- The cost and resource requirements for the increasing pharmacovigilance demands.
- The retention of the global marketing authorisation.

Market factors identified in additional comment in the GBS 2015 interview programme in Europe:

- Continued consolidation in the industry – the top 3 at the time of interview commanding more than 50% of the market – but also in all elements of the chain from wholesalers to customers.
- 2011-2013 market was at best flat, even down, but 2014 onwards has been much more positive and economically dynamic.
- Organic growth is slower, so acquisitions of companies or products are increasing to create a broad enough portfolio. All companies now have generics, now competing in every segment, which may relate to the apparent reduced cost of NPD.
- There has been a huge level of money inflow, with investment in companies of all sizes, high multiples being paid for acquisitions and the realisation over the last 5 years that animal health is growing faster than human health.
- There is growing interest in medicated petfoods and animal nutraceuticals, with some associated regulatory difficulties.

Additional comments from interviews on **negative** aspects

- Many RAs (regulatory agencies) still have difficulties dealing with the uncertainties of innovative products, and may try to use human guidelines on developments such as biotech biologicals.
- The RAs of a significant minority of member states were individually recognised for their unreliability, slowness, insistence on national requirements or other difficulties; and some eastern European and Baltic states were noted as requiring national-language labelling and information, putting viability pressures on small-sales products for these small-size markets.
- The significant challenges presented by AMR will continue for the foreseeable future. The regulatory impact of AMR has had deep effects on company willingness to invest in innovation, not only in AMs; a main problem is seen to be ignorance of facts and the abandonment of science-based arguments by Governments and politicians.
- The draft new Veterinary Medicines Regulation is regarded as an evolution and not a revolution; there was concern that the opportunity hasn't been taken to rationalise the existing four procedures (CP, DCP, MRP, national).
- The relationship with EFSA (European Food Safety Agency) is seen as a growing problem, with slow response times and unpredictability.

Additional **positive** comments include:

- The larger RAs of north-west Europe are perceived as open to dialogue, with efficient processes and reliable outcomes.
- The AH industry is at the beginning of the Digital Revolution, but this could be pervasive, not just for sales channels but for data collection, feedback into NPD, recruitment of vets and trials subjects, tailored production and product supplies for specific customers and seasonal profiles, and increasing the links between vets and their customers.

Future actions have been identified:

- The industry should be involved closely in developing the implementing Acts for the new Veterinary Medicines Regulation.
- Alignment and forced harmonisation of EU Member States is needed to make the new Regulation work.
- Close attention is needed to ensure that old but well-used, safe and effective products do not get regulated into non-viability and withdrawn from the market.
- PV reporting should ensure it is in context, ie not just number of cases but incidence compared with usage (per-dose reporting), and signal identification processes should be designed and agreed in consultation with companies, not imposed.
- HealthforAnimals & IFAH-Europe could work with vets and farmers, who need new products, to develop a broad platform advocating for science-based innovations.
- IFAH-Europe could arrange seminars or workgroups on medicated petfoods and nutraceuticals, Digital Technology in the 21st century, Risk Contextualisation & Communication and other emerging topics.

2 The HealthforAnimals Global Benchmarking Survey 2015 – core findings for Europe

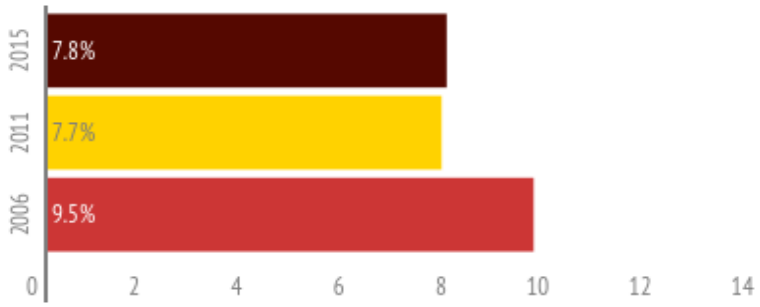
Company profiles

2015 is the 5th time that IFAH-Europe has participated in the GBS. 13 companies were involved in GBS 2015, 2 more than in 2011. All are international companies or their subsidiaries. 77% have their headquarters in Europe and 23% are subsidiaries of US-based multinationals.

R&D spend

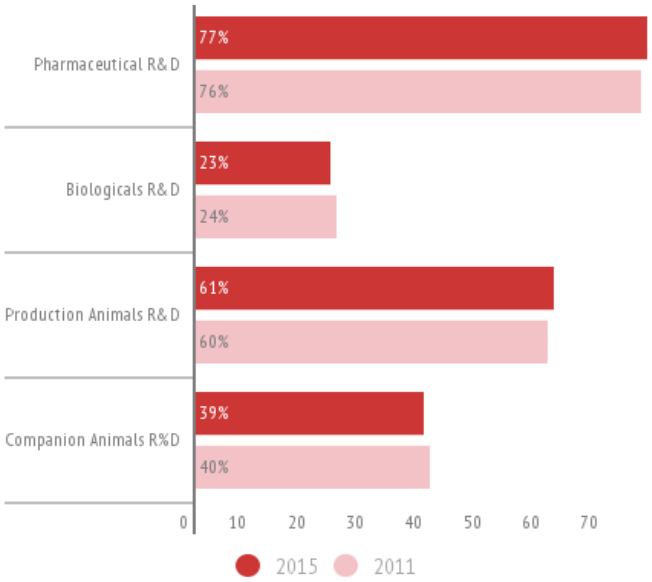
An average of 7.8% of turnover spent on R&D each year was reported for 2015, only slightly different from 2011's figure (**Figure 1**). This appears to confirm a trend in a step change from the typical figure of approximately 10% reported in the 1996, 2001 and 2006 surveys, to the reduced value of 7.8%. The possible causes for this change warrant further investigation.
As a percentage of the overall sales reported in the GBS 2015 by respondents in Europe, this amounts to approximately €1.24B.

Figure 1. R&D as a percentage of global sales – Europe 2006-2015



The overall split between pharma and bios products appears to have hardly changed since 2011. However, 5/13 respondents (38%) are primarily or completely vet pharma companies; for the 8 mixed-range companies, the adjusted R&D split is 63% pharma, 37% bios, reported as '2015 adj.' in **Figure 2**.

Figure 2. Percentage of global R&D spent on pharma vs. bios products & on production and companion animal projects– Europe 2011-2015



The proportion of total R&D contributed by companion animal projects has continued to fall since 2006, down from 45% to 40% in 2011 to 39% in 2015 (also shown in **Figure 2**). This seems anomalous given that the companion animal sector is booming, but may represent the relative costs of carrying out work on the two different categories of species (i.e. the increased costs of NPD for livestock).

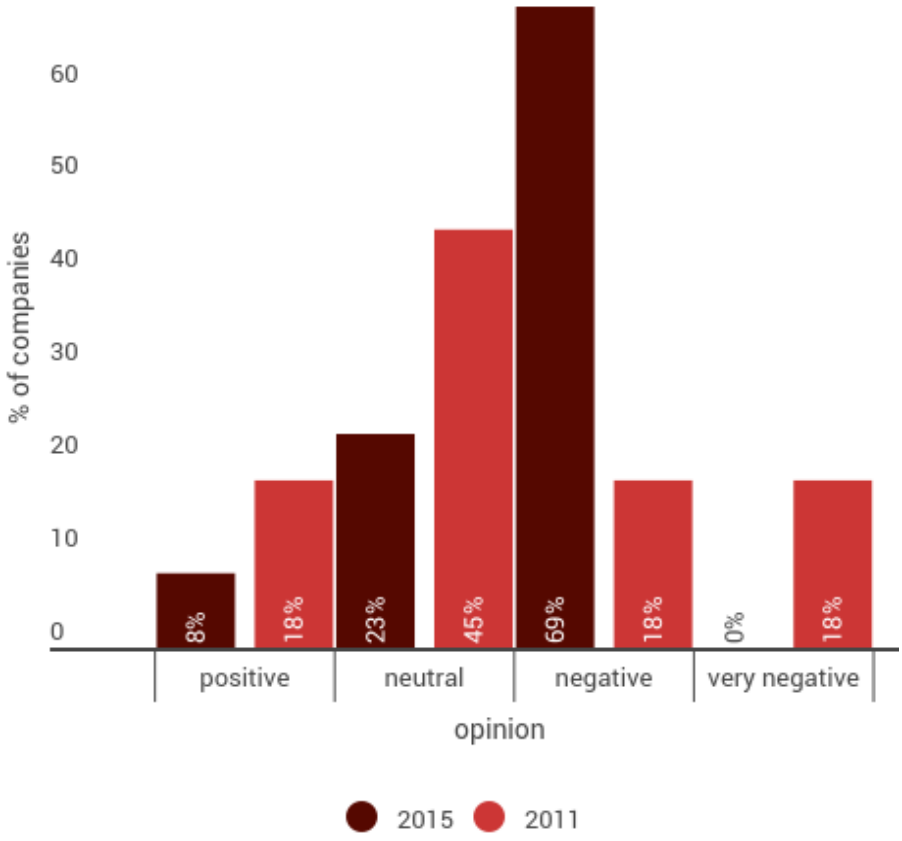
Regulations and innovation

Innovation is generally recognised as the development of new molecules, new technologies, new formulations and routes of administration. However innovation may also be seen as a new product for a company using an existing active ingredient.

The majority of respondents in 2015 regard the regulatory environment as negative towards innovation, 69% compared with 36% in 2011 (though half of these classed the environment as very negative then). The percentage regarding it as positive fell from 18% to 8%, suggesting an overall worsening of opinions and experience (**Figure 3**). This is in spite of general agreement in the interviews that the current authorisation procedure, especially the Centralised Procedure, is predictable and effective. \However, this is conditioned by the experience of rising demands for maintenance and compliance, for pharmacovigilance, and the increased costs of ecotoxicity data for ERAs (Environmental Risk Assessments) , as well as the lack of harmonisation between national agencies.

The RAs of Italy, Spain, Greece, Denmark, Poland and Croatia were individually recognised for their unreliability, slowness, insistence on national requirements or other difficulties; and Estonia, Latvia, Lithuania, Slovenia, Hungary and Bulgaria were noted as requiring national-language labelling and information, putting viability pressures on small-sales products for these small-size markets. The RAs of UK, Ireland, Germany and France are perceived as open to dialogue, with efficient processes and reliable outcomes.

Figure 3. Impacts of the regulatory environment on innovation – Europe 2011-2015



The impact of specific areas of regulations on the industry's ability to innovate is summarised in the following table showing the top 4 positive areas and the top 4 negative areas, together with a figure that represents its perceived relative helpfulness[4].

Top 4 positive areas	RHS	Top 4 negative areas	RHS
1. Centralised procedure	+85%	1. Environmental risk assessments	-100%
2. Decentralised procedure	+54%	2. AMR requirements	-58%
3. Patent protection	+38%	3. Protection of technical documentation (data protection)	-23%
4. Mutual recognition procedure	+23%	4. Maximum residue limit data requirements	-23%

All the positive areas have increased their relative helpfulness scores since 2011 while all the scores for the negative areas have become worse.

The survey also investigated those regulatory reforms that are expected to have the highest impact on a company's ability to innovate, and to what extent these reforms have been achieved (see question E1 in appendix 3). It is striking that the reform that is expected to have the greatest impact – i.e. an improved data protection package (protection of technical documentation) – is also the reform that has been least achieved; this is a major negative outcome for industry.

Mandatory Defensive R&D (MDR&D)

Mandatory defensive R&D is the cost of studies and regulatory activities necessary simply to keep a product on the market. This is represented by the costs of new data requested by authorities, particularly at product reviews, referrals and renewals, and any compulsory variations that follow the assessment of these new data.

Although overall the situation seems to have improved since 2006 & 2011, with a decline from 35% to 29% of total mandatory defensive R&D expenditure (**Figure 4**), figures for individual companies range from 6% to 50%, and the 5 biggest spenders averaged 45% of their total R&D spend on MDR&D. In the survey, no company reported a decrease in MDR&D spend since 2006. A greater proportion of respondents reported an increase in MDR&D spend than in 2011, 54% vs 47%. In fact, almost a quarter of companies in 2015 reported that it had increased a lot (**Figure 5**). 76% of companies gave 'increased referrals' as a highly important cause of increased MDR&D expenditure. This is a subject of great concern for the companies surveyed.

One company reported that in fact it had reduced its MDR&D expenditure from 30% in 2011 to 21% in 2014, not because the situation had improved, but because it had decided to spend fewer resources in defence and maintenance of existing products.

[4] RHS – total percentage of companies regarding a procedure or requirement as helpful or very helpful minus the total regarding it as unhelpful or very unhelpful.

Figure 4. Mandatory Defensive R&D as a % of total R&D

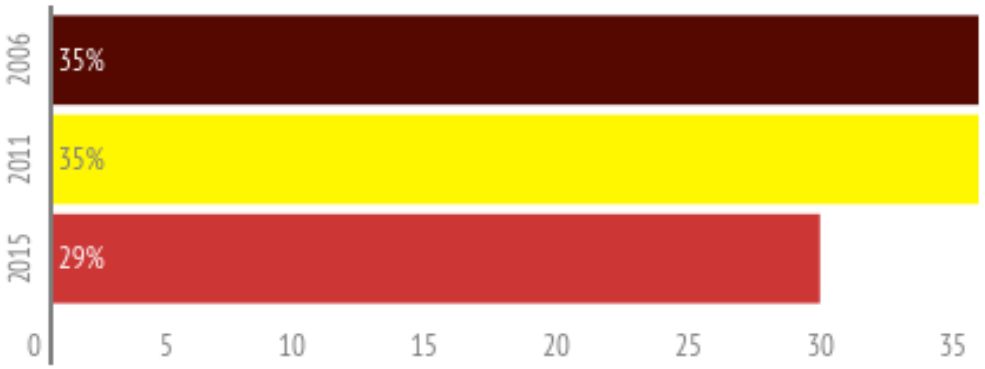
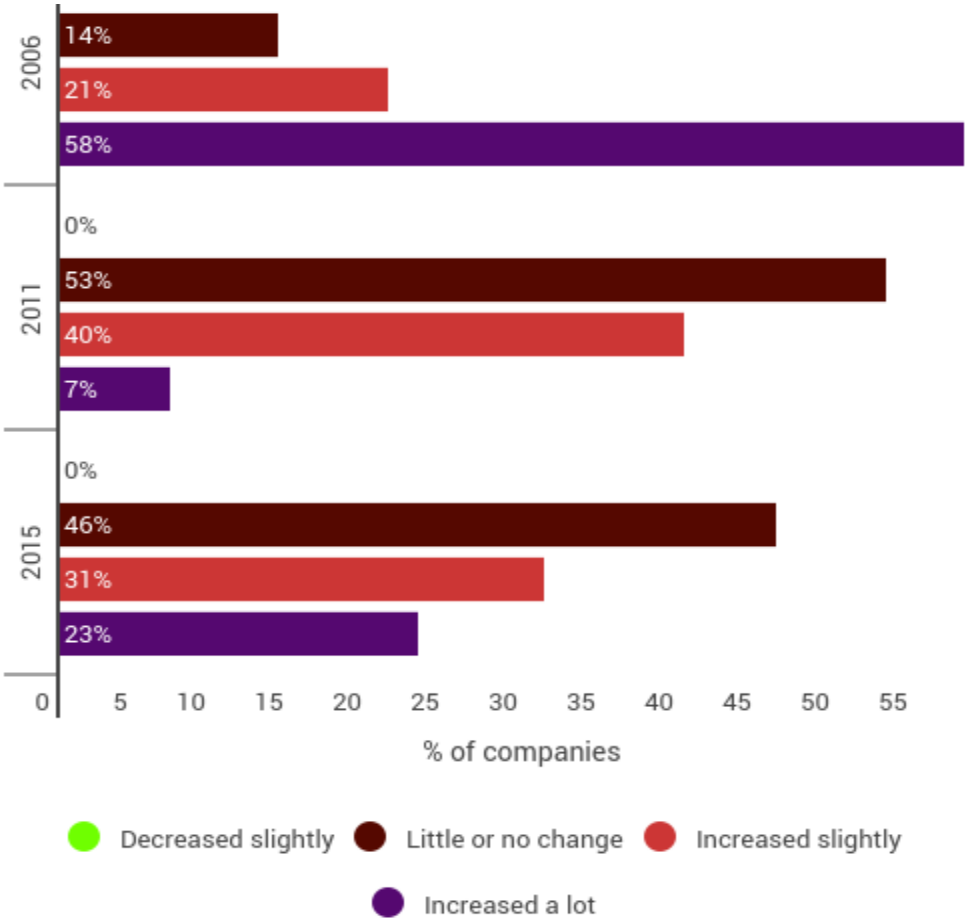


Figure 5. Change in amount of MDR&D spend – Europe 2006-2015



New Product Development (NPD)

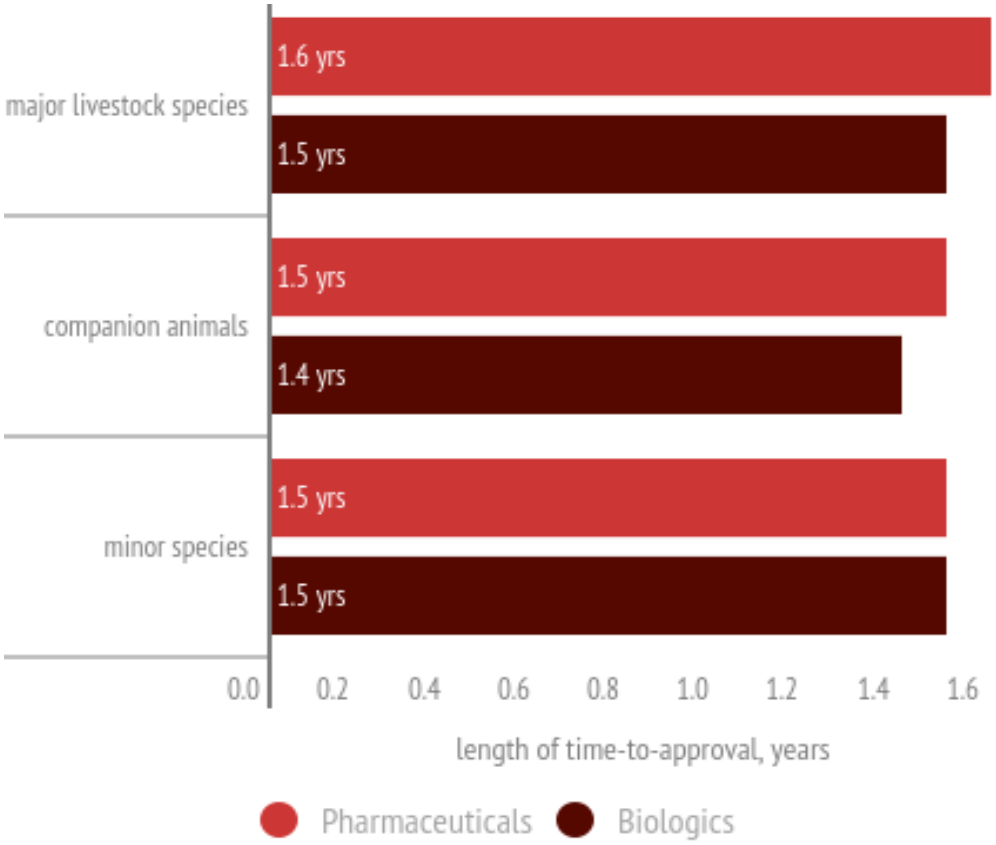
Data was provided on products for PAPs (products for major livestock/production animal species, CAPs (companion animal products) and MSPs (minor species products).

Time for New Product Development

The NPD times are examined in two ways: (a) the time of just the regulatory step - the time to approval – which is the time from the submission of a dossier to the authorities until a marketing authorisation is issued by the authorities, and (b) the total time for NPD, from the beginning of the research project until a marketing authorisation is obtained.

Looking at just the regulatory step, 41 examples of dossier **times-to-approval** were provided, 27 for pharmaceutical products, 11 for biologicals, two medicated feed products and one pesticide-based product. Generally the regulatory approval step for pharmaceutical and biological products took approximately 1½ years (**Figure 6**).

Figure 6. The average length of time to gain registration for a major new product from dossier submission to approval – Europe GBS 2015



19 PAPs, 14 CAPs and 8 MSPs were included in the 41 examples. The average time-to-approval has reduced a little compared with the average reported in GBS 2011 (**Figure 7**). For PAP and CAP biologics, and CAP pharma products, there is indeed no reported change, while for PAP pharma, CAP biologics and MSP pharma a small reduction is recorded (the statistical relevance has not been investigated).

For the pesticide-based products there is a single example in 2015 so no conclusions on trends can be drawn, although it is noted than pesticide-based products were reported to take on average 2 years to approve in the 2011 survey.

The full NPD process from research to first approval takes at least an additional year for a major livestock species in 2015 compared with 2011. For companion animal products and minor species the increase in development time is still seen but usually in the order of ½ year (**Figure 8**).

In summary, the NPD times have increased for all product types and animal types (significantly for production animals) while dossier assessment times have reduced marginally.

Figure 7. Changes in time-for-approval of dossiers – Europe 2011-2015

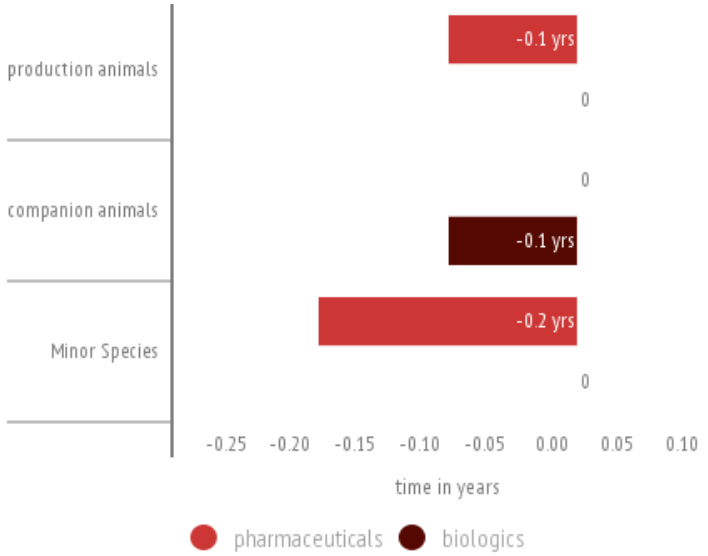
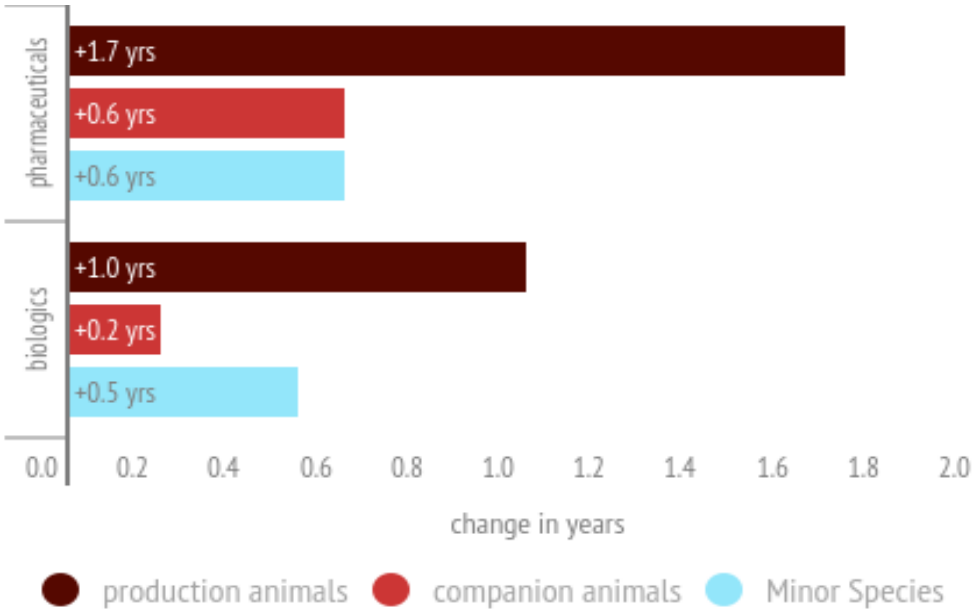


Figure 8. The average change in time for NPD (New Product Development) from research to first approval – Europe GBS 2015

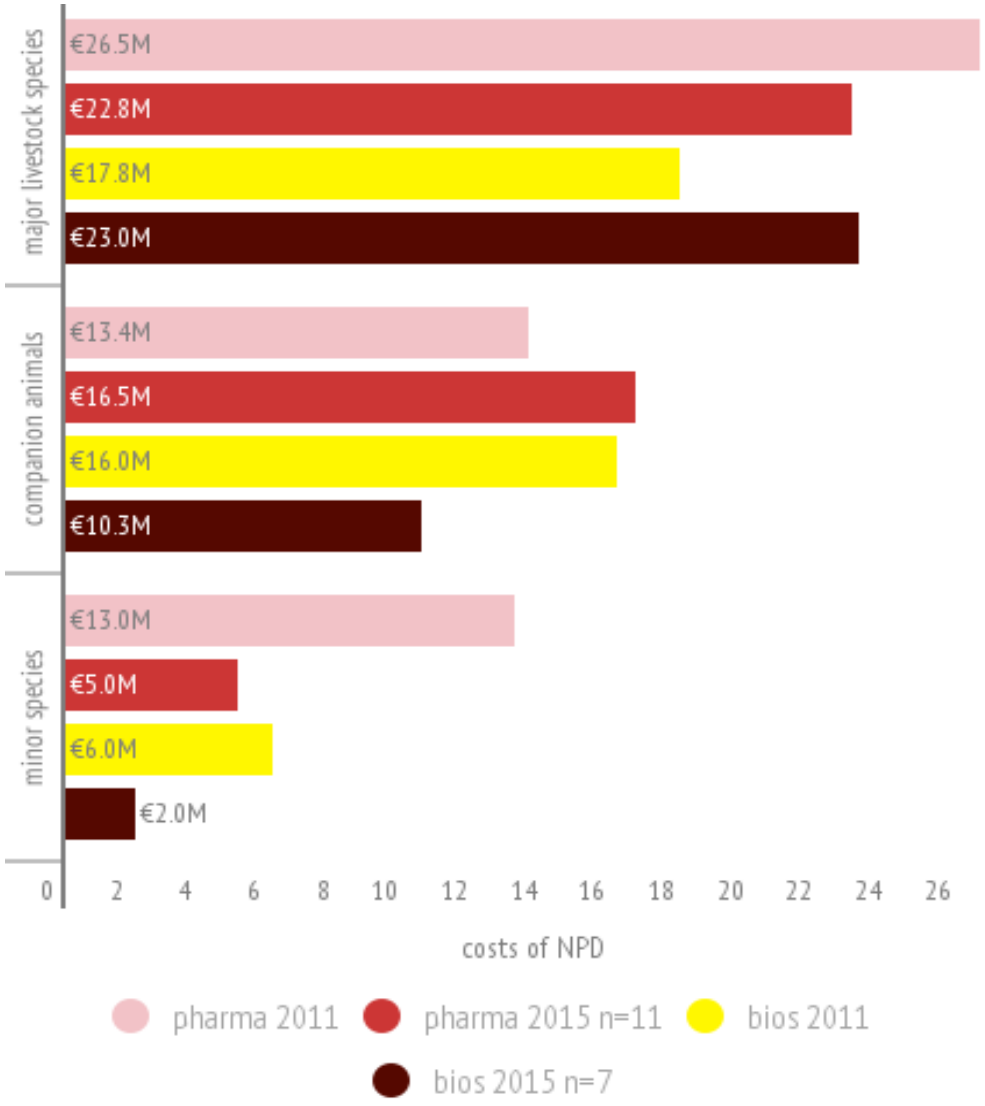


The costs of New Product Development

Companies provided 18 examples of costs of NPD, 11 for pharma products and 7 for biologicals. No examples of pesticide-based products were given. Compared with 2011, it is a mixed picture. The 2 examples of reported costs for MUMS NPD are much-reduced compared with 2011, but the overall comment on MUMS products is that that data demands are still as onerous, making MSP development unattractive. The costs in the examples provided for pharma PAPs and biological CAPs were lower, by an average of 14% and 36% resp. But the averages shown here disguise individual cases of products (pharma and biological PAPs and pharma CAPs) with reported costs as high as €49M-€62M, compared with a similar high-band of €48M-€50M in 2011. These high cost products are likely to be associated with new molecules or new technologies.

Adjusting by removing this band of high cost projects results in averages for PAP and CAP pharmaceutical NPD of €9.8M and €9.6M respectively, and for PAP and CAP biological products of €10M for both types, all roughly the same.

Figure 9. Costs of NPD for pharma and bios products – Europe 2011 & 2015

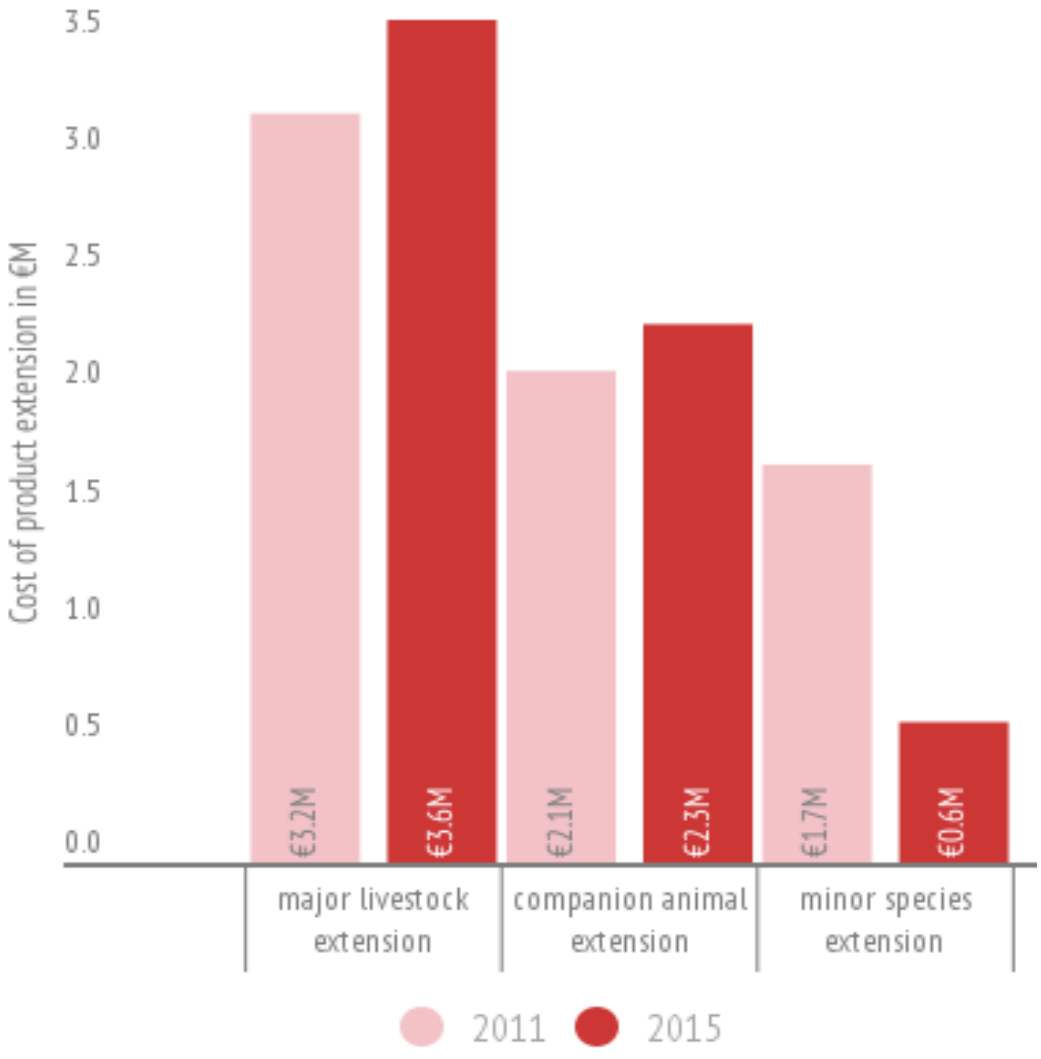


The costs of product extension

Companies reported 17 examples of pharma product extension, 9 for major livestock species claims, 6 for companion animals and 2 for minor species; there were no examples of biological products, but one medicated in-feed PAP, one pesticide-based PAP and one pesticide-based CAP. MSP extensions appear to have reduced considerably in cost; the increases in CAP and PAP extensions, at just over 10%, are only slightly over the cumulative rate of inflation, about 8% from 2010-2015 (**Figure 10**).

Overall little has changed, except MSP extensions cost less. A PAP extension costs approximately 35% of the NPD cost on average.

Figure 10. The average costs of adding a new claim or use to an existing product – Europe 2011-2015



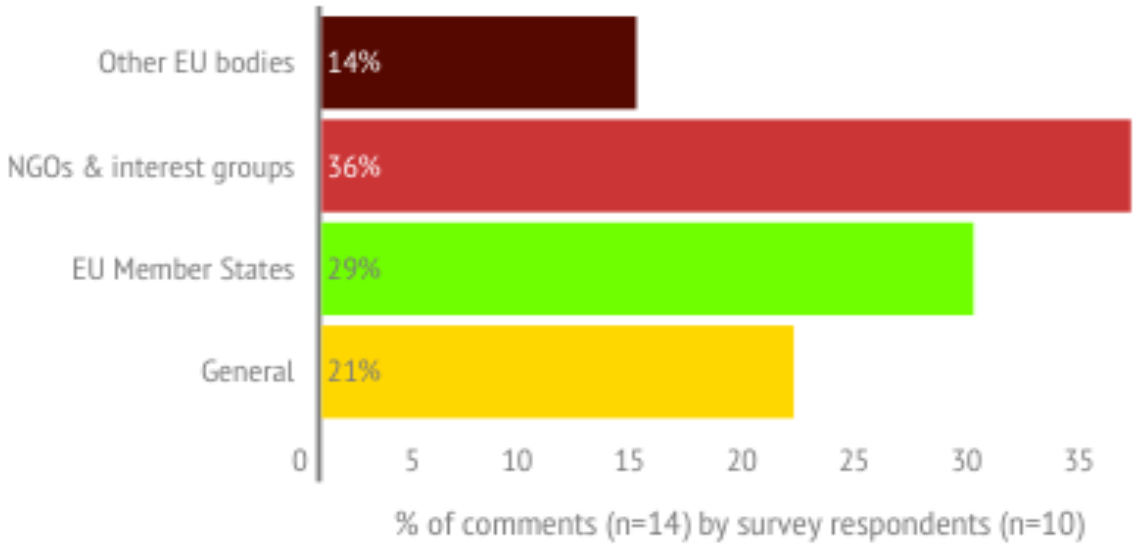
Stakeholders and their influence

Political and stakeholder involvement in regulatory process continues to be a substantial issue for industry (**Figure 11**), with 77% of the respondents reporting this, compared with 88% in 2011. The concern is that the interventions of NGO and politicians tend to push the regulatory framework away from science-based decision making towards risk adverse regulations.

Other EU bodies, notably EFSA, are regarded as having a very detrimental effect on animal health products; NGOs and other interest bodies command the highest share of comments, for involvement in issues such as ecotoxicology, antimicrobials and food safety, and are seen as having an adverse impact via regulators on data requirements and regulatory predictability.

Member State parliaments, politicians and agencies make national decisions impacting Veterinary Medicinal Products, such as the French 'Loi d'avenir' concerning antibiotics, and the assessment of ecotoxicology in Germany, where a separate body assesses the environmental risk independent of any benefit:risk assessment by the responsible national competent authority. The industry also sees discussion and decisions taking place in the general business and public environment that are often in the absence of any knowledge of the existing regulatory framework, and are based on non-scientific arguments.

Figure 11. Stakeholders and their influences – Europe GBS 2015



Regulatory changes still wanted for the future

These include not only overarching changes, such as improvements to processes and procedures and a more determined effort for harmonisation, within the EU and internationally, but also attention to the two specific areas of pharmacovigilance and data protection (**Figure 12**):

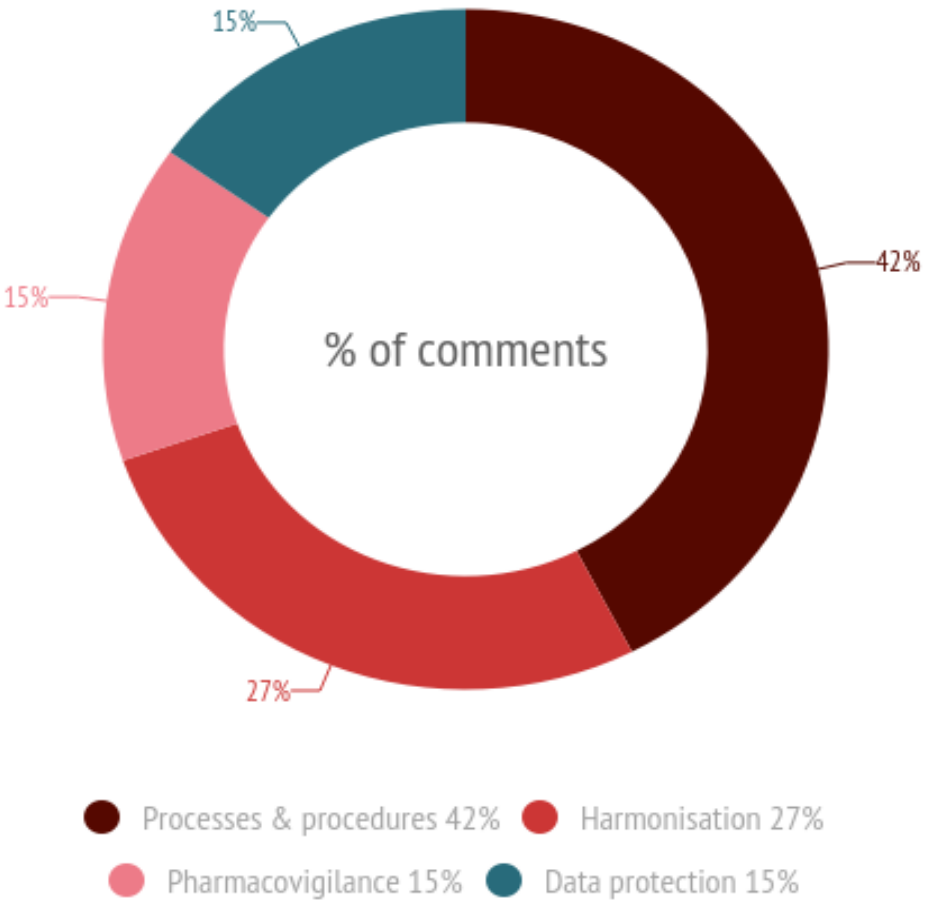
- more pragmatism
- risk- and science-based decisions
- more dialogue with rapporteurs and during scientific advice
- better SPC harmonisation processes
- involvement of industry in the implementing Acts for the new Regulation
- much better harmonisation between Member States
- more global alignment
- single-dossier, single-process
- removal of PSURs (periodic safety update reports) for PV (pharmacovigilance)

- reduced PV requirements, ensuring incidence rates and not individual numbers of adverse reactions are available to the public
- better data protection for antibiotics, to encourage continuing investment in microbial disease control
- additional data protection for new species and for additional indications for existing species.

The regulatory reform identified as potentially having the greatest impact on a company's ability to innovate, while showing the lowest score for having been achieved, is regulatory data protection (see figure E1 in appendix 3). For existing products the most important changes, in terms of a high relative impact and a low score for having been achieved, are basing dossier reviews solely on pharmacovigilance data and other relevant progress in science (see figure E2 in appendix 3). The majority of expected regulatory improvements that have yet to be achieved occur in the areas of reducing the administrative burden and greater harmonisation between member states (see figure E3 in appendix 3).

Regulations have had the most impact on the following business decisions: reduced product range in Europe and reducing the coverage of species in Europe, with both reported by 100% of surveyed companies (see figure E5 in appendix 3).

Figure 12. Regulatory changes companies would like for the future – Europe GBS 2015



3 The HealthforAnimals Global Benchmarking Survey 2015 – global review

Introduction

Since 1996 HealthforAnimals has been reviewing and benchmarking the status of the different regional regulatory frameworks for veterinary medicines, the impacts these have on the industry, and the practices and impacts of the regulatory processes.

The Global Benchmarking Survey (GBS) 2015 focuses on animal health and veterinary products in the following sectors: pharmaceuticals, in-feed medicinals, biologicals and pesticide-based products. It does not consider nutritional products, feed additives that are not regulated as therapeutics, or non-regulated semi- or pseudo-medical products used in animals.

Information has been obtained from companies through an on-line survey and interviews and is anonymised. The survey has the same core of questions from region-to-region, but is tailored to each region. Interviews were held with business, regulatory, R&D and Government Affairs heads, plus interviews with company leaders on the HealthforAnimals Board for a global view.

- GBS 1996 + 2001: Europe USA
- GBS 2006: Europe, USA, Australia, Canada, Japan
- GBS 2011: Europe, USA, Australia, Canada, Japan - 60 surveys, 72 interviews
- GBS 2015: Europe, USA, Australia, Canada, Japan, China, Brazil - 73 surveys, 67 interviews

A total of 99 companies' representatives were invited to take part in the on-line 2015 GBS, representing HealthforAnimals regional member organisations and some local companies. The on-line survey return rate was 74%. The Japan, China and Brazil regional surveys were translated into local language to aid communication.

This report contains:

1. Summary
2. Positive aspects
3. Negative aspects
4. Markets
5. Key findings
6. The future and suggestions for action
7. Methodology

Summary

The Global Benchmarking Survey 2015 covers the following 7 countries or regions: Australia, Brazil, Canada, China, European Union, Japan and USA. The survey has collected 73 survey responses and 67 interviews, from 10 multinational companies and their local subsidiaries and 20 local or regional companies.

Introduction

1. The Animal Health (AH) industry, in addition to benefiting the health and welfare of animals, has direct impacts on human and social health via the safety and security of food and the relationship with pets. The provision of safe, effective medicines – pharmaceuticals, biologics, feed products and parasiticides – is a vital part of that function.

2. Regulatory regimes can make or break the industry's ability to fulfil its function in an effective, cost-efficient and sustainable manner. A prevalent concern is that regulatory expectations for AH products are conditioned by human pharmaceutical frameworks, guidelines and procedures and are inappropriately applied to animal health products. The AH products market is estimated at $24B in 2015, about 2.5% of the global human health market. The diversity of species and types of business continue to provide a challenge of how to manage small and larger markets, niche and major products, and routes-to-market, given the costs of regulatory burdens.

3. Two of the important factors which stand in the way of industry investing in innovation are: the investment required to ensure that data packages are valid for all parts of the world relevant for the marketing strategy; and the very significant expense of maintaining products on the market (consuming on average 15-39% of the available R&D budget depending on the region).

4. Contrasting the US with the EU, issues identified in 2011 have not gone away, for example incompatibilities in e-submission requirements, need for trials protocol approval in US, different approaches to statistical methodology and validation of quality methods, absence of timetables in US compared with the EU and different approaches to data protection periods, with US much less favourable. Positive aspects in the US, including the staged submission process and the regulatory and public acceptance of biotechnology for vaccines and API (Active Pharmaceutical Ingredient) production, are not necessarily compatible with processes, procedures, dossiers and product acceptance in other regions.

5. Globally there are some highlights of improvement but there remain tremendous areas of concern, notably the failure of harmonisation to make progress. VICH continues to aim for mutual recognition of standards and data. While there is mutual recognition and information-sharing in some topics or actual cooperation in assessment in others (e.g. between Canada and USA for pharmaceuticals and some pesticidal products), the differences in expectations and approach between the 3 parties, USA, EU and Japan, mean there is still no prospect of a single dossier, or even a core technical dossier (CTD or common technical document), that would be accepted as-is across the three territories. Brazil and China are not main members of VICH and are thus not fully-involved in all discussions and agreements, as their importance would suggest, but are part of the VICH Outreach Forum.

6. GBS 2015 interviewees note an apparent local protectionism in China and that China and other countries were at risk of putting regulatory systems in place that took what they liked best from other countries, making it very complex and very demanding to get approval for new products. Markets such as Brazil and Australia were seen as more conservative than the US towards innovation, and companies had IP concerns over the amount of data and material such as antigen strains demanded by China.

7. Over the past 4-5 years, the biggest external challenge has been the continuously mounting pressure on the use of all antibiotics in animals. In the contentious debate between the industry's science and politicians' decisions, the voice of science has often not been heeded. Whilst continuing political pressure might result in novel non-antibiotic ways of controlling or preventing disease, the current situation also introduces tremendous strategic and financial uncertainty into the industry. In the absence of a list of antibiotic classes that can be developed for animal health use, because they are not likely to be of value for human treatment, companies who have spearheaded the present portfolio of modern antimicrobials cannot risk investment in developments that might be banned at some unknown point in their pathway to the market, with incalculable cost.

8. Planning for innovation remains difficult. Regulatory assessors might not take account of special characteristics of innovations, because there are no precedents in guidelines, or the agency lacks staff with expertise in that type of innovation. In 2011, industry suggested that there could be a real advantage in improving and expanding the coordination of scientific advice that occurs already to some extent between FDA and EMA, across global regulatory agencies, certainly within the VICH model, to improve all the coordination of regulating new technologies and the accompanying communication strategy that needs to occur. This suggestion remains valid today, as does the concept of fast-tracking innovative new products (as in Brazil) or offering conditional licences for any innovative new product, subject to additional data provision, eg on shelf-life and post-marketing surveillance.

9. But business innovation is increasingly coming from activities that might not be regulated, such as providing tailored diagnostics, business management support for practices, or nutraceutical products for food animals. The Digital World and its accompanying media are upon us. Understanding and taking advantage of this, exploring and accepting the concept of Big Data management, and exploring the Internet for items of relevance to the AH industry will require innovative approaches and a change in corporate mentality. This was prefigured in 2011 by one or two interviewees, but is now a compelling area for AH companies to grasp and run with.

10. Interviewees and survey respondents have made suggestions for the future for policy improvements, performance and processes that will aid the drive to greater global harmonization without reducing product safety and quality:
    - Deeper more consistent application of risk-based approaches, and product-appropriate risk:benefit analyses that determine the regulatory requirements, are important targets. Increased accessibility of agency staff for discussion and advice on new technologies and new products before submission would assist this.
    - Transparency, predictability, efficiency and flexibility of agencies, with enhanced staff training and expertise and increased staff numbers, are seen as critical for agencies to overcome the disruptive effects of changes in regulations and guidelines, and to become innovation-ready.
    - Expanding e-submissions and inter-agency working, and mutual recognition of GCP, GMP, high-quality foreign data and approvals from well-regulated countries.

- Streamlining of excessive regulation of minor or frequent changes to products and manufacturing, and shortening timescales for approving applications for changes are seen as important steps to reducing the costs of maintaining products on the market.
- There are examples of regional regulatory practices that may be transferrable from region to region as part of future improvements.

Positive aspects

11. The effects of government regulations on preventing dangerous products from reaching the market and providing assurance about safety and high quality of AH products from legitimate, regulated companies.

12. The overall belief that agencies base their approvals on expert evaluation of all quality, safety and efficacy data.

13. Increasing acceptance of foreign data produced according to GLP, GCP or VICH guidelines, though foreign-format dossiers are generally not yet accepted.

14. The trend to acceptance of e-submissions, although there is concern about incompatibility of data format demands and system structures between regions.

Australia positives

- Improved timeliness, responsiveness and handling of import permits for biologicals by AQIS (the Australian Quarantine and Inspection Service).
- The onward impacts of the AVCLAA (Agricultural and Veterinary Chemicals Legislation Amendment Act 2013) and related legislation, including removal of re-approval and re-registration requirements and possibility of lists of notifiable variations, streamlining the handling of post-approval requirements, and stock and pet feed reform.
- Considerably improved industry relations at APVMA under new CEO, with potential for further improvement related to intake of new staff.

European Union positives

- Continued satisfaction with the Centralised Procedure.
- Good experiences with the work-sharing and grouping processes for variations.
- A cautious welcome for many aspects of the proposed Veterinary Medicines Regulation, including the approaches to data protection, pharmacovigilance, labelling and variation simplification
- The RAs of UK, Ireland, Germany and France continue to be perceived as open to dialogue, with efficient processes and reliable outcomes

USA positives

- Continued satisfaction with adherence to ADUFA timelines and standards and, in general, the CVM's predictability.
- The CVM is proactive in seeking discussion of innovations; it has also consulted industry for the GFI (Guidance for Industry) 209 and GFI 213, which have helped the situation with Use of Antimicrobials.
- The commitment by the regulatory agencies to more rapid approval of generic products is a positive.
- The actions of APHIS CVB (USDA's Animal and Plant Health Inspection Service's Center for Veterinary Biologics) on vaccine reference re-qualification and willingness to pursue *in vitro* rabies vaccine release.

Japan positives

- Stabilization or a fall of up to 6 months in the time-to-approval for most types of products, except pharma PAPs.
- Acceptance of clinical studies from VICH member countries is helpful, in terms of time to approval, compared with companies using overseas data.
- J-MAFF has followed an active policy of deregulation, 20 of 25 reforms have been achieved since 2012 in many areas, which have saved costs and time.
- J-MAFF has made it easier for companies to apply to switch a human product to animal health use without clinical study.
- J-MAFF has a positive attitude for information exchanges.

Canada positives 

- Continued improvement in the review times applied by the Veterinary Drugs Directorate (for pharmaceutical products) and Canadian Food Inspection Service (for biological and in-feed products).
- The Low Risk Products programme, originally for certain CAPs and now to be extended to PAPs.
- Proposed action against Own Use importation and compounding of APIs and against unlicensed claims for in-feed products.

Brazil positives 

- Introduction of processes for fast-track review and approval of innovative products.
- Introduction of e-submissions.
- Openness to biotechnology-derived products.
- Greater emphasis on traceability of products and their use, favouring companies with higher procedural and quality standards.

China positives 

- 50-78% of companies had seen little change in time for full new product development cycle from first research to approval since 2011 and a significant proportion of companies had experienced little change or a fall in development costs for new PAPs.
- Discussions concerning a specific regulatory approach for companion animal products.
- Promised new rules for field studies, reducing the number of animals required from the current rather high requirements e.g. 10,000 per trial.

Negative aspects

15. Lack of pre-submission dialogues and advice on choice of regulatory options, in many countries.

16. In many but not all countries, insufficient staff and inappropriate or inadequate training of staff within agencies, especially for manufacturing inspections and ability to deal with innovations.

17. In some countries, lack of transparency of the review and approval process.

18. Failure of agencies to contact applicants proactively to discuss new developments (information or regulatory procedures) that might impact the review and approval of their product.

19. Increasing industry concerns that AH manufacturing inspectors in many countries are applying inappropriate human product-based criteria and benchmarks and inspection timelines are increasingly not aligned with dossier review timelines.

20. Continued failure of certain agencies to adapt their approaches according to the type of product (PAP, CAP or MSP; innovative, new-to-market or generic), stage of product (full approval or post-approval change) or product specific risk profile and benefit:risk analysis.

21. Inability of either applicant or primary agency to influence the quality or timeliness of delivery when other agencies are involved in approvals, whether these are other national/federal agencies or are at state or provincial level.

22. The ability of outside bodies such as politicians, competitors, food companies, NGOs and other governmental agencies to influence the regulatory process, including political actions on Antimicrobial Resistance and parasiticides, and trade-driven impositions of longer withdrawal periods for exported livestock products.

Japan negatives 

- For PAPs, companies hoped J-MAFF, FSC and MHLW would evaluate dossiers in parallel and shorten approval times. This hasn't happened and there is continued poor predictability and quality of performance of MHLW and FSC. Added requirements for residue confirmation studies for generic PAPs, and review of field studies beforehand to set withdrawal periods, will give more delays.
- For bios, continued requirement for live animal potency tests in product development and in batch quality testing is seen as an important concern. Removing this would harmonize standards with EU and USA and also considerably reduce costs, time and unnecessary use of animals.
- The Conditional License applies only to regenerative therapy products, but it would be helpful to have this for other types of product, to accelerate innovation.

European Union negatives 

- Serious concern about the future of antimicrobials and AM innovation, because of the current climate about AMR in the EU and the approach to AMs in the proposed Vet Meds Regulation.
- Unanimity that requirements for environmental risk assessments have very adverse impacts on both innovation and existing products.
- The costs involved in maintaining and defending products.
- The disproportionate regulatory burdens and costs involved in servicing small Member-State markets.
- Continued freedom of Member States to impose their own conditions, begin referral processes despite majority agreement at European level on marketing authorisations and usage conditions and take too long to issue national approvals.
- The relationship with EFSA for PAPs is seen as a growing problem, with slow times and unpredictability.

Canada negatives 

- Health Canada's Drug Establishment Licensing practices and processes for APIs and production, including inspections and listing of foreign sites, cause significant problems, including overlong review and listing period of 250 days, which is out of step with the VDD regulatory process.
- The PMRA's management of the environmental impact review for new chemicals and APIs is regarded as inefficient, requiring improvement. For veterinary pharmaceuticals, the regulators' approach to ecotoxicology is not aligned with VICH guidelines, causing difficulties in industry's ability to comply with New Substance Notifications, has added on-hold periods to reviews, and imposed a public consultation period for new actives.

Brazil negatives 

- Although VICH studies are accepted, all the raw data for all analytical and clinical studies has to be provided. There aren't enough staff at the Agency to review this.
- A very low percentage of respondents regard the regulatory environment as positive for innovation, in spite of the new fast-track procedure.
- Respondents found that MAPA reached consistent satisfactory levels for only 2/19 criteria for predictability and quality of performance. In bringing the regulatory system up-to-date, MAPA has produced uncertainty and lack of predictability, eg the failure to publish a number of decrees and INs that are anticipated by industry as part of the new Veterinary Medicines regulations, or to institute new INs in a logical progression.

USA negatives 

- Still difficulties with FDA over zero-risk approaches to products; AMR and parasite resistance policies; increasing requirements for pharmacokinetics studies and statistics rather than clinical relevance; efficacy requirements for conventional products not being fit for use in assessing new therapeutics for unmet needs.
- USDA review times have not become shorter, with delays and difficulties in review and approval relating to lack of scientific knowledge to evaluate new innovations; there are obstacles to the timely processing of biotech biologics, due to delays in the FONSI (Finding of No Significant Impact) process; and no progress on Categorical Exclusions for biologics.
- Inconsistency in EPA review processes; concerns about the increasing impacts of environmental legislation and an increasing focus on worst-case scenarios for environmental safety rather than expected-use patterns; and specific concerns that animal health pesticide-based products are treated the same as environmental and crop pesticides, so the AH industry has to mount defenses against issues like Endocrine Disruption although usage is much less than other pesticide types.
- Regulations for combination in-feed products under the ADAA (Animal Drug Availability Act) are over-restrictive.
- Problems with NGOs, activist groups and special interest groups, especially mounting lawsuits against FDA or activating legislators at State level.
- Conventional regulatory frameworks are becoming difficult and costly, and favour generics and OTC products such as animal nutraceuticals, which are not being regulated by FDA though they make claims; in addition, the EPA process favors the OTC route for pesticide-containing products.

China negatives 

- Too many stakeholders and decision-makers in the regulatory process, who can be difficult or impossible to identify – eg there are more than 50 members for vaccines on the marketing authorization committee, but fewer than 20 for pharmaceutical products, and review experts who may themselves be researching or developing competing products to the applicant's.
- Too-frequent modifications of AH product regulation by MOA's Veterinary Bureau, and the very short times to respond and put necessary changes in place within companies, eg for 2D-coding of products and packaging, even on the smallest presentations.
- Excessive MOA requirements for import of vaccines, including provision of vaccines seed samples, and data for three sequential vaccine batches, and a general slow-down in new vaccine approvals due to stricter implementation of regulations.
- Restrictive practices concerning development of vaccines within China, especially for the Class A diseases of livestock (avian influenza, Foot & Mouth disease, swine fever and porcine reproductive and respiratory syndrome).
- The adverse change in attitude to biotechnology-based vaccines, with license sign-off only once a year.
- A new regulation on MRL and residues has been issued but there is no detailed guidance, creating uncertainty in the regulatory process.
- The perceived tendency of MOA to combine EU and US AH product laws into conflicting and impossible requirements rather than instituting rational regulations.

Australia negatives 

- The undesirable impacts of the AVCLAA 2013 include disorganisation of agency staff, failure to hit statutory timelines for new products but sticking to the new longer period, for simple post-approval variations.
- The difficulties of dealing with ESIs (Export Slaughter Intervals) and a feeling that the regulators do not support science-based withdrawal periods against trade pressures.

Markets

23. The pet market is expanding and therefore CAPs are becoming more prominent; veterinarians are becoming more influential.

24. Every link in the supply chain is consolidating, not just retailers or livestock producers. For PAPs, food retailers and food producers are more influential than 5 years ago.

25. The swine and poultry markets are each consolidating, the FMD vaccine market is much more competitive; the bovine sector is growing but customer consolidation in integrated meat producers and processors is creating additional difficult pressures for the AH industry, especially via more stringent residue requirements in international trade.

26. In emerging markets, increased competition is generating overall market growth but there is pressure on profit margins, which customer consolidation is also contributing to.

27. Also in emerging markets, MNCs find that local plants usually have fewer compliance requirements, including inspection frequency. It's therefore hard for MNCs to make the decision on scale manufacturing, whether to use regional plants with lower local regulations or building state-of-the-art facilities with either heavier compliance oversight or import challenges.

Japan markets  • Companies believe that the falling human population and increasing aging population will impact the AH market. • Companies have reorganised, focusing on therapeutic sectors and links with other companies to service these. • Issues of corporate compliance have also occurred in the AH industry and companies are taking steps to avoid this by increasing documentation and compliance procedures. • The Trans-Pacific Partnership Agreement, while delivering free trade, is expected to further depress livestock numbers. • There has been stringent price control by the livestock mutual insurance association.	**European Union markets**  • 2011-2013 market was at best flat, even down, but 2014 onwards has been more positive and economically dynamic. • Organic growth is slower, so acquisitions of companies or products are increasing to create a broad enough portfolio. All companies now have generics, and are now competing in every segment, according to interviewees. • Because of rising market demand, there is growing interest in medicated pet-foods and animal nutraceuticals, with some associated regulatory difficulties. • High consolidation at the top end of the market, with 3 companies commanding more than 50%.
USA  **markets** • Consolidation in the contract research sector has reduced the pool of reliable sites for clinical trials. • The increased spotlight on the sector through public offerings and private investment in small innovator companies has brought additional funds and supported start-ups in developing human biotechnology innovations for animal health, but has also increased ROI (return-on-investment) expectations to levels that are difficult for small companies, and exposed them to activist investors. • Increased use of the internet by pet-owners for information and improved consumer education give opportunities for increased market differentiation.	**China markets**  • The Government efforts to remove sub-standard companies from the market by compliance and insistence on Good Supply Practice are resulting in stronger domestic companies with high quality standards and intentions to develop new products, as well as attention to compliance/standard operating procedures. • Fake or dangerous products are still on the market and interfere with market price and the health of the legitimate AH industry. • The concept of joint ventures is now well-established; MNCs are also beginning to invest in R&D centres in China. • Domestic companies are beginning to acquire overseas AH companies and internationalise their business • Consumers are becoming more sensitive to safe food concept. • The influence of OIE and China's membership of the WTO are resulting in some increase in transparency and openness with respect to technical and commercial aspects of AH.

Canada markets  • The relatively small size of the market – 91% of the companies responding to the survey reported sales of less than US$100M – and the risk of disproportionate regulation. • The prominence of OUI (Own-Use Importation) by veterinarians and compounding of APIs.	**Brazil markets**  • Increased competition is providing overall market growth but there is pressure on margins. • The vaccine market, especially for diseases such as Foot and Mouth Disease, is now much more competitive. • The market is sensitive to trade pressures on meat exports.
Australia markets  • Relatively small size of the market – 88% of the companies responding to the survey reported sales of less than US$100M – and the risk of disproportionate regulation.	

Key findings

Full data for inter-regional comparisons is given in Appendix 4.

Company profiles

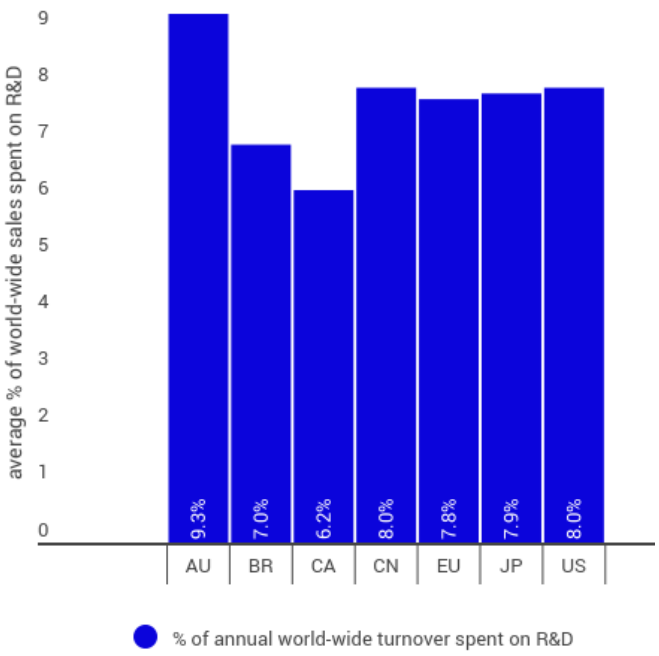
10 multinational companies (MNCs) and their subsidiaries, and a further 20 local, regional and internationally-active companies were involved in GBS 2015, with a total of 79 respondents, involved in 73 surveys and 61 interviews **(Figure 13)**. In addition to the interviews of regional staff, 6 leaders of HealthforAnimals' corporate members were also interviewed.

R&D

Average R&D expenditure as a percent of total sales varies from 6.2% in Canada to 9.3% in Australia (**Figure 14**). 60% of companies spend 7%-10.9%; the modal spend is 8%-8.9%.

Figure 13. Respondents per country	Figure 14. R&D as a % of global sales

	7 Surveys 7 Interviews
	10 Surveys 5 Interviews
	12 Surveys 0 Interviews
	8 Surveys 0 Interviews
	10 Surveys 5 Interviews
	12 Surveys 15 Interviews
	11 Surveys 22 Interviews
Health for Animals global animal medicines association	6 Interviews



Regulations and innovation

Australia, Brazil and the EU are on the whole negative about the regulatory environment as far as the impact on innovation is concerned – 87%, 82% and 69% of companies, respectively (**Figure 15**). These perceptions reflect the difficulties produced by a new regulatory approach in Australia, a rapid regulatory upgrading in Brazil plus occasional non-scientific based decisions, and issues with pharmacovigilance, environmental risk assessments, and EFSA and member state processes in the EU.

For Canada, China, Japan and USA, there is positive feedback about the regulatory environment for up to 45% of companies, depending on region (**Figure 16)**. In Canada and China, a few respondents even see it as very positive, 8% and 18% respectively. In Canada, this reflects the efforts by agencies to reduce review times and increase regulatory certainty over the past 5 years.

For Australia, Brazil, EU and USA, the regulatory framework has the most important negative impact on innovation, shared for the EU by market closures for certain products. The concerns about market closure are likely to reflect current challenges with AMR (Antimicrobial Resistance) and attitudes to certain classes of antimicrobials. In China, inadequate IP protection is the most important concern; in Japan, lack of financial resources and small size of market segments are equally important as negative influences on innovation.

In Brazil and China companies are concerned about a lack of access to specialist biotechnology companies. For Australia, availability of research input credits is regarded as the strongest incentive for innovation.

The most negative aspects of regulations on innovation are the increase in costs and time for NPD (New Product Development), and creation of significant uncertainty or unpredictability.

All regions are concerned about the effect on increase in costs, and 83% about increases in time, except in Canada (where overall NPD time has fallen since 2011 due to the decreases in the regulatory review component).

For Australia, Brazil, China and Canada, it is the uncertainty and unpredictability associated with the regulatory systems that are highly-important. Re-direction of resources into defensive R&D is a particular concern in Brazil, Japan and USA; diversion of management time is seen as another high-impact problem in the US. However, for Canada, the biggest concern expressed by companies is the impact of regulatory-promoted closure of markets for AH products.

Figure 15. Impacts of the regulatory environment on innovation, Australia, Brazil and the EU

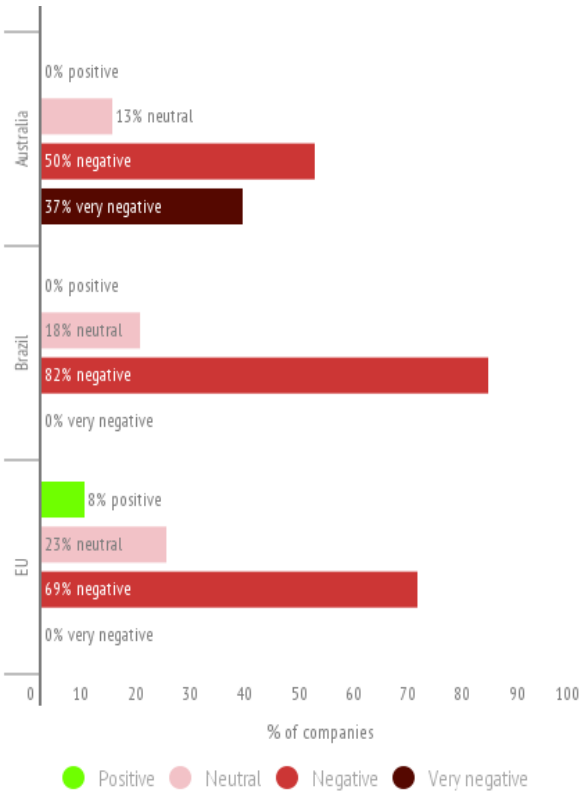
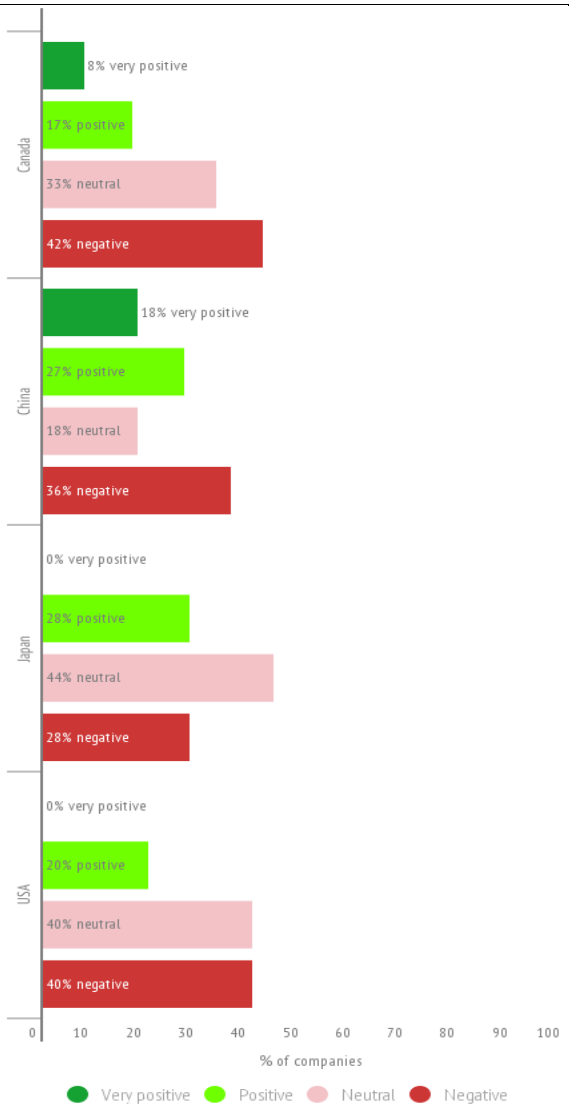


Figure 16. Impacts of the regulatory environment on innovation, Canada, China, Japan and USA



Mandatory Defensive R&D (MDR&D)

Mandatory defensive R&D is the cost of studies and regulatory activities necessary simply to keep a product on the market. This is represented by the costs of new data requested by authorities, particularly at product reviews, referrals (in the EU) and renewals, and the cost of subsequent dossier variations and studies demanded by the authorities.

In the survey, respondents were asked to relate the percentage of MDR&D (Mandatory Defensive R&D) to their actual local R&D spend, rather than their global R&D spend. The range is 15%-39% (**Figure 17**). These averages disguise a large range for individual companies. A number of companies in each region except Europe and Japan report zero expenditure on MDR&D.

Figure 17 shows the overall average including the 0% responses, and the adjustment required when the 0% responses are excluded from the averages. The biggest impact is seen on figures for Canada, where companies performing MDR&D spend almost 40% of their local R&D budget on defence. Smaller impacts of 2%-6% are seen in the USA, China, Brazil and Australia. The maximum reported MDR&D spends in each region are shown in **Figure 18**.

Figure 17. Mandatory Defensive R&D (MDR&D) as a % of total R&D

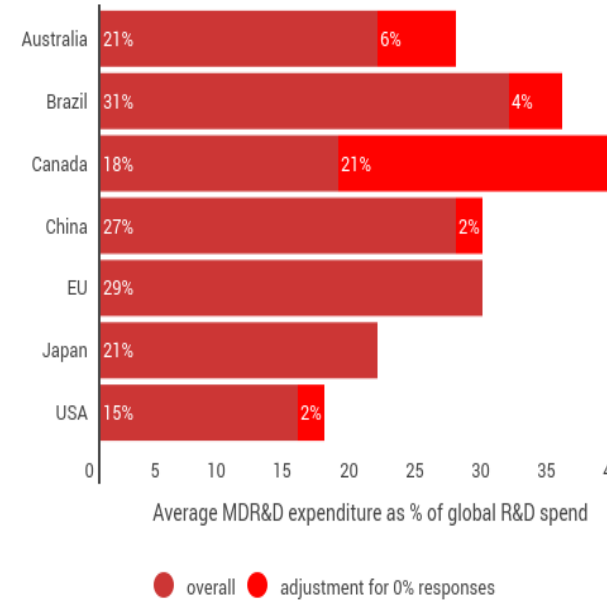
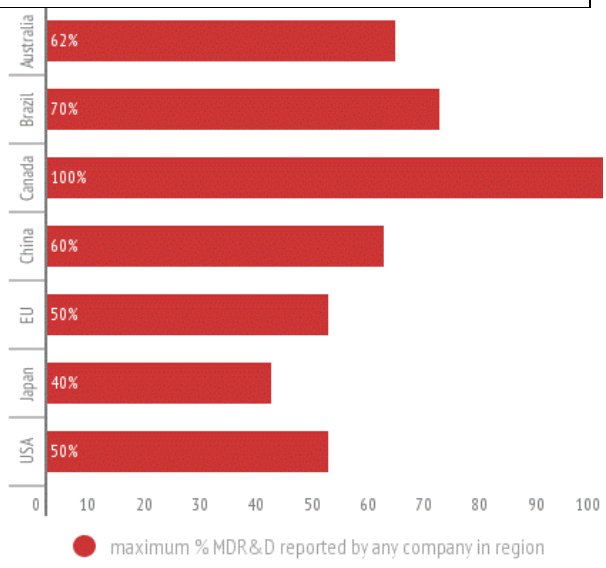


Figure 18. Maximum MDR&D reported in each region



In Brazil and USA, a high percentage of companies reported some increase in MDR&D expenditure since 2011, 93% and 80% respectively. In Brazil, 85% of companies reported a large increase, which is a reflection of the upgrading of the regulatory system and the need for a large amount of new data to maintain products on the market, and defend avermectins. In USA, the majority (67%) reported only a slight increase.

In China, the EU and Japan, 54%-57% of companies have experienced some increase in spend over the past 4-5 years. In Australia and Canada, only 20%-25% of companies report an increase, and the remainder mostly little change. In Canada, this is because over half the companies perform their MDR&D elsewhere. . As noted, above and in the figures, those that do perform MDR&D in Canada have had to use much or all of their local R&D budget.

Overall, more than 55% of companies report an increase in percentage of R&D expenditure on MDR&D – 26% slight and 30% a lot. An increase in regulator product review activities is a very important factor in this. Acquisition of companies with products already on the market is also important, as this triggers numerous dossier changes, such as changes to the name of the marketing authorisation holder, that have to be submitted as variations.

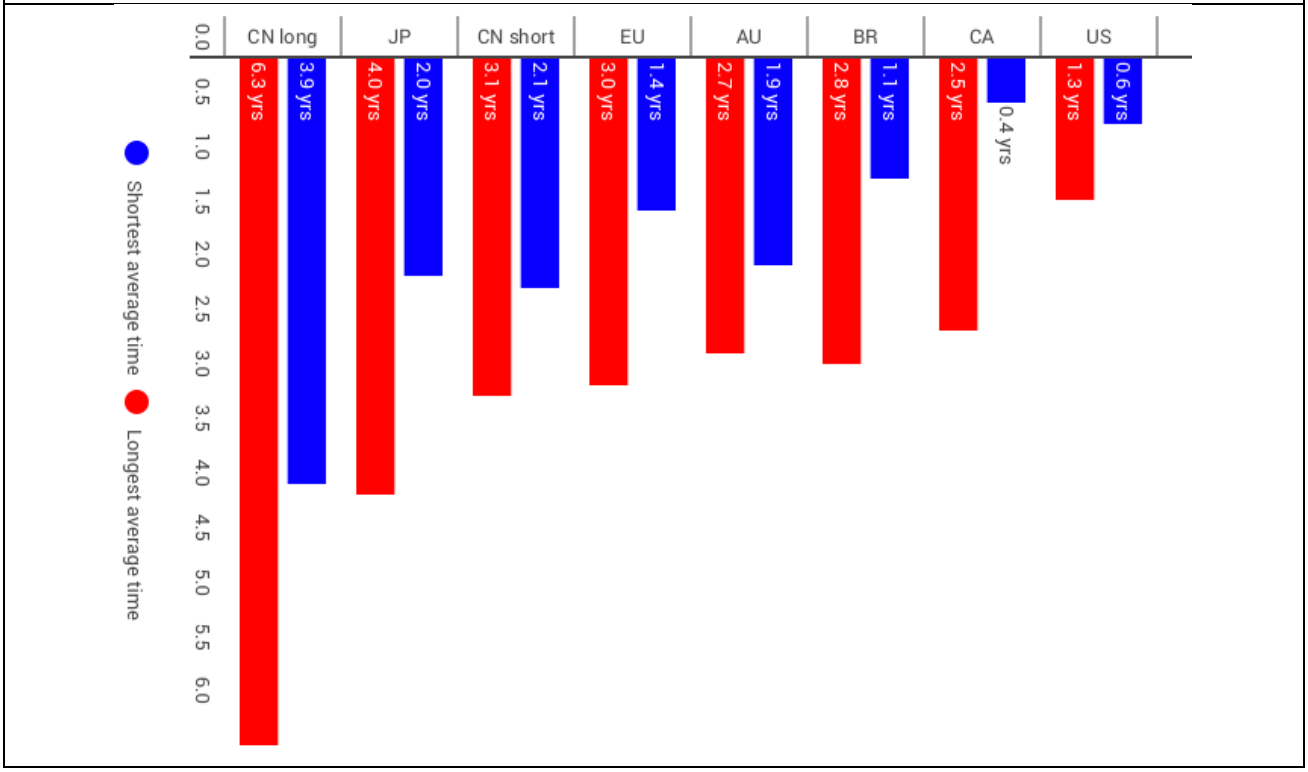
Times-to-approval for new products: submission to licence issue

The NPD times are examined in two ways: (a) the time of just the regulatory step - the time to approval – which is the time from the submission of a dossier to the authorities until a marketing authorisation is issued by the authorities, and (b) the total time for NPD, from the beginning of the research project until a marketing authorisation is obtained.

For all regions except USA, dossiers need to be submitted completely or substantially in final form with all necessary data. In USA, there is staged submission, and a simple comparison with other regions of time-to-approval from filing to licensing is misleading. **Figure 19** shows average shortest and longest times-to-approval over all types of products, PAPs (production animal/major livestock species), CAPs (companion animal products) and MSPs (minor species/minor uses products), pharmaceutical, biological and pesticide-based, for the categories with sufficient data-points for analysis. In most cases, there is a reasonably tight range of time for dossier review and license issuance.

In China there are strong differences between shorter and longer times, often reflecting a difference between local companies and multinational companies respectively (see also **Figure 24**). In Canada, products approved in USA are likely to be licensed almost on an administrative basis, especially biologics, reflecting their low 'shortest periods', whereas those from other regions will require full assessment.

Figure 19. The average shortest and longest times-to-approval from submission for new products



Figures 20, 21, 22 show average times-to-approval for new products by animal type and product types. For China, average short and average long times are shown and, for USA, the staged submission period and the time for final review and license issue. With the exception of China (and Australia for PAPs), time-to-approval for biological products is usually considerably shorter than for pharmaceutical products. Exceptions sometimes relate to longer times for biotechnology-based biologics (based on modification technologies or containing live organisms), because of the requirement to confirm safety before undertaking field trials. Times-to-approval for minor species, where this legal category exists, are often shorter than for other products.

Figure 20. The average times-to-approval for new PAPs

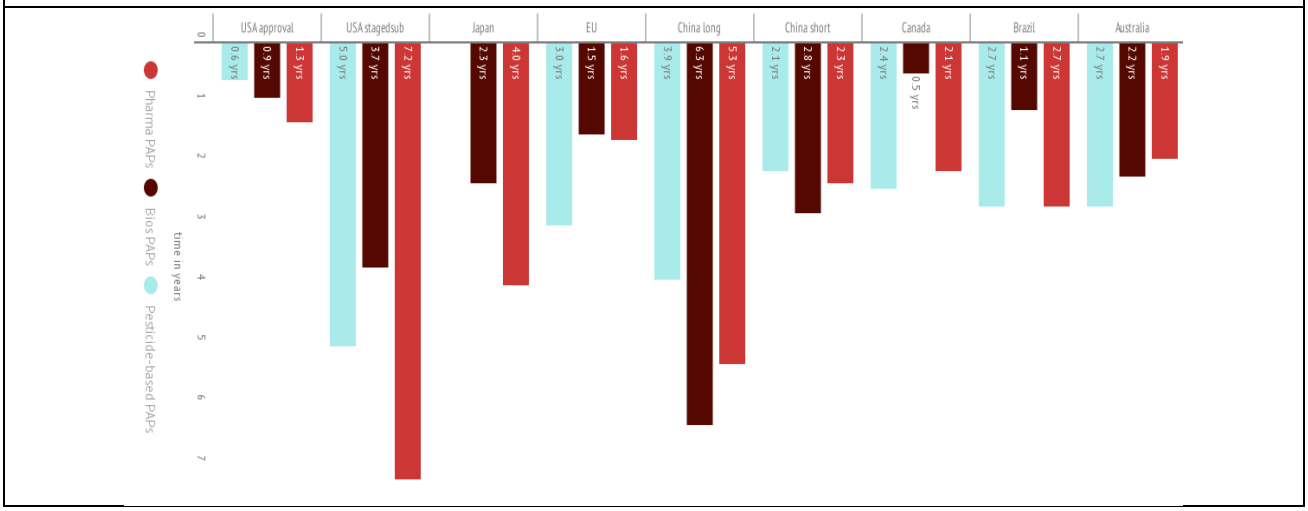


Figure 21. The average times-to-approval for new CAPs

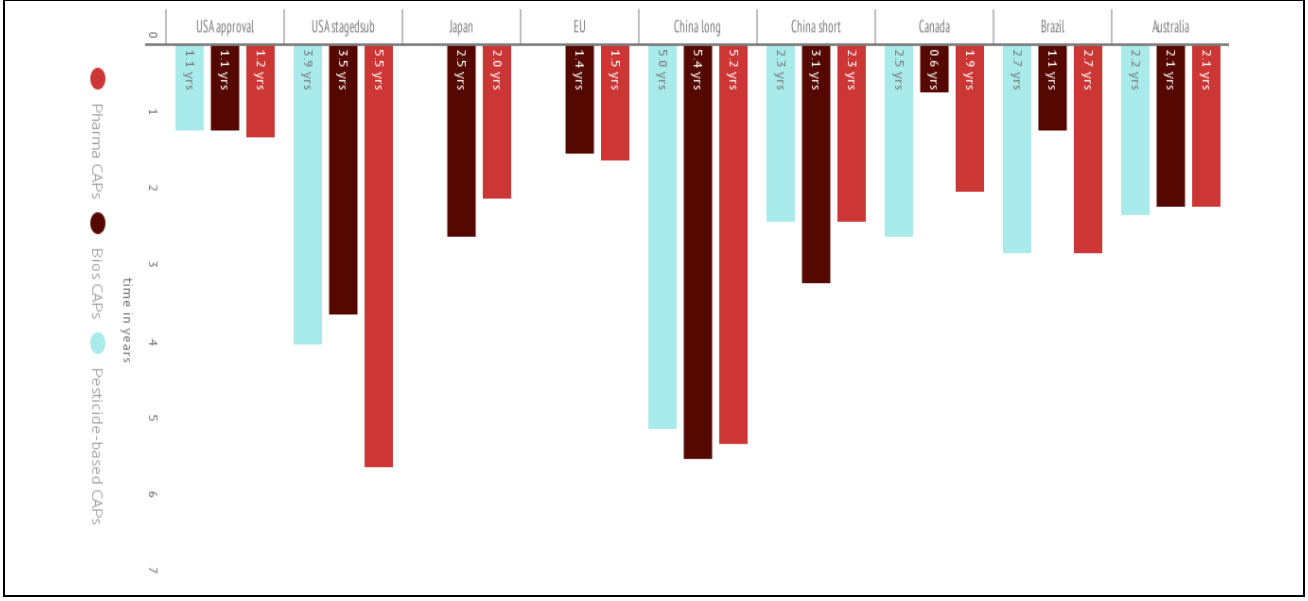


Figure 22. The average times-to-approval for new MSPs

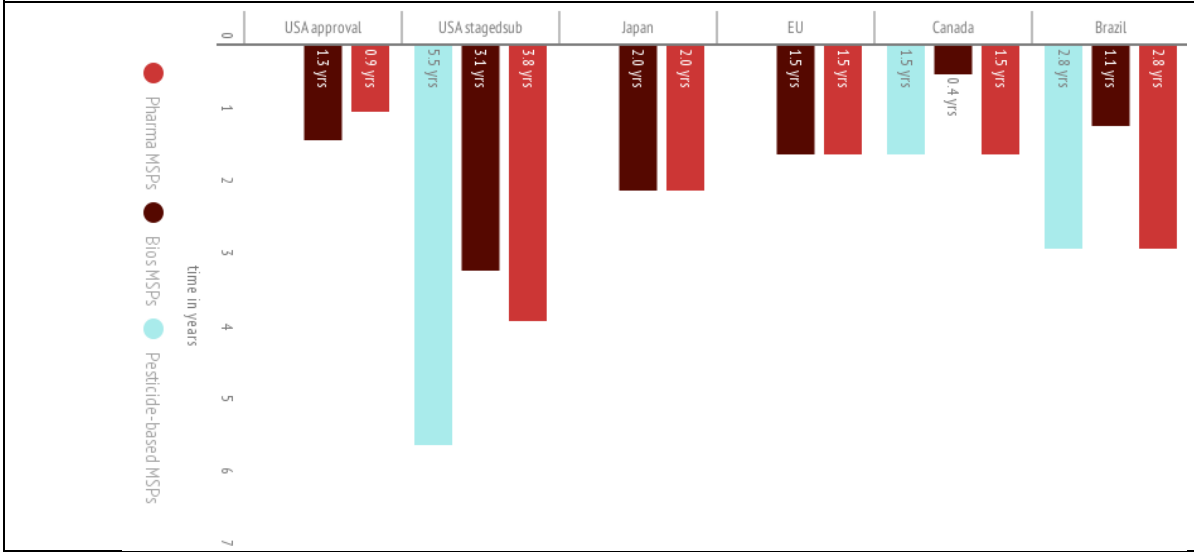
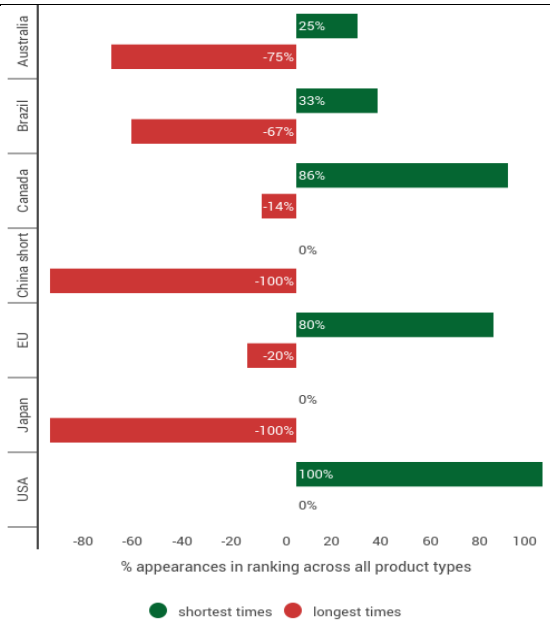


Figure 23 analyses how often overall a region provides the shortest or the longest times-to-approval and underlines the results shown in the previous graphics. The staged submission process in USA allows the FDA's CVM to appear in the shortest-times category for 100% of cases, although the staged submission period may be as long as 10 years. Companies in Canada commented that they would like the staged submission approach to be adopted by the agencies there, including for biological products.

By contrast, Japan and China appeared in the longest-times category in 100% of cases. In Japan, there is a continued impact of the failure by MHLW and FSC to change their approach to the review of PAP dossiers, residues and withdrawal periods to a simultaneous review with J-MAFF. Changing this might well have the single biggest impact on times-to-approval.

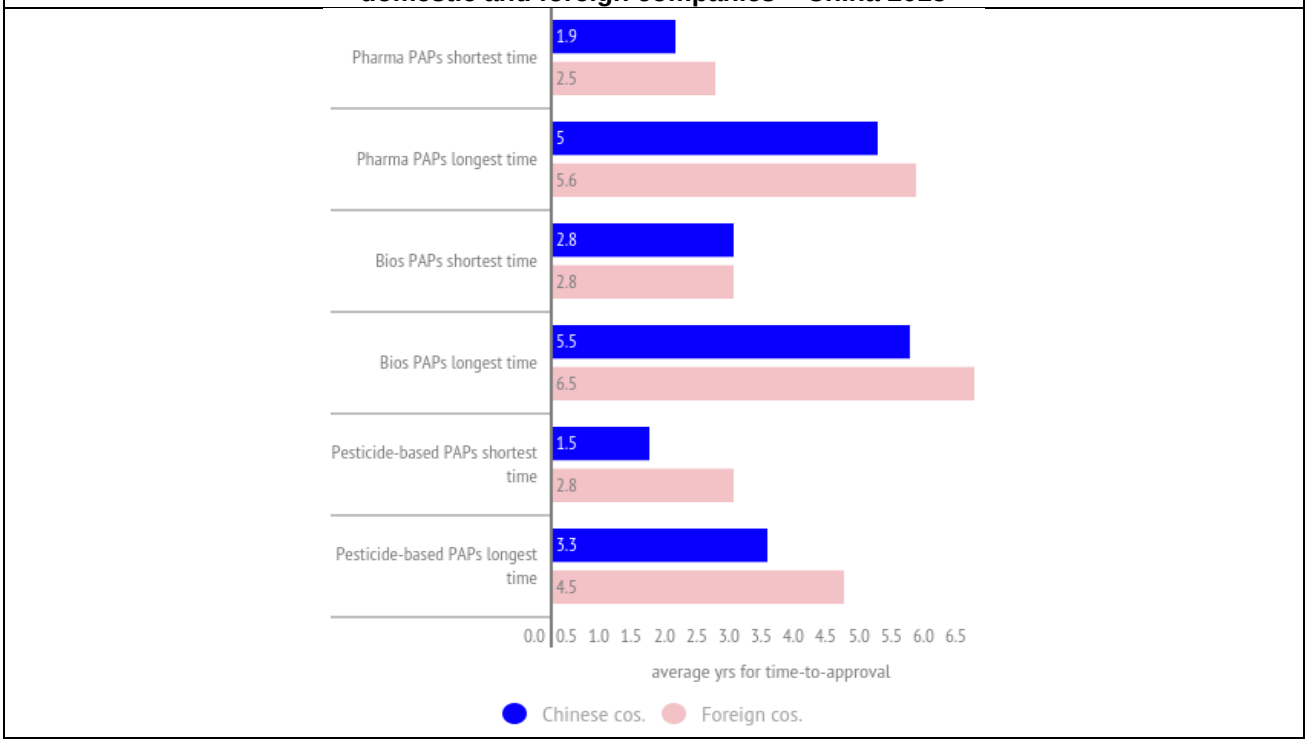
67%-75% of cases in Australia and Brazil fell into the longest-times category. As time-to-approval impacts time-to-market, any approaches that can reduce this are to be welcomed.

Figure 23. Regions with shortest and longest times-to-approval



China seems a special case. Reviewing 20 PAP times-to-approval, 20 cases for Chinese companies and 31 cases for foreign companies, it would seem that Chinese companies are likely to gain their approvals more quickly than foreign companies (**Figure 24**). For example, the shortest & longest averages for Chinese companies are 1.5 & 3.3 years for pesticide-based products versus 2.8 & 4.5 years for foreign companies. Interviews suggest this reflects the better navigation of the regulatory system by domestic companies and the speed of approval for institute-produced vaccines for Class A diseases (avian influenza, classical swine fever), rather than bias against MNC subsidiaries. However, other reasons may exist and should be explored.

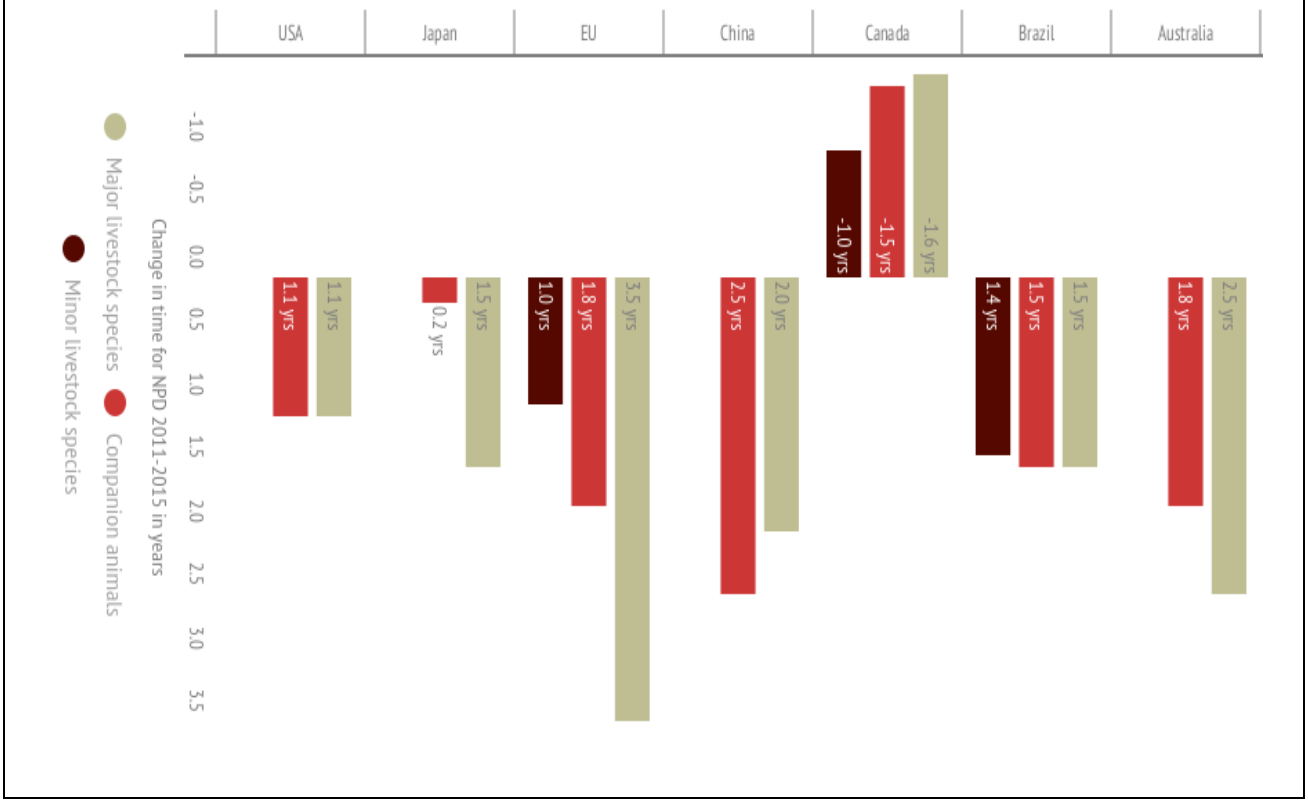
Figure 24. The average times-to-approval from dossier submission for a major new product, domestic and foreign companies – China 2015



Trends in time for New Product Development

The averages for those companies reporting an increase in the time for NPD since 2011 range from 0.2 years to 3.5 years (**Figure 25**). The increase in NPD time for MSPs appears to be the lowest. The increase in NPD time for CAPs tends to be smaller than that for PAPs except in China, where the regulatory approach does not differentiate between types of products. There are signs that the MOA (Chinese Ministry of Agriculture) wishes to speed up the process for CAPs and there is consultation with industry and plans to revise the regulatory framework. The exception to the general picture of increase is Canada, where NPD time is reported to have decreased overall. The general decrease reflects the reduction in average times-to-approval that has been experienced in Canada. Only one company reported an increase in time, of 1.0 year for livestock NPD.

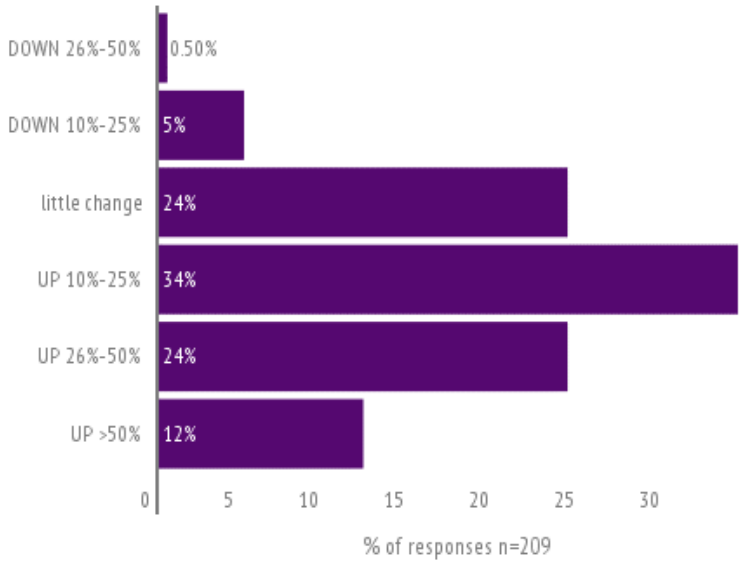
Figure 25. Changes in time for full NPD 2011-2015



Costs of NPD

The pattern of costs across the regions is rather complex and is covered in more detail in the individual regional reports**.** There is a mixture of large-scale full development in the region concerned, bridging or top-up studies needed to adapt a foreign dossier to local requirements, and very low costs, for example for administrative fees for recognising an overseas license and issuing a local one. Costs specified for a CAP ranged from US$0.003M to US$74M and for a PAP from US$0.004M to US$75M. The lowest costs were for PAP and CAP biological products in Canada, where little full NPD is done. The highest costs for PAP and CAP pharmaceutical products were reported in Europe, linked in part to increased costs related to environmental risk assessments and, for PAPs, studies addressing the potential for development of antimicrobial resistance.However, when asked about trends in costs of NPDs (**Figure 26**) approximately 70% of all respondents had observed increases in costs.

Figure 26. Overall trends in NPD costs 2011-2015



Product extensions – costs

Figures 27 and **28** show the costs of adding a new claim or use to an existing PAP or CAP. The regions fall broadly into two classes – less expensive (**Figure 27**), comprising Australia, Brazil, China and Japan, and high-cost (**Figure 28**), comprising Canada, EU and USA. Pharmaceutical and biologic products represent the majority of the data points and extensions for these are most costly on average in Canada, then USA, and least costly in Brazil and China. The same picture is seen for in-feed medicinal products, where these were reported. In Canada, the relative expense may be related to the transition from performance enhancement to therapeutic uses of antimicrobials, or to MUMS claims; or, for biologicals companies, the costs of performing work in Canada to satisfy APHIS requirements for claims in the USA.

Figure 27. The costs of adding a new claim or use to an existing PAP or CAP (in US$M) in Australia, Brazil, China and Japan

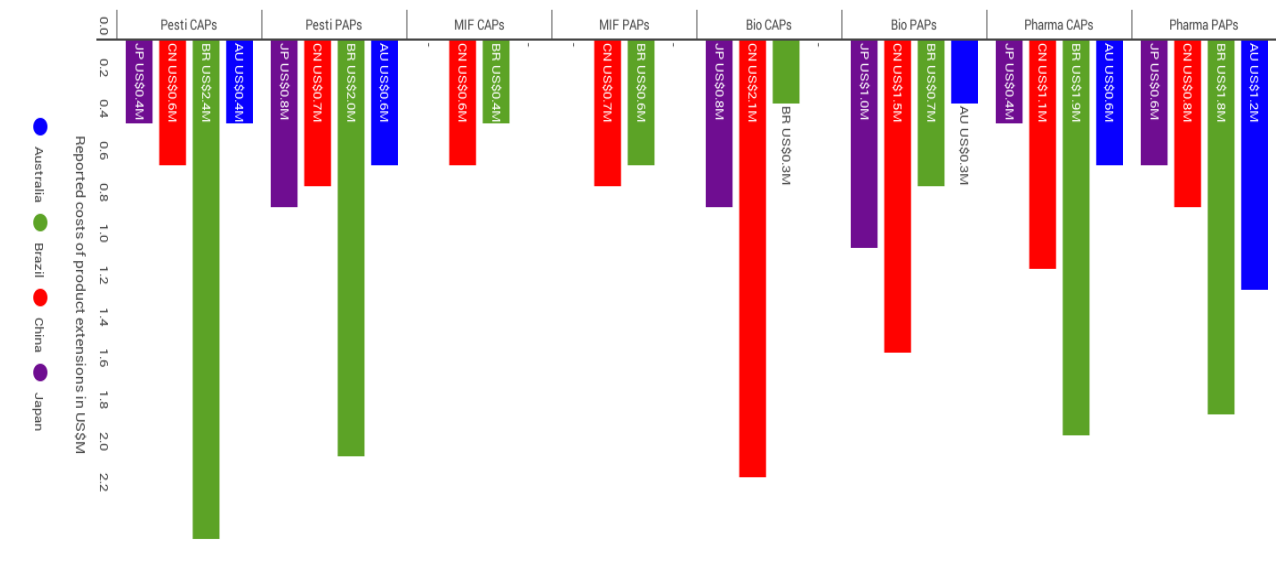
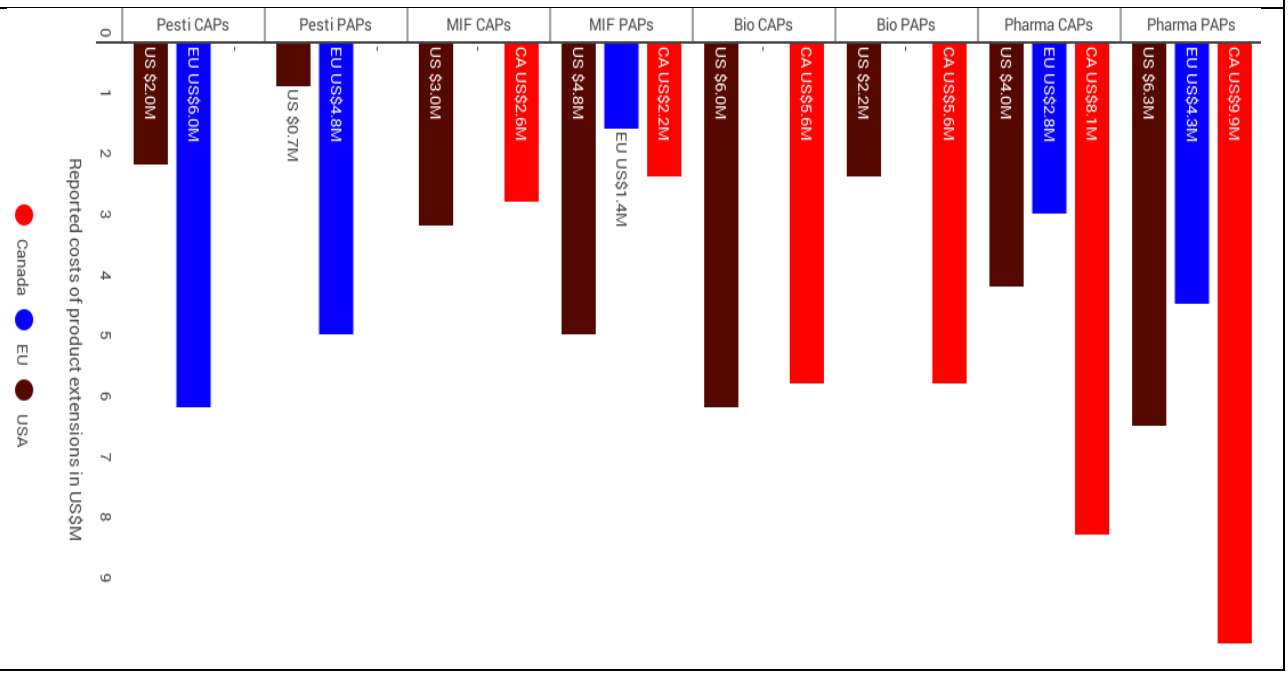


Figure 28. The costs of adding a new claim or use to an existing PAP or CAP (in US$M) in Canada, Europe and USA



The future and suggestions for action

28. The industry is beginning to make more use of new digital tools and approaches. Over the next period, these will become pervasive for sales channels, data collection, feedback into NPD, recruitment of vets and trials subjects, tailored production and product supplies for specific customers and seasonal profiles, and increasing the links between vets and their customers.

29. **Figure 29** shows companies would like to see further improvement in policy, performance and processes, drive to harmonization. i.e.:
    - Deeper more consistent application of risk-based approaches, and product-appropriate risk:benefit analyses that determine the regulatory requirements, are important targets.
    - Transparency, predictability, efficiency and flexibility of agencies, with enhanced staff training and expertise and increased staff numbers, are seen as critical for agencies to overcome the disruptive effects of changes in regulations and guidelines, and to become innovation-ready.
    - Expanding e-submissions and inter-agency working, and mutual recognition of GCP, GMP, high-quality foreign data and approvals from well-regulated countries.
    - Streamlining of excessive regulation of minor or frequent changes to products and manufacturing, and long timescales for approving applications for changes.
    - Increased accessibility of agency staff for discussion and advice on new technologies and new products before submission.
    - Some differences can be seen in the importance given to the need for policy changes (particularly EU and Canada), for specific processes (e.g. Japan), for internationalisation (e.g. China) and performance (e.g. agency efficiency in Brazil and Australia) in the different regions (**Figure 30**).

Figure 29. Regulatory changes companies would like for the future

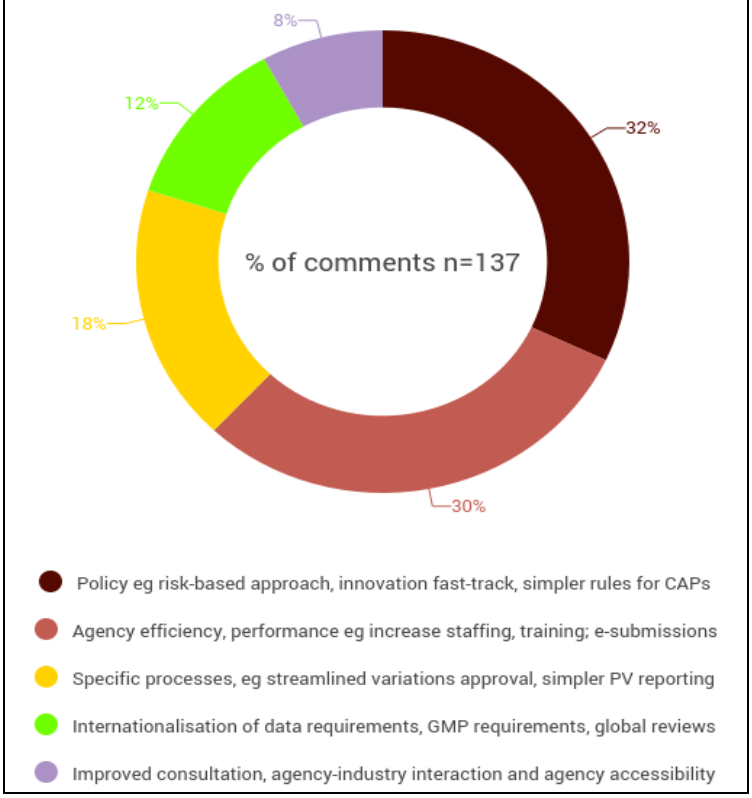
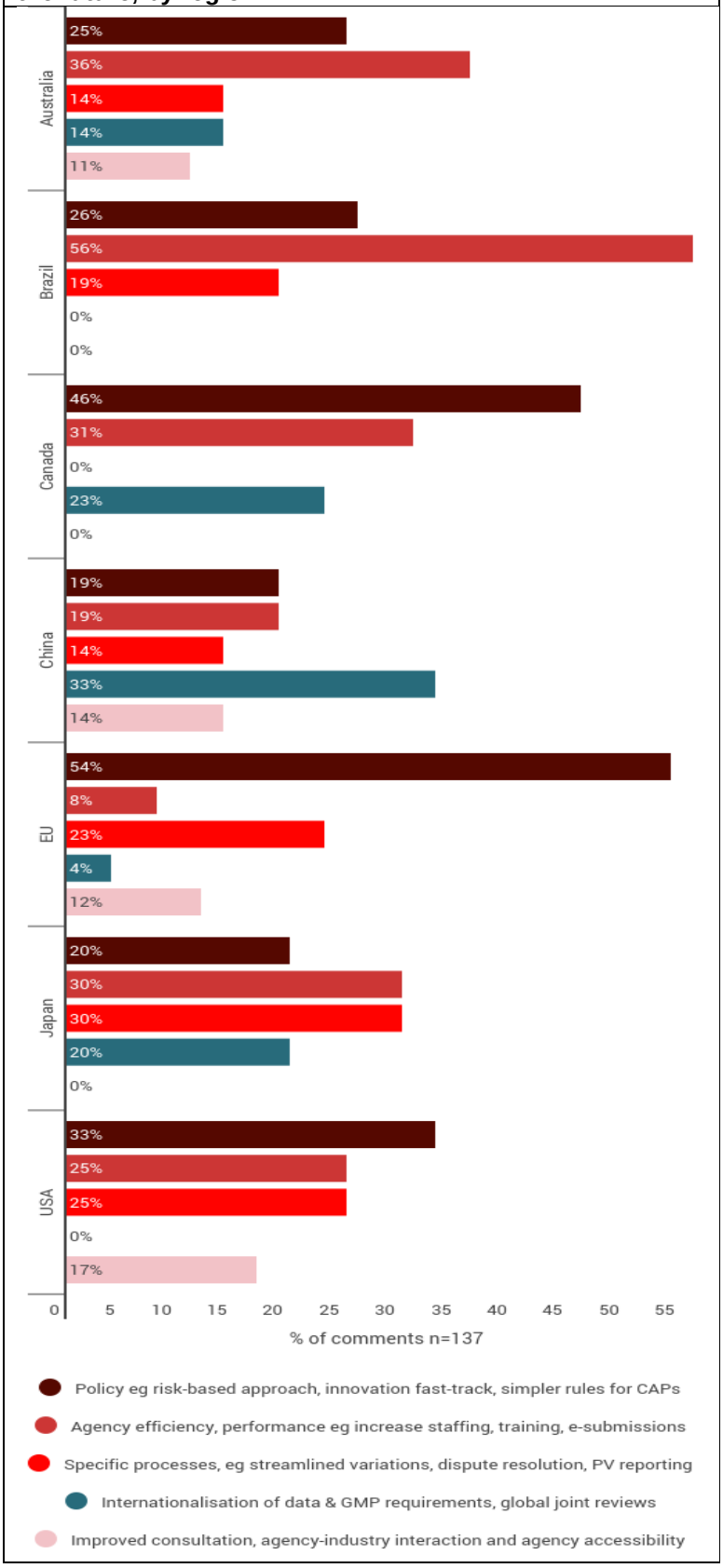


Figure 30. Regulatory changes companies would like for the future, by region



Practices and initiatives that could be very helpful if applied across all regions include:

1. The LRP (Low Risk Products) programme in Canada (https://www.lrvhp.ca/), and similar moves in Australia.
2. Regional collaboration on simultaneous assessments, exemplified by the US-Canada Regulatory Cooperation Council and joint VDD-CVM reviews, and on shared work, seen in the EU's work-sharing activity for review of post-approval variations.
3. Brazil's fast-track process for innovative products.
4. ADUFA in USA and similar fee-for-service approaches.
5. e-Submission of licence applications, post-approval variation requests and pharmacovigilance reporting, in formats compatible between regions.
6. Streamlining of the review process for post-approval changes including product and manufacturing-site variations.
7. Acceptance of foreign study reports and data if produced using appropriate Good Practice (GLP, GCP) and/or according to appropriate VICH guidelines.
8. Mutual recognition of GMP and acceptance of the quality standards, SOPs and documentation for foreign products made using recognised appropriate GMP.
9. Acceptance of the MRLs recommended by Codex Alimentarius.
10. Ability of staff of all regulatory agencies to use risk:benefit assessment and product-specific risk analysis for a flexible approach to regulatory requirements.
11. Fast-track, Conditional License or similar procedures that allow innovative products to reach market more rapidly with a risk-related regulatory review.

Hopes and actions for agencies in the future requested by specific regions

Japan	**European Union**
• Routine acceptance of Codex Alimentarius-agreed MRLS would assist in removing the current sequential 3-agency evaluation of PAPs. • In place of the current Committee/ sub-Committee process, set up a new investigational system similar to the human PMDA (Pharmaceutical Medical Devices Agency), paid by user fees. • Replace the requirement for laboratory efficacy studies for anthelmintics by field trials conducted according to GCP • Institute a conditional license for biotechnology-based biologics, eg DNA (deoxyribonucleic acid) vaccines, based on the specific risk:benefit assessment for each new development, and/or shorten review for those products that have been approved and are marketed in other major countries.	• The industry should be involved closely in developing the implementing Acts for the new Veterinary Medicines Regulation. • Pharmacovigilance reporting should ensure it is in context, i.e. not just number of cases but incidence compared with usage (per dose reporting), and signal identification processes should be designed and agreed in consultation with companies, not imposed. • Alignment and forced harmonisation of EU Member States is needed to make the new Regulation work. • Avoid the risk that the new Regulation regulates old but well-used, safe and effective products into non-viability. • High expectations of the new legislation to reduce administrative burden and improve data protection.

USA

- A revised more flexible approach is needed to the effectiveness/efficacy requirements for new therapeutics for unmet needs, to reverse the lag in AH product regulation, especially compared with human health product regulations.
- Increasing the annual treatment numbers limit used for definition of a Minor Use, eg from 70,000 for dogs, to encourage MUMS product development.
- Action against nutraceuticals companies who sell OTC but make AH claims.
- Acceptance by CVM of biomarkers for efficacy, already accepted as a principle by human-product regulators CDER, rather than owner-evaluation of outcomes, which is biased by placebo -response reporting.
- A flexible approach is needed to acceptance of data from other regions; movement away from zero-risk/worst-case scenario towards risk:benefit approach and analyses that reflect real use.

China

- Introduce conflict of interest statements for expert advisors to avoid doubts about their objectivity and science-basis for dossier reviews.
- Build more mutual respect between US, EU and China, to work towards more acceptance of foreign data and studies by IVDC/CVDE and a realistic alignment of Chinese regulatory requirements and standards with other key countries.
- Open up government vaccine tenders to commercial companies, and remove uncertainties about the regulatory progress for products to control Class A diseases.

Canada

- Continued work needed to align and harmonize approaches to the CMC requirements for EU, USA and Canada.
- Establish a phased review of biological dossiers and a risk-based assessment for file updates for vaccines.
- Tackle the problem of independent action by provincial government that over-rides the federal government position, eg MAPAQ Quebec's legislation restricting the use of 3rd and 4th generation cephalosporins in absence of a specific clinical diagnosis.
- Ensuring that the proposed Health Canada changes for OUI/API compounding have the effect that the regulated industry needs.

Brazil

- MAPA needs to issue guidelines and INs (Normative Instruction) that will provide certainty to areas like safety and efficacy for target species.
- Dividing products into three classes and regulating them in different ways would be helpful – livestock, companion animal and innovative products.
- A specific IN for innovation is indicated, or MAPA will not be able to define some new products well enough to decide how to handle them.
- Review some local requirements eg for clinical studies so they are brought into line with VICH.

Australia

- Reducing reliance on other agencies, to allow consistent achievement of statutory time-limits for review and approval.
- Enhancing the flexibility and speed in handling new science and technology, especially for new manufacturing processes.
- Harmonization of residue screening methods across Australia would assist the situation with MRLs.
- APVMA to take action to control compounding pharmacies.
- Industry would like to see the promised comprehensive risk-based guidance compendium as soon as possible.
- APVMA to offer priority assessment for higher fees.