

GLOBAL BENCHMARKING SURVEY 2015

Benchmarking the competitiveness of
the global animal health industry

A report produced by



BioBridge[®]

for HealthforAnimals

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.

SUMMARY

- 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 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 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.

SUMMARY

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, e.g. 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 suggested 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

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.

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

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

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 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.
- Improved industry relations at APVMA under new CEO, with potential for further improvement related to intake of new staff.



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.



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 Veterinary Health 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.



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.

POSITIVE ASPECTS



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.



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.



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.

NEGATIVE ASPECTS

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

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.

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

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.

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.

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.

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.

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.



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 and a feeling that the regulators do not support science-based withdrawal periods against trade pressures.



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.

NEGATIVE ASPECTS



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.



China negatives

- Too many stakeholders and decision-makers in the regulatory process, who can be difficult or impossible to identify – e.g. 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, e.g. 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 change in attitude to GMO-based vaccines, with license sign-off 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.



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.

NEGATIVE ASPECTS



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.



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.

MARKETS

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

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.

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.

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

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.



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.



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.



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 Own-Use Importation by veterinarians and compounding of APIs.



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.

MARKETS



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%.



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.



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.

KEY FINDINGS

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 67 interviews including 6 global companies (Figure 1).

R&D

Average R&D expenditure as a percent of total sales varies from 6.2% in Canada to 9.3% in Australia (Figure 2). 60% of companies spend 7%-10.9%; the modal spend is 8%-8.9%.

Figure 1: Respondents per country

| | | | |
|-------------------------------------------------------------------------------------|-----------------------|------------|---------------|
|  | Australia | 8 Surveys | 0 Interviews |
|  | Brazil | 12 Surveys | 15 Interviews |
|  | Canada | 12 Surveys | 0 Interviews |
|  | China | 11 Surveys | 22 Interviews |
|  | European Union | 13 Surveys | 12 Interviews |
|  | Japan | 7 Surveys | 7 Interviews |
|  | USA | 10 Surveys | 5 Interviews |

Figure 2: R&D as a % of global sales



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 3). 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 3). 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

KEY FINDINGS

Japan, lack of financial resources and small size of market segments are equally important as negative influences on innovation.

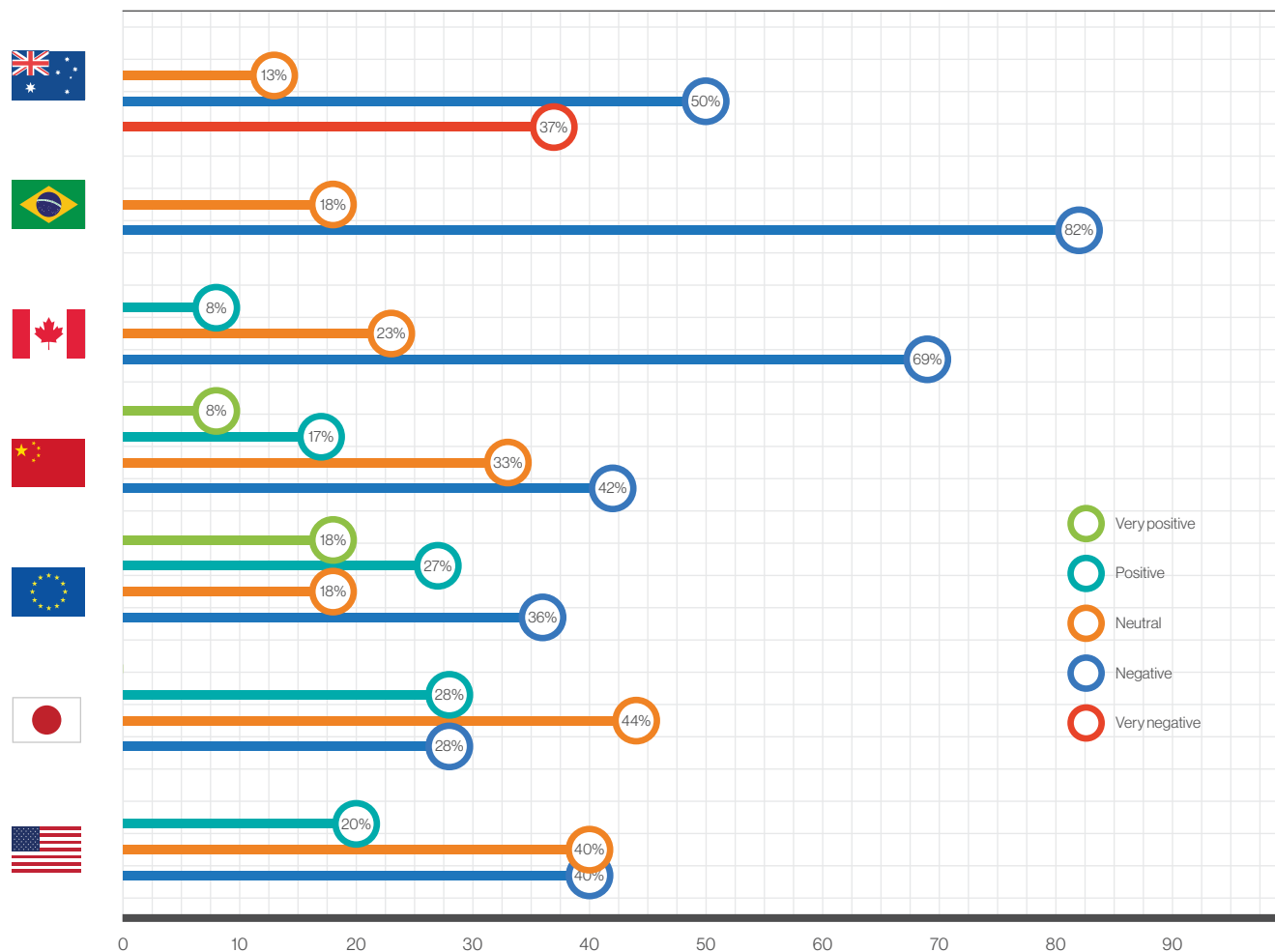
In Brazil and China companies are concerned about a lack of access to specialist biotechnology companies. For Australia, availability of research input credits is regarded as the strongest incentive for innovation.

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 3: Perceptions of impacts of the regulatory environment on innovation



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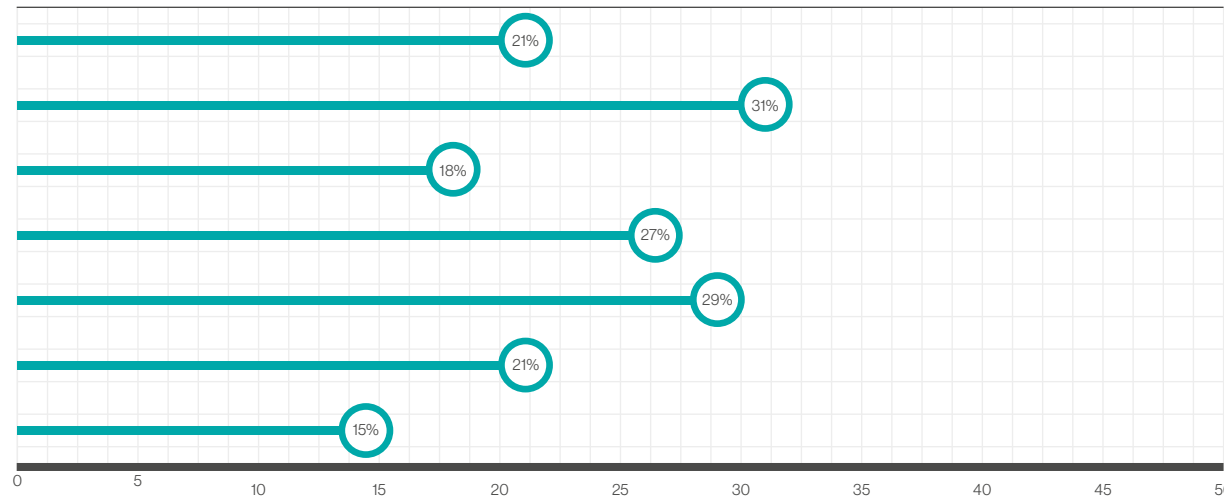
Mandatory Defensive R&D (MDR&D)

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 and renewals, and the cost of subsequent dossier variations.

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%-31% (Figure 4). These averages disguise a large range for individual companies.



Figure 4: **Mandatory Defensive R&D (MDR&D) as a % of total R&D**



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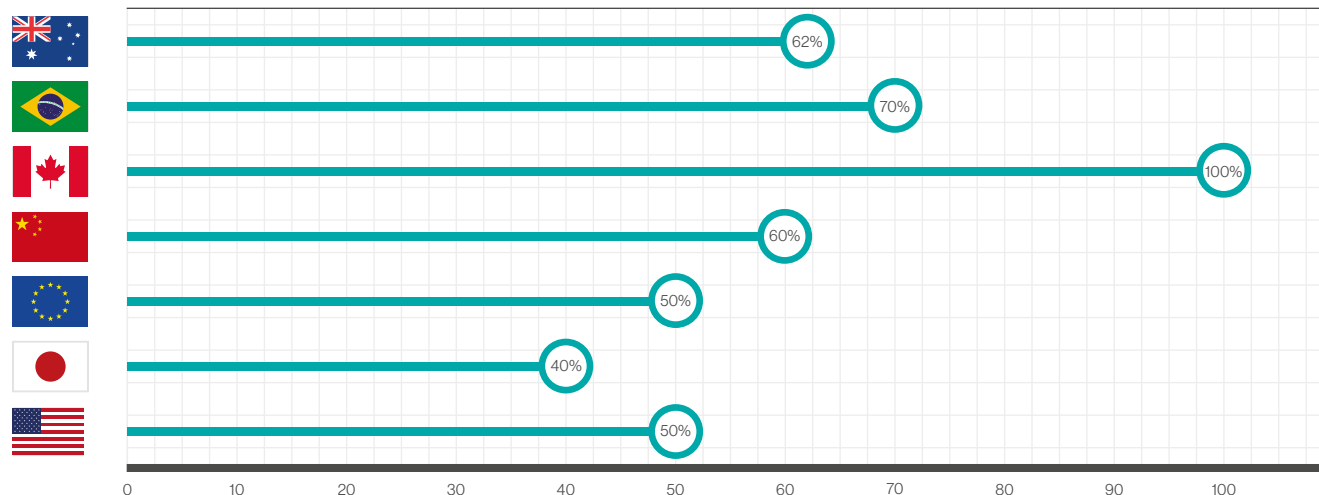
The maximum reported MDR&D spends in each region are shown in Figure 5.

In Brazil and USA, a high percentage of companies reported increases in MDR&D expenditure since 2011, 93% and 80% respectively. In Brazil, 85% of companies reported a large increase vs. 11% in USA, 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 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.

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.

Figure 5: **Mandatory Maximum Defensive (MDR&D) reported in each region as a % of total R&D**



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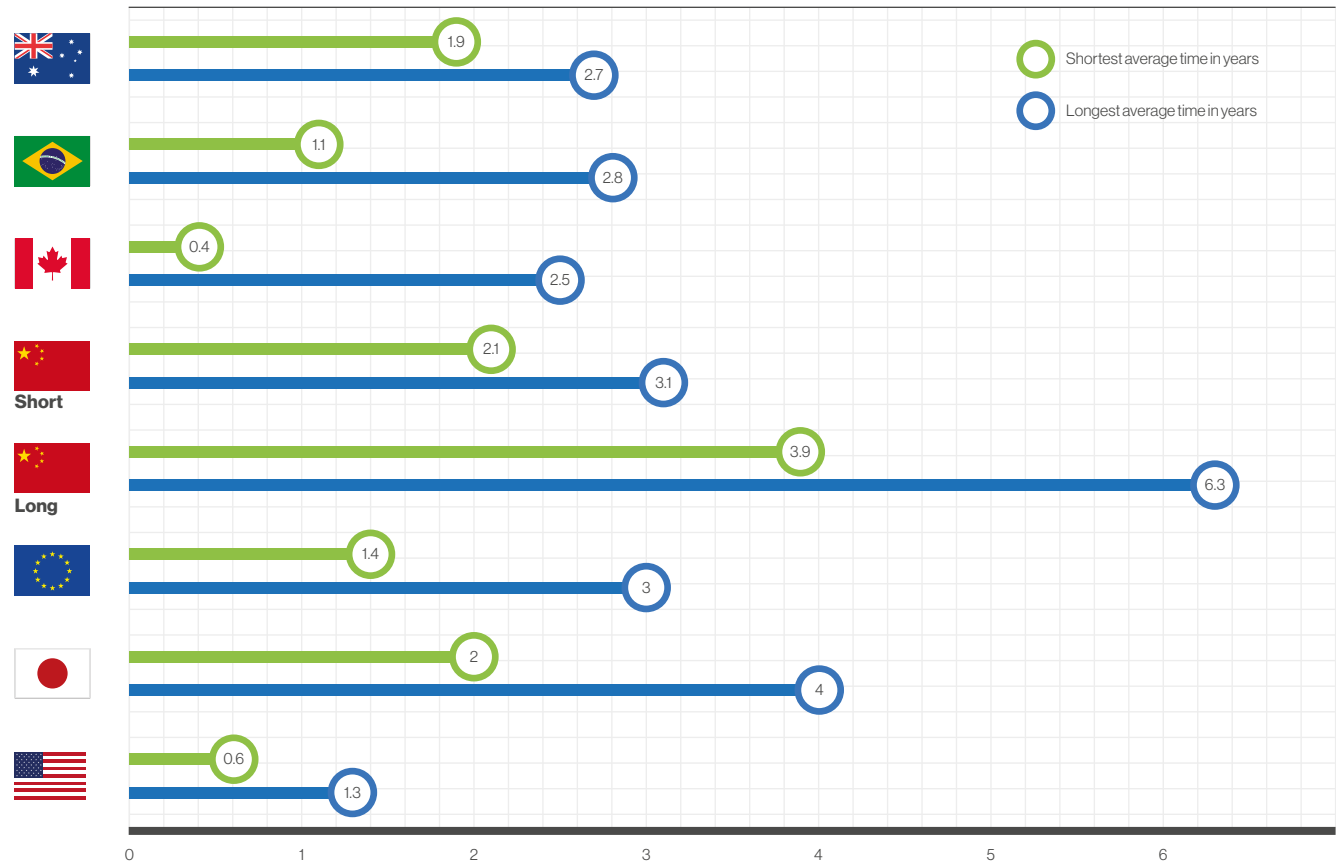
Times-to-approval for new products: submission to licence issue

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 6 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 11). 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.

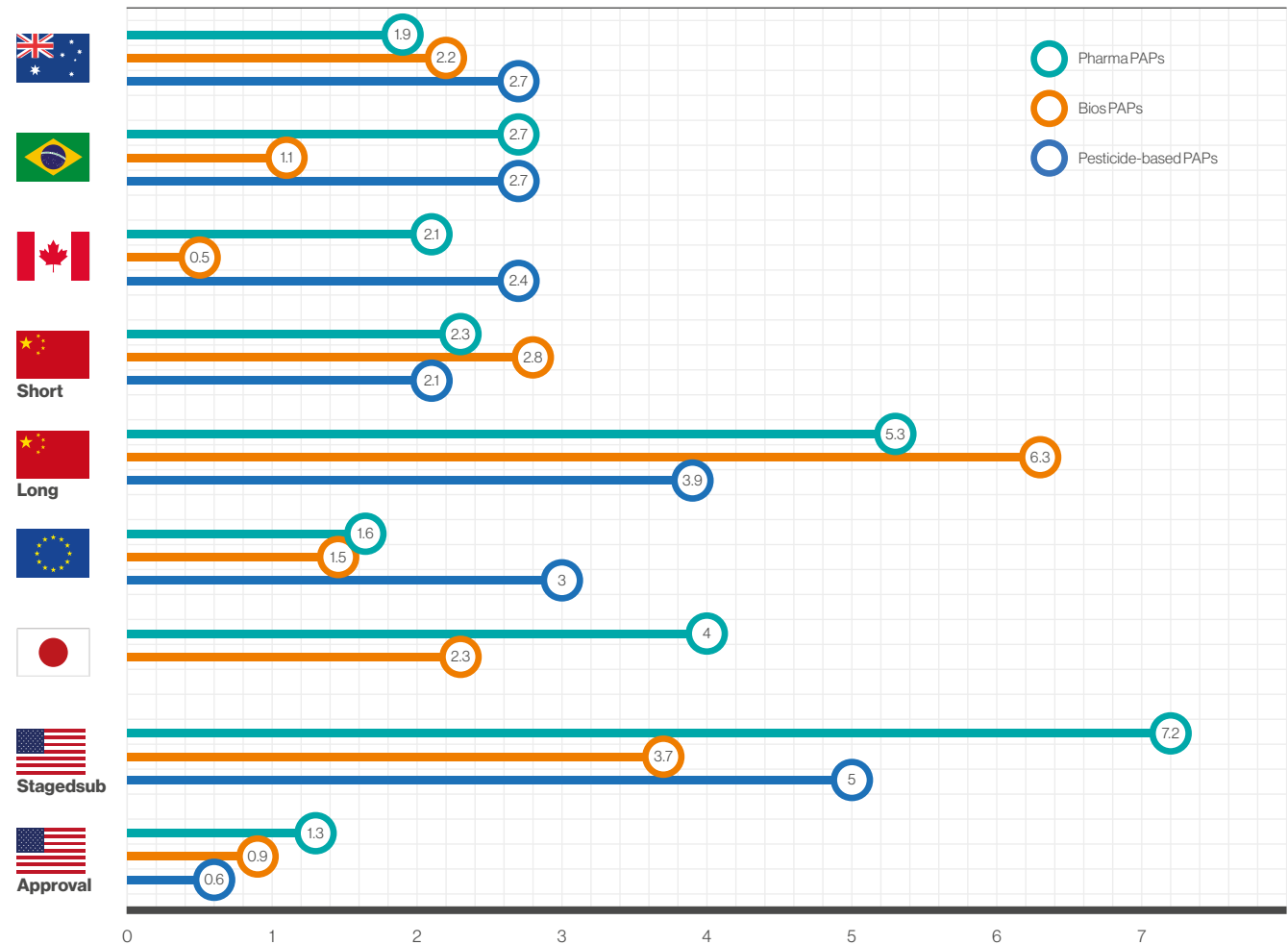
Figure 6: The average shortest and longest times-to-approval from submission for new products



KEY FINDINGS

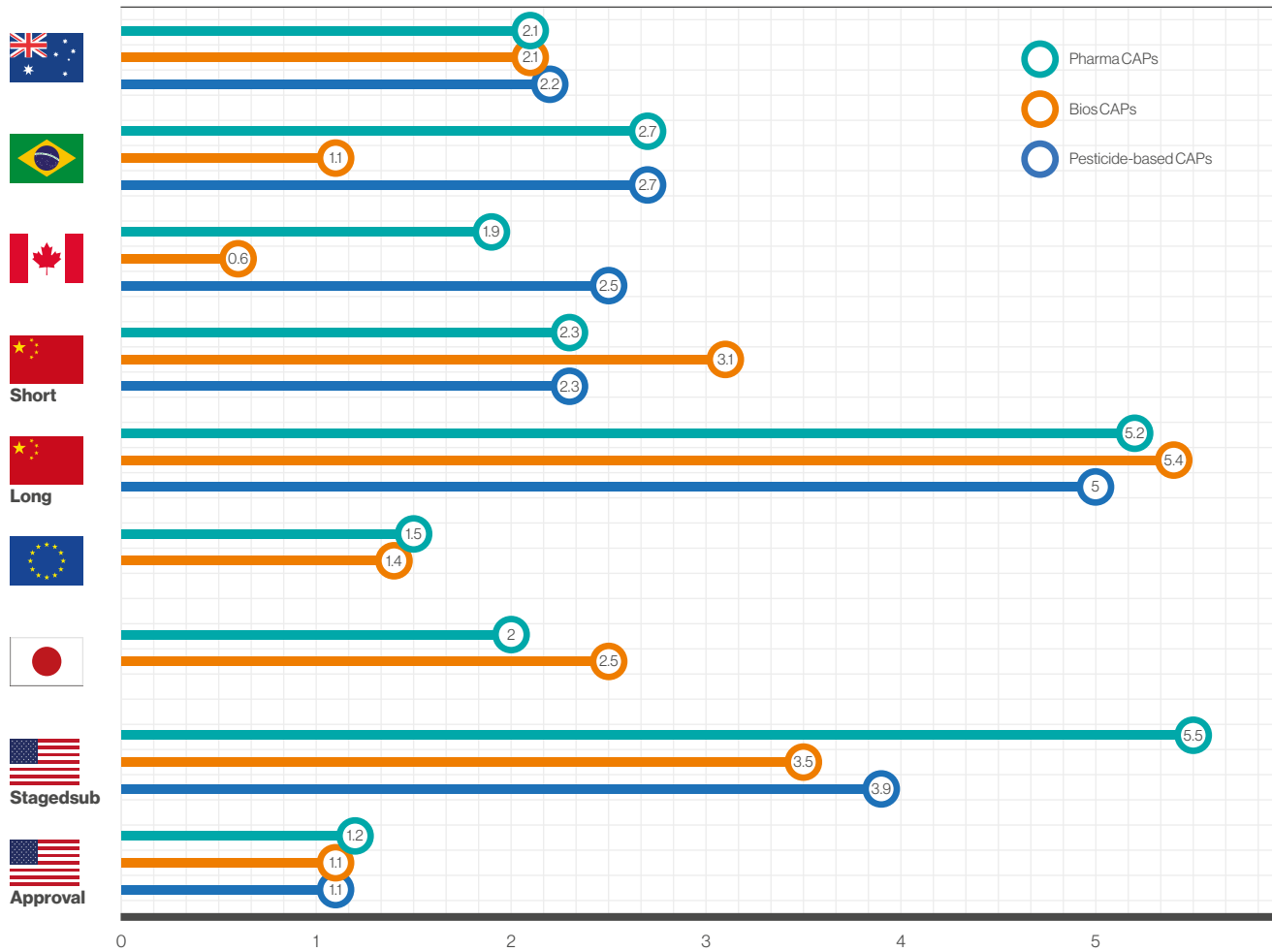
Figures 7, 8, 9 show average times-to-approval for new products by animal type and product types. For China, average short and average long times are shown and, for USA, the staged submission period and the time for final review and license issue. With the exception of China (and Australia for PAPs), time-to-approval for biological products is usually considerably shorter than for pharmaceutical products. Exceptions sometimes relate to longer times for GM biological products (based on gene-modification technologies or containing genetically-modified 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 7: **The average times-to-approval for new PAPs in years**



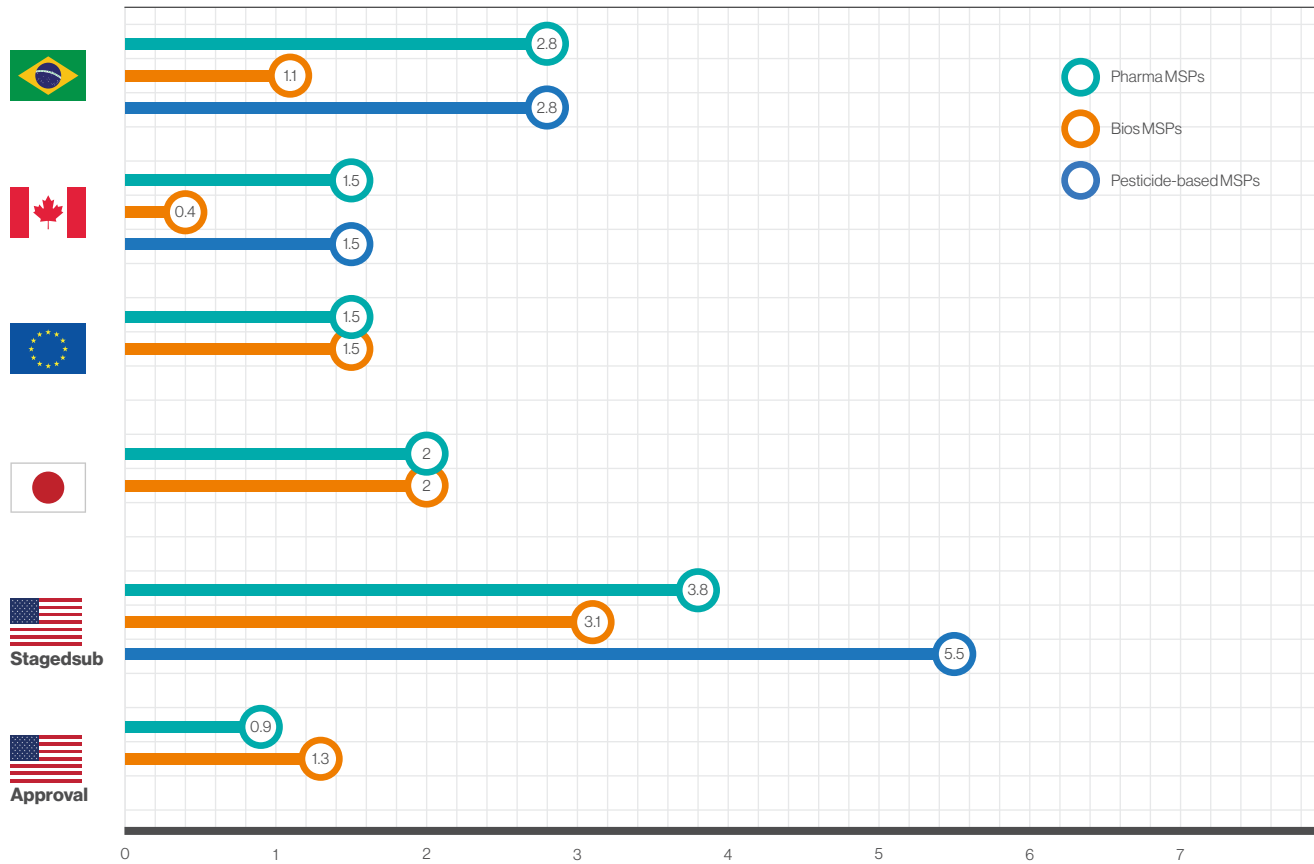
KEY FINDINGS

Figure 8: The average times-to-approval for new CAPs in years



KEY FINDINGS

Figure 9: The average times-to-approval for new MSPs in years



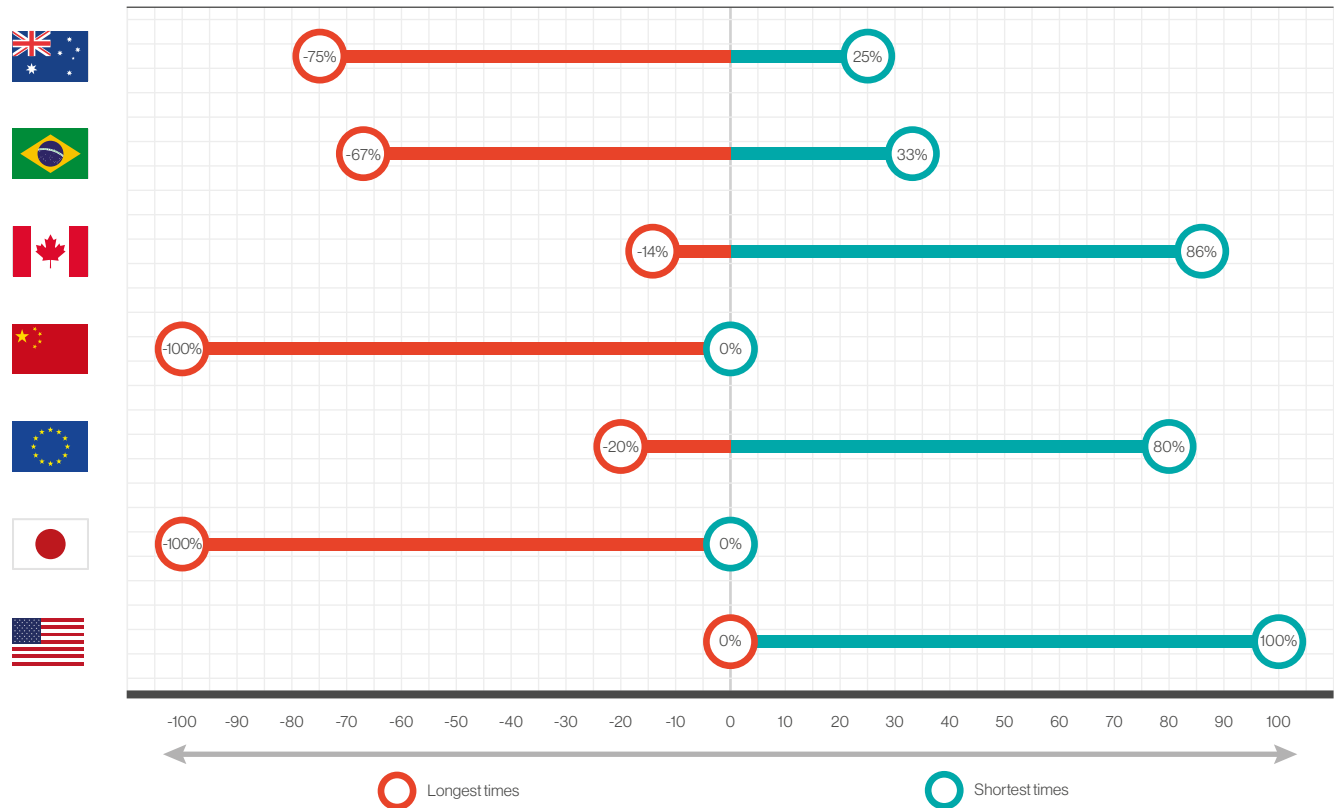
KEY FINDINGS

Figure 10 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.

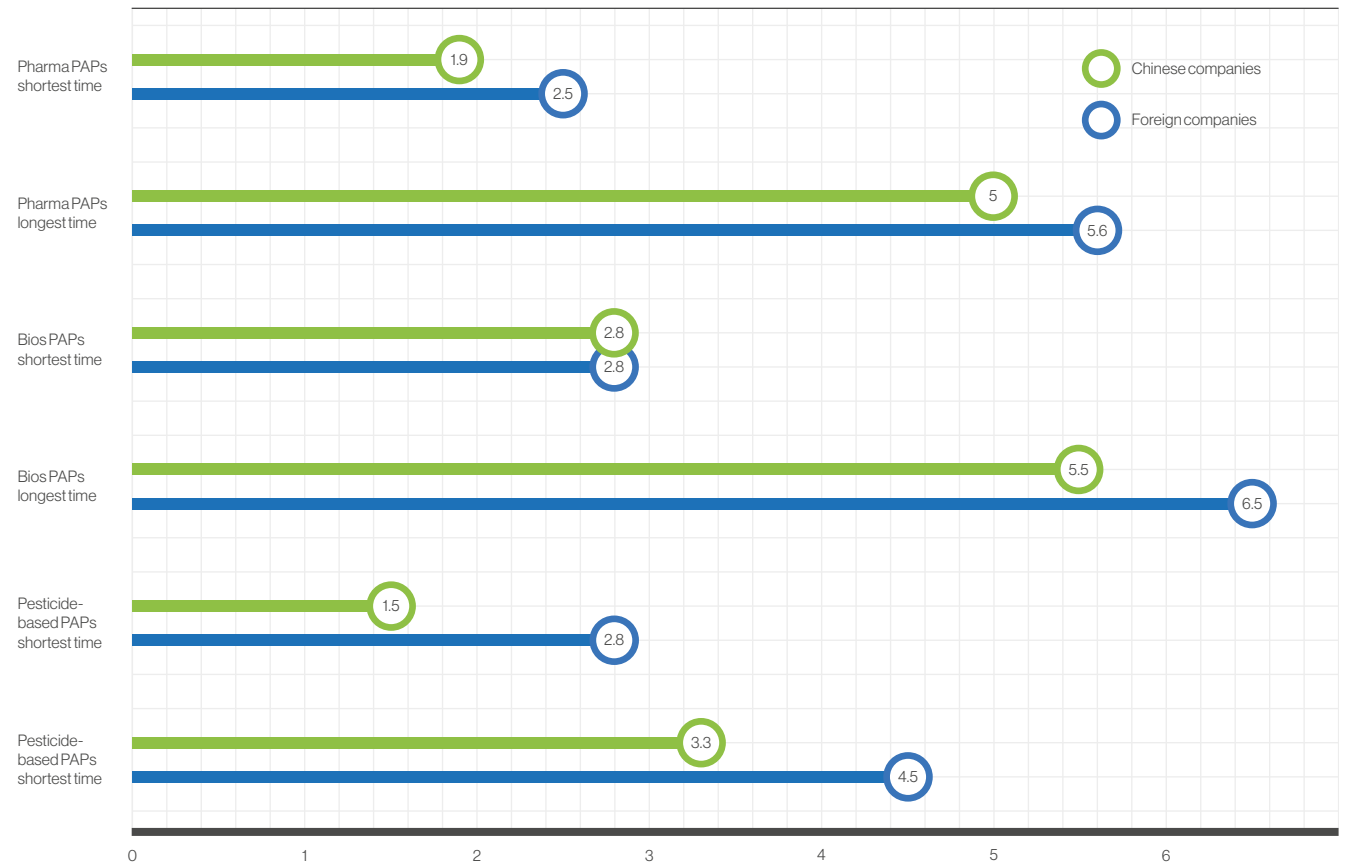
Figure 10: **Regions with shortest and longest times-to-approval**



KEY FINDINGS

China seems a special case. Reviewing over 50 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 11). 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 11: **The average times-to-approval from dossier submission for a major new product in years, domestic and foreign companies – China 2015**

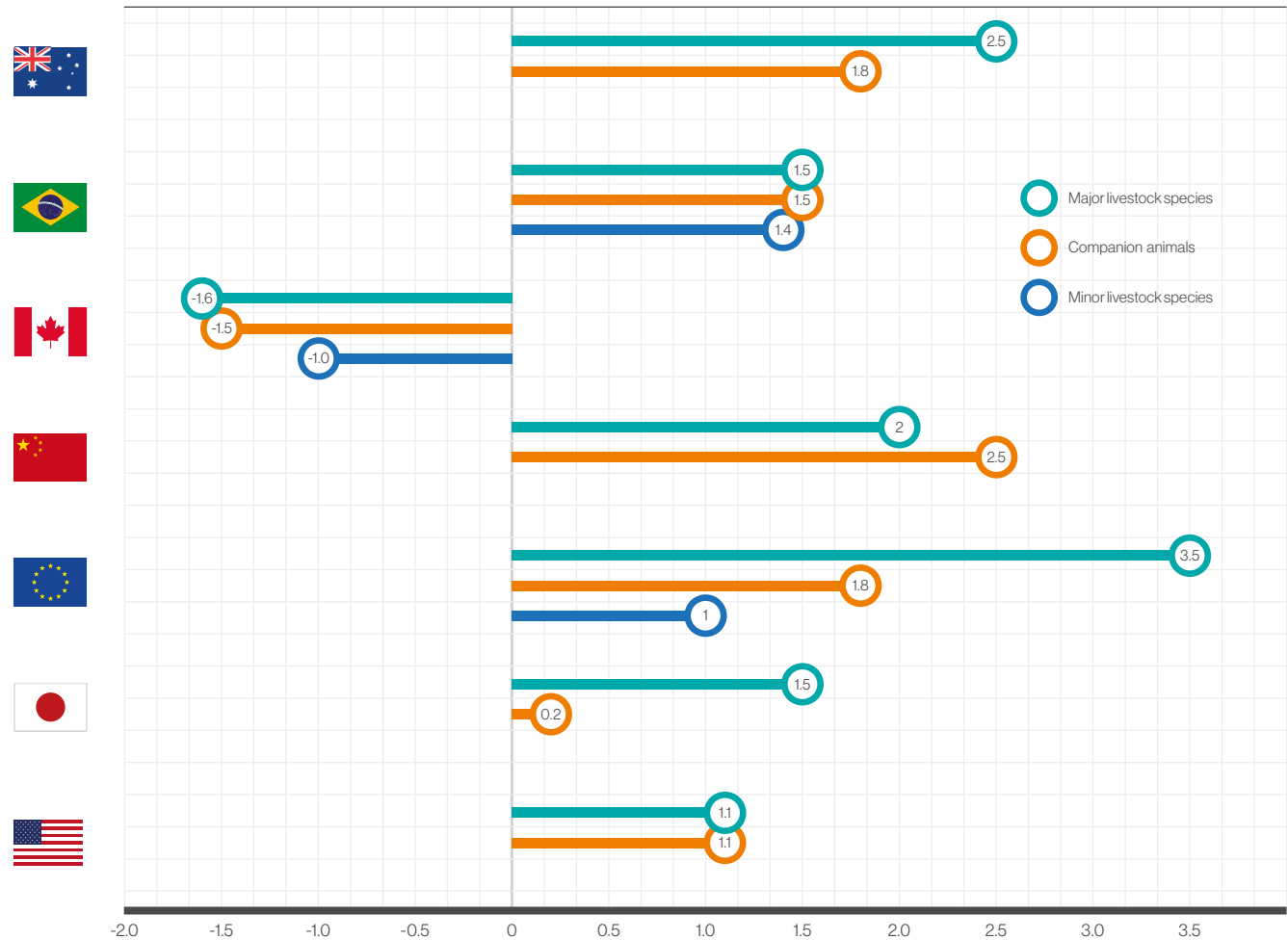


KEY FINDINGS

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 12). 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 12: Changes in time for full NPD in years, 2011-2015

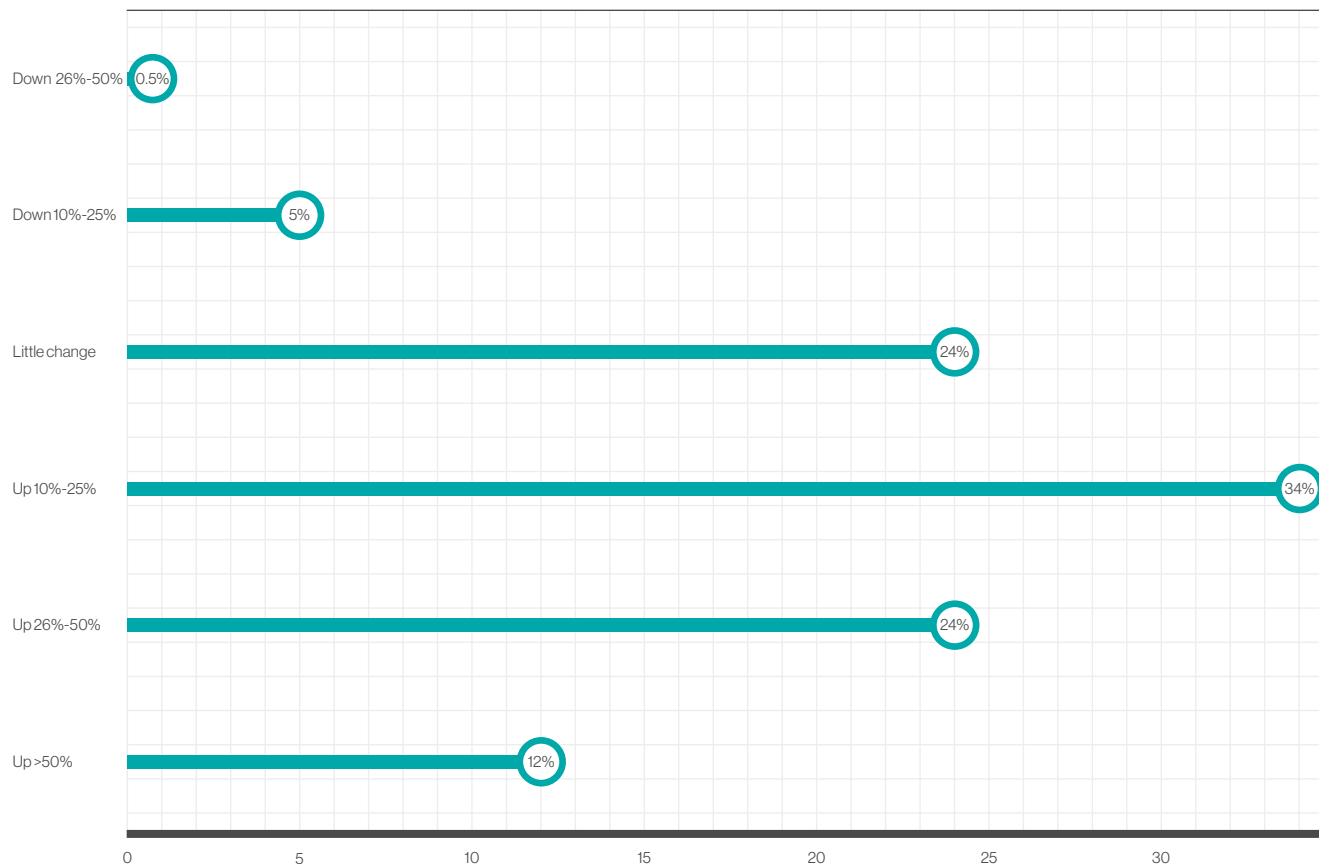


KEY FINDINGS

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, reflecting increased costs related to environmental risk assessments and studies addressing the potential for development of antimicrobial resistance. However, when asked about trends in costs of NPDs (Figure 13) approximately 70% of all respondents considered there had been increases in costs.

Figure 13: Overall trends in NPD costs 2011-2015

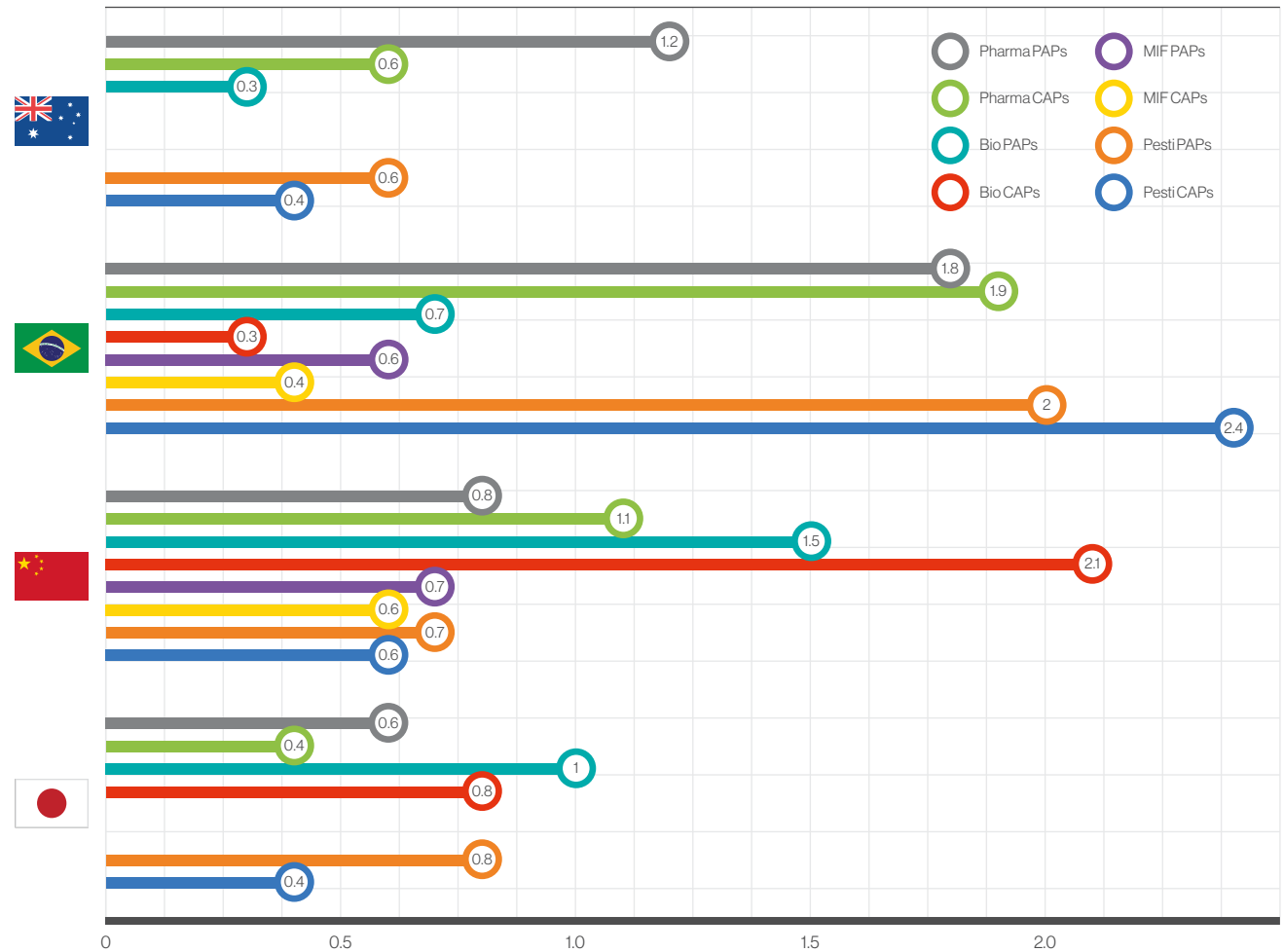


KEY FINDINGS

Product extensions – costs

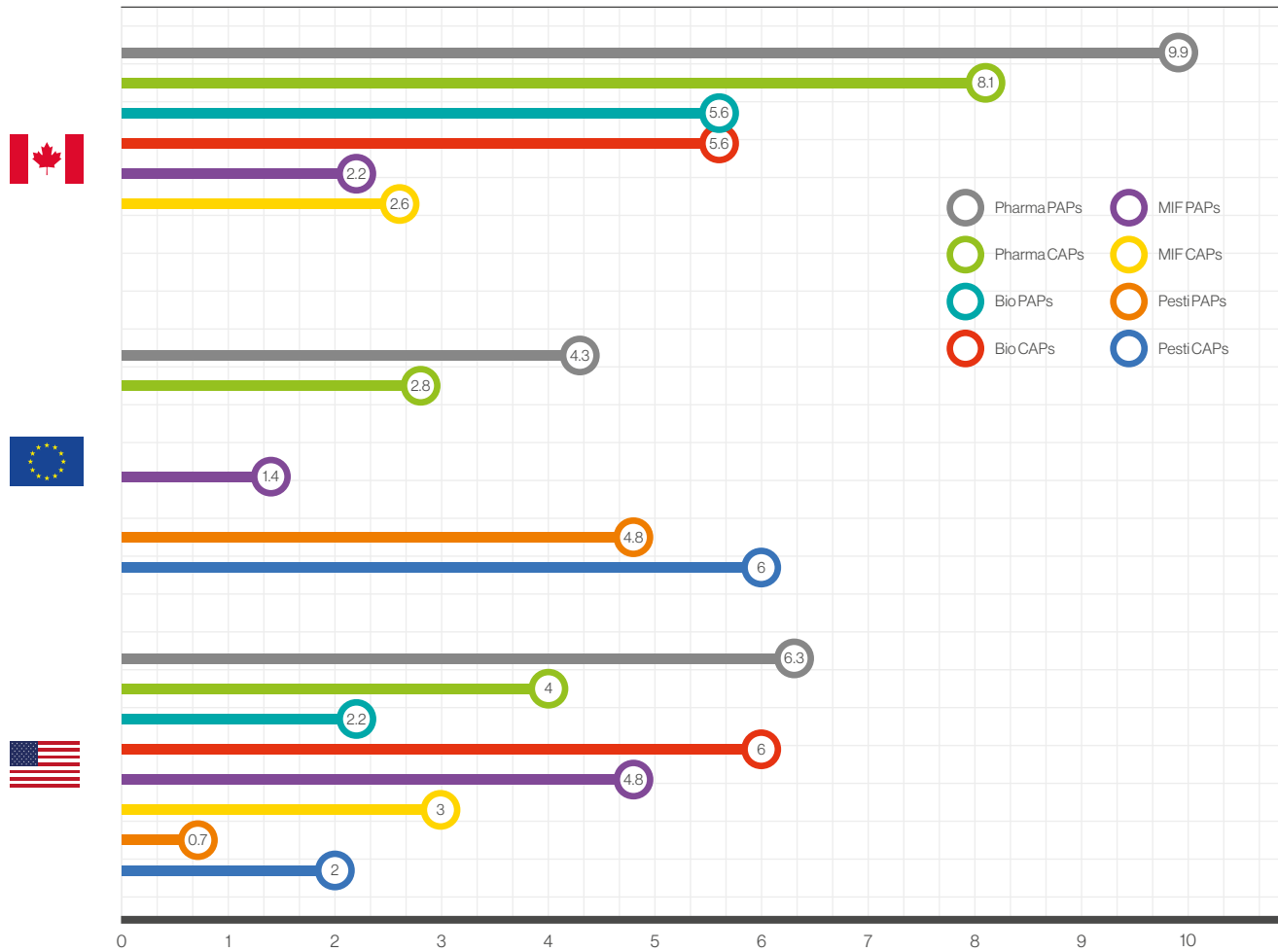
Figures 14 and 15 show the costs of adding a new claim or use to an existing PAP or CAP. The regions fall broadly into two classes – less expensive (Figure 14), comprising Australia, Brazil, China and Japan, and high-cost (Figure 15), comprising Canada, EU and USA.

Figure 14: The costs of adding a new claim or use to an existing PAP or CAP (in US\$M) in Australia, Brazil, China and Japan



KEY FINDINGS

Figure 15: 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

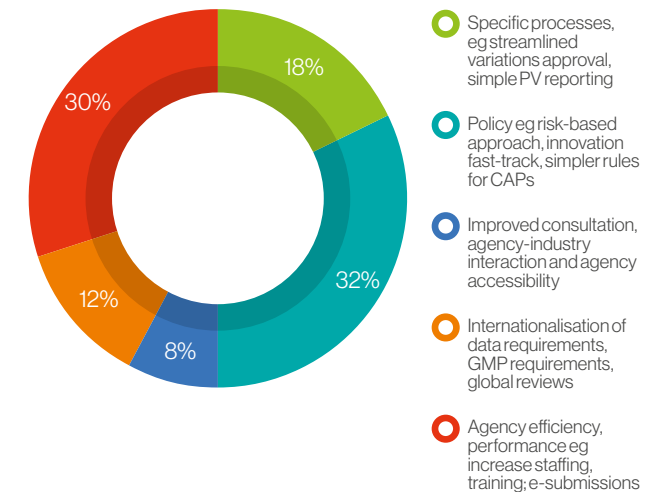
The industry is beginning to make more use of new digital tools and approaches. Over the next period, these will become pervasive for sales channels, data collection, feedback into NPD, recruitment of vets and trials subjects, tailored production and product supplies for specific customers and seasonal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

Figure 16 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.

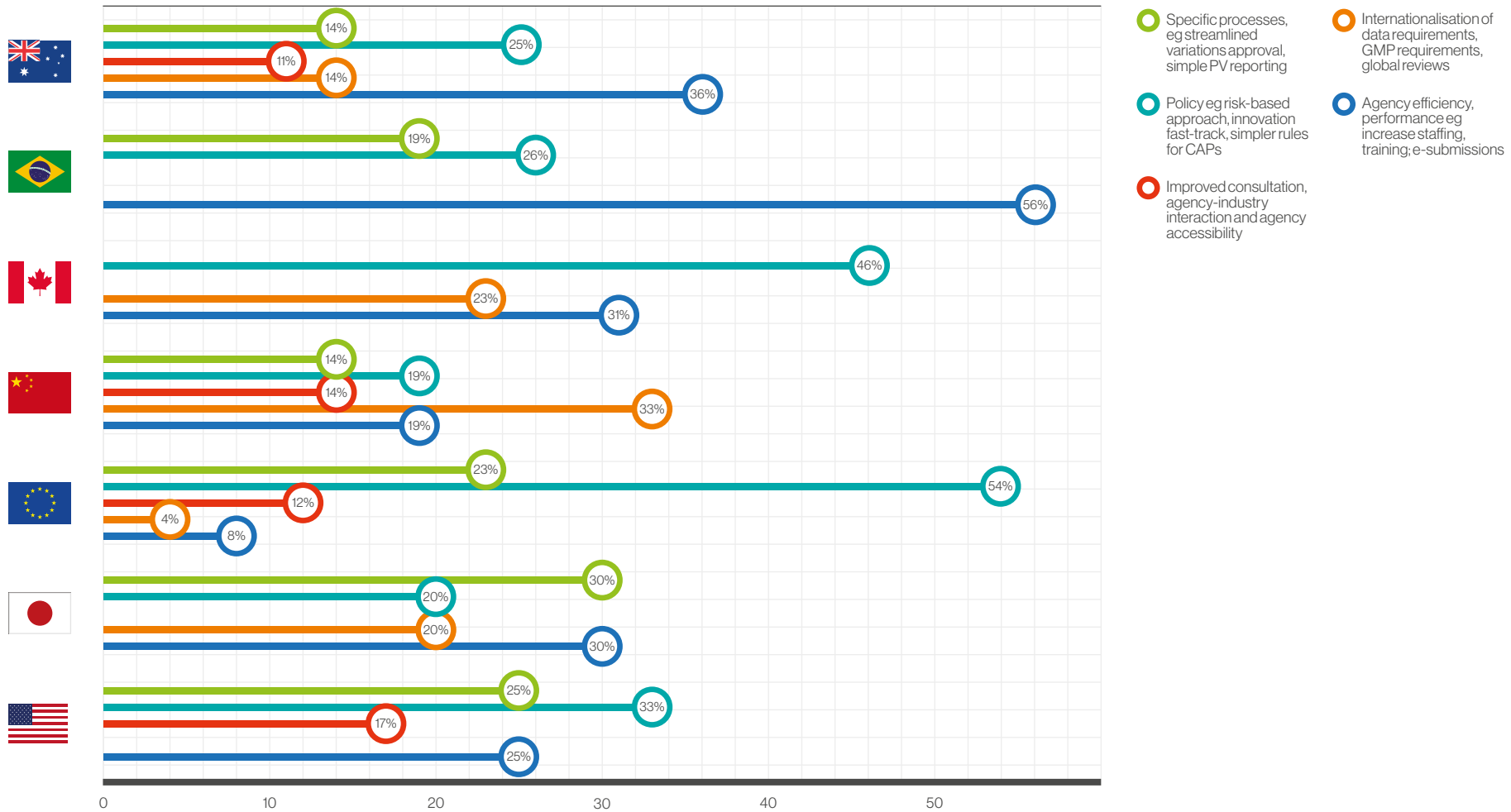
- Expanding e-submissions and inter-agency working, and mutual recognition of GCP, GMP, high-quality foreign data and approvals from well-regulated countries.
- Streamlining of excessive regulation of minor or frequent changes to products and manufacturing, and shorter timescales for approving applications 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 17).

Figure 16: **Regulatory changes companies would like for the future**



THE FUTURE AND SUGGESTIONS FOR ACTION

Figure 17: Regulatory changes companies would like for the future, by region



THE FUTURE AND SUGGESTIONS FOR ACTION

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

- The LRVHP (Low Risk Veterinary Health Products) programme in Canada (<https://www.lrvhp.ca/>), and similar moves in Australia.
- 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.
- Brazil's fast-track process for innovative products.
- ADUFA in USA and similar fee-for-service approaches.
- e-Submission of licence applications, post-approval variation requests and pharmacovigilance reporting, in formats compatible between regions.
- Streamlining of the review process for post-approval changes including product and manufacturing-site variations.
- Acceptance of foreign study reports and data if produced using appropriate Good Practice (GLP, GCP) and/or according to appropriate VICH guidelines.
- Mutual recognition of GMP and acceptance of the quality standards, SOPs and documentation for foreign products made using recognised appropriate GMP.
- Acceptance of the MRLs recommended by Codex Alimentarius.
- Ability of staff of all regulatory agencies to use risk:benefit assessment and product-specific risk analysis for a flexible approach to regulatory requirements.
- Fast-track, Conditional License or similar procedures that allow innovative products to reach market more rapidly with a risk-related regulatory review.

THE FUTURE AND SUGGESTIONS FOR ACTION

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



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.



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 e.g. for clinical studies so they are brought into line with VICH.



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.

THE FUTURE AND SUGGESTIONS FOR ACTION



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 process for products to control Class A diseases.



European Union

- 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.



Japan

- 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 GM 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 FUTURE AND SUGGESTIONS FOR ACTION



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 from e.g. 70,000 dogs.
- 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.

METHODOLOGY

The overall methodology is described in the introduction.

Definitions

- Innovation is defined as new APIs (active pharmaceutical ingredients), antigens products, technologies and services that bring new benefits to the market.
- R&D costs included all relevant internal costs, such as personnel, apportioned establishment costs, and allocated research costs, and those for outside resources such as CROs (Contract Research Organizations), field trials etc; and expenditure on defensive R&D.
- Defensive R&D was regarded as having two components: business defensive expenditure and mandatory defensive expenditure.
- Business defensive expenditure is what a company decided to undertake in order to defend its products against competition in the market.
- Mandatory defensive expenditure was undertaken as a direct result of legal requirements by the regulatory authorities if the company is to maintain existing products in the market, including compliance with requirements for license renewals.

- 'Pharmaceuticals' should include pharmaceuticals, in-feed therapeutic products and in-water therapeutic products, biocides and animal pesticides, and biopharmaceuticals only if regulated by the same agency as therapeutics.
- 'Biologicals' should include vaccines, antibodies, antitoxins, antisera, and biopharmaceuticals only if regulated by the same agency as biologicals.
- Minor Species were considered according to any definition applied by the appropriate regulatory agency/ agencies.
- Internal regulatory processes' were internal review committees, enhanced quality management procedures for regulatory process, additional oversight processes for external R&D and other internal procedures that impact product development and regulatory activity.
- To estimate the cost for developing a new product, all relevant internal costs, such as personnel, apportioned establishment costs, and allocated research costs should be included, plus those for outside resources such as CROs, field trials etc.
- 'Safety' includes all aspects (target species, human, consumer, environmental).
- When responding to questions concerning interactions with agencies, all levels of staff should be included.

The analytical methodology used an automated extraction of all data by region and question into a spreadsheet, which allows data to be aggregated then processed to obtain percentages, rankings and other summations and comparisons and provide the basis for visualisation as graphs, charts and other images. Rules established for evaluation of the results:

- not all companies reply to all questions, so the sample for each question is not always constant;
- turning results into percentages may be less valid for responses with fewer than 9 respondents, but it allows comparisons to be made across regions;
- for questions involving ranking we have taken into account the percentage of companies ranking each criterion at position 1 (the single most important factor) and sum of ranks 2-4 or 2-3 ('very important' factors) depending on whether there are more or less than 9 criteria or other choices;
- for questions about impact, or asking how important or helpful aspects were, positive and negative scores have been separately summed and the negatives subtracted from the positives, as a percentage of companies, providing a Relative Importance/Impact Score RIS or Relative Helpfulness Score RHS.

METHODOLOGY

For the global benchmarking, these RISs and RHSs can be further assessed to form a Relative Ranking of criteria, factors etc., visualising which have a consensus and which are divergent between regions.

For questions on regulatory predictability and quality of performance, we have taken the sum of the answers 'always' and 'mostly' and expressed these as a percentage of respondents.

For free-text comments, we have established the total number of respondents, separated off each comment by topic, and categorised by percentage of comments.

For the interview programme, interviewees were nominated by HealthforAnimals, HealthforAnimals constituent organisations and company CEOs/Presidents. Interviews were recorded and transcribed when conducted by phone. The transcripts have been coded and edited to anonymise the interviewees as much as possible. The recordings have been eliminated after transcription validation. The interviews covered issues in a more strategic way. They allowed interviewees to address the topics they felt were most important in the relationships between companies, business, R&D and innovation and regulation, complementing and amplifying the data available from the on-line surveys, with a wealth of experience and commentary. The most prominent points from the interviews are used in the report to provide context to the survey findings and to emphasise areas of opportunity, concern, pessimism and optimism.

The team

The BioBridge team: Dr Meredith Lloyd-Evans MRCVS, Mrs Sue Addison & Dr Ed Rayner; Dr Bruce Chick; Dr Byron Silva; Dr Sue McGee; Dr Jishu Shi & his colleagues; Dr Tony Dutton; Dr Atsuo Hata & Dr Yuki Ujimasa; Dr Johnny Jacobsen; Richard Tieken & Prelude Dynamics for the web component. Acknowledgements: the members of HealthforAnimals' Regulatory Strategy, GBS Project Teams and colleagues in Brazil, China and Japan; the staff of HealthforAnimals and the regional associations; and above all to all the survey respondents and interviewees, who have provided the raw information in 140 sessions in 7 regions, from which the GBS reports are composed.

Acknowledgement

If you use the illustrations in this report, please acknowledge BioBridge Ltd and HealthforAnimals 2016 in doing so.

The information in this report has been compiled from many sources, which cannot be attributed for reasons of confidentiality; Meredith Lloyd-Evans and BioBridge Ltd cannot guarantee the accuracy of the statements in this report, which represents the views of the industry, the findings of surveys and the outcomes of interviews, but any inaccuracies are not the responsibility of HealthforAnimals or its member associations.

January 2016

ABBREVIATIONS

| | | | | | |
|-------------------|-------------------------------------------------------------------------------------|-------------|----------------------------------------------------------|----------------------|-----------------------------------------------------------------------------------------------------------------------|
| ADAA | Animal Drug Availability Act, in USA | CDER | US FDA's Center for [human] drug evaluation and research | ESIs | In Australia, Export Slaughter Intervals |
| ADUFA | Animal Drug User Fees Act, in USA | CMC | Chemistry, Manufacture and Controls | EU | European Union |
| AH | Animal Health/animal health | CRO | Contract research organization | FDA | US Food & Drug Administration |
| AM[s], AMR | Antimicrobial[s], Antimicrobial Resistance | CTD | Common Technical Document | FMD | Foot & Mouth Disease |
| APHIS | The USA's Animal and Plant Health Inspection Service | CVDE | China's Center for Veterinary Drug Evaluation | FONSI | Finding of No Significant Impact by USDA APHIS in relation to a live/GM organism's potential for environmental damage |
| API | Active pharmaceutical ingredient | CVB | IN USA, APHIS's Center for Veterinary Biologics | FSC | Japan's Food Safety Commission |
| APVMA | Australian Pesticides and Veterinary Medicines Authority | CVM | In USA, the FDA's Center for Veterinary Medicines | GBS | Global Benchmarking Survey |
| AQIS | Australian Quarantine and Inspection Service | DNA | Deoxyribonucleic acid | GCP, GLP, GMP | Good Clinical Practice, Good Laboratory Practice, Good Manufacturing Practice |
| AVCLAA | The Agricultural and Veterinary Chemicals Legislation Amendment Act 2013, Australia | EFSA | European Food Safety Agency | GFI | Guidance for Industry, in USA |
| CAP[s] | Companion Animal Product[s] | EMA | European Medicines [Evaluation] Agency | GM, GMO | Genetically-modified/genetic modification, genetically-modified organism |
| | | EPA | US Environmental Protection Agency | | |

ABBREVIATIONS

| | | | | | |
|------------------|---------------------------------------------------------|-------------|------------------------------------------------------------|-----------------|-------------------------------------------------------------------------------------------------------------------------------------|
| INs | Normative Instructions, in Brazil | MUMS | Minor Uses-Minor Species | R&D | Research and Development |
| IP | Intellectual Property | MSPs | Minor Species products | RAs | Regulatory Agencies |
| IVDC | China's Institute for Veterinary Drug Control | NGOS | Non-Governmental Organisations | RHS, RIS | Relative Helpfulness, & Relative Importance or Impact Scores, according to context |
| J-MAFF | Japan's Ministry of Agriculture, Forestry and Fisheries | NPD | New Product Development – from discovery to final approval | ROI | Return-on-Investment |
| LRVHP | Canada's Low Risk Veterinary Health Products Program | OIE | World Organisation for Animal Health | USDA | US Department of Agriculture |
| MAPA | Brazil's Ministry of Agriculture, Livestock and Supply | OUI | In Canada, Own Use Importation | VDD | Canada's Veterinary Drugs Directorate |
| MDR&D | Mandatory Defensive R&D | OTC | Over the counter (non-prescription VMP) | VICH | Veterinary International Cooperation on Harmonization (of Technical Requirements for Registration of Veterinary Medicinal Products) |
| MHLW | Japan's Ministry of Health, Labour and Welfare | PAPs | Production Animal (major livestock species) products | WTO | World Trade Organization |
| MNC | Multinational company/corporation | PMDA | Japan's Pharmaceutical and Medical Devices Agency | | |
| MOA | China's Ministry of Agriculture | PMRA | Health Canada's Pest Management Regulatory Agency | | |
| MRL[s] | Maximum Residue Limit[s] (or level[s]) | | | | |

BioBridge are consultants in building business from bioscience innovations. We have a long history and successful track record in strategic aspects of science and business strategy for innovations and new developments as an early actor, technology translator, IP development advisor, profiler and communication facilitator. Meredith Lloyd-Evans, a veterinarian with almost 40 years' experience of animal health and its associated industries, founded BioBridge in 1989. Clients include industries, individuals, equity companies, universities, research institutes and public bodies, involved in animal health, human health, biotechnology, medical devices, biomaterials, agricultural resources, green industries, marine biotechnology and food. BioBridge has extensive experience in providing technology diligence for investment decisions, introducing potential sources of investment, technology and market analyses of university and research inventions, and mentoring and supporting start-ups. It helps clients understand the market, its dynamics, the impact of innovations, and who the real customers are. It also helps clients manage regulatory processes and develop business strategies.



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HealthforAnimals is a non-profit, non-governmental organisation representing manufacturers of veterinary pharmaceuticals, vaccines and other animal health products throughout the world, as well as the associations that represent companies at national and regional levels (referred to as Members). The animal health industry provides value to society by protecting animals and as a consequence, humans, from disease. Our products help keep pets and farm animals healthy. The public health benefits we bring include safer and more secure food supplies, more efficient production for increased food security, improved sustainability, and prevention of the transmission of zoonotic diseases.



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