Benchmarking the Competitiveness of the Global Animal Health Industry 2015 Survey

USA
Japan
Europe
Canada
Australia
Brazil
China

2015 Report

Report by BioBridge Ltd for HealthforAnimals and IFAH-Europe
Supporting informed policy making in Europe

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EXECUTIVE SUMMARY

The Global Benchmarking Survey 2015 report examines the interactions between industry and regulatory systems, particularly the impact of regulations on the animal health industry's ability to be innovative and competitive. The outcome of this survey provides a wealth of information to support informed policy decisions in the continual search for best regulatory practice and opportunities for improvement.

This leaflet provides a high-level overview of the Global Benchmarking Survey 2015 report for Europe. The first section covers the key conclusions and core findings for Europe. The second section outlines the key conclusions and findings from the global report which covers Australia, Brazil, Canada, China, Europe, Japan and the USA. The third section provides a Europe versus global comparison of these findings.

The overall Europe report shows that respondents note continued satisfaction with the Centralised Procedure for registering veterinary medicines. There is also a general welcome for many aspects of the proposed Veterinary Medicines Regulation, including the approaches to protection of technical documentation, pharmacovigilance, labelling and variation simplification. There remains concern however about antimicrobial resistance (AMR) and the future of innovation in antibiotics because of current opinions on the issue in the EU. High costs involved with maintaining products on the market and lack of harmonisation amongst member states for marketing authorisations also remain a challenge.

KEY CONCLUSIONS

- 69% consider EU regulatory environment to have negative impact on innovation:
  - restrictions on certain types of product
  - complex regulatory framework
  - insufficient data protection
- Major barriers included requirements for:
  - environmental risk assessments (ERA)
  - Europe's activities relating to antibiotic resistance
  - uncertainties on future data protection in the new Regulation
- R&D spend has fallen by 20% since 2006
- High cost of defending and maintaining products, especially manufacturing, compliance and variations costs is biggest factor impacting innovation
- Mandatory Defensive R&D (MD-R&D), as % of global R&D, has reduced to 29% (from 35% in 2011), but still considered high in comparison to other regions
- Proposed new Veterinary Medicines Regulation is a major change in the landscape; companies expect positive outcome following revision, noting that a large number of implementing acts cause uncertainty

Progress since the 2011 survey

GOOD PROGRESS

Improvements welcomed:

- management of variations (e.g. work-sharing and grouping)
- use of e-submission
- use of a benefit:risk approach
- acceptance of Codex Maximum Residue Levels (MRL)

NO PROGRESS

Insufficient improvement:

- Distrust between member states and increasing national autonomy in the national phases of Mutual Recognition Procedure (MRP)/ Decentralised Procedure (DCP) causes delays:
  - last-minute objections and demands for changes in labelling
  - delays in issuing approvals (from 2 to 8 months)

UNHELPFUL PROGRESS

Unanimously regarded as very unhelpful:

- retention of the 'global marketing authorisation concept' (seriously undermines innovation)
- new data transparency initiatives (commercially sensitive data exposed)
- unpredictable socio-political environment; lack of facts and science-based arguments

CORE FINDINGS

Positives:

- Work-sharing and grouping for variations
- Satisfaction with the Centralised Procedure, and to a lesser extent with the Decentralised Procedure
- Positive expectations on aspects of the future Veterinary Medicines Regulation
- Progress with E-submissions
- EMA approach to assisting innovations
- Larger regulatory authorities of NW Europe are perceived as open to dialogue, with efficient processes and reliable outcomes
- Apparent reduction in the cost of, or investment in, new product development (NPD) projects (except livestock biologicals)

Challenges:

> *"The regulatory impact of AMR has had deep effects on company willingness to invest in innovation, not only in antibiotics."*

- Increase in opinions regarding the regulatory environment as negative for innovation
- The retention of the global marketing authorisation
- Serious concern about the future of antimicrobials and antimicrobial innovation
- Continued concern about the small and fragmented market resulting in disproportionate regulatory burdens
- The increase in new product development time, especially for livestock products
- Adverse impact of ERA requirements on innovation and attrition of existing products
- Challenging socio-political environment impacts predictability and science-based approach to decision-making for regulations (e.g. antimicrobials)
- The absence of a unified outcome in the EU; national agencies still have their own interpretations of guidelines; additional demands; own timescales to issue a marketing authorisation (MA)
- 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
- Difficulties with national language labelling and 'same-language' packs
- Negative aspects of variations - high numbers needed for minor changes in products
- The cost and resource requirements for the increasing pharmacovigilance demands

Market factors:

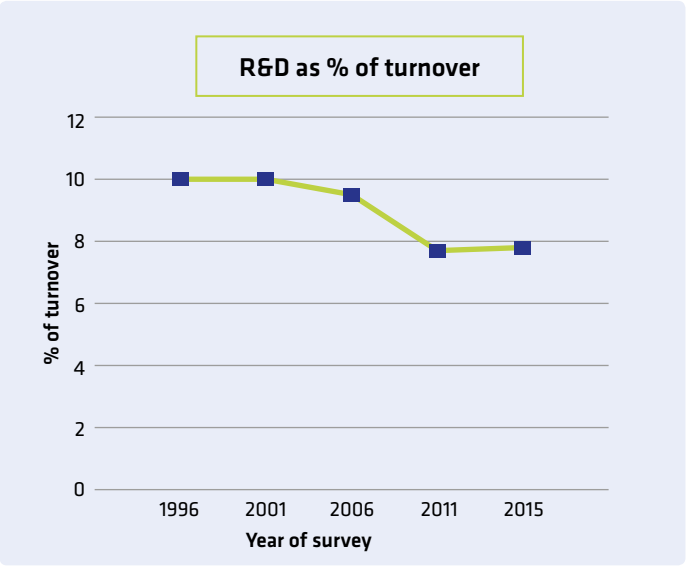
- Continued consolidation in the industry – 3 companies command >50% of the market
- Stagnant market – more recently becoming more positive and economically dynamic
- Organic growth is slow - acquisitions of companies or products are increasing
- All companies now have generics, competing in every segment (which may relate to the apparent reduced cost of NPD)
- Significant level of investment in companies of all sizes as animal health gains importance
- Increased interest in medicated pet foods and animal nutraceuticals, with some associated regulatory difficulties
- The digital revolution is arriving

The impacts of regulation

Research & Development (R&D) spend

- Average R&D spend is 7.8% of turnover
- After 2006 there was a step change from 10% to 7.8% (see graph)
- 77% spent on pharmaceuticals, 27% on biologicals
- 61% spent on food-animals, 39% on companion animals
- The % spend on food-animal products is increasing, reflecting the increased costs of NPD for food-animals

Innovation

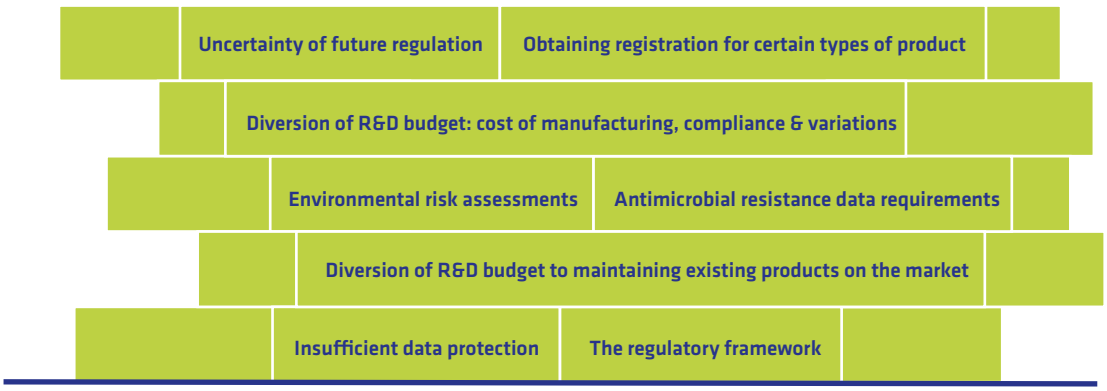


Observation:
The timing of this step change coincides with the new EU legislation coming into operation in 2005, after which there was a large shift in product development away from new products to generic products.
The drop in spend on product development is believed to be compensated by an increased spend in less highly regulated areas. These include nutraceuticals, or customer support areas, such as diagnostics, disease predictions, and business management support for veterinary practices.

All companies now have generic products in their portfolios

- Overall worsening of opinions despite satisfaction that the Centralised Procedure is predictable and effective:
- 69% regard the regulatory environment as negative towards innovation (36% in 2011)
- Those regarding it as positive fell from 18% to 8%
- Concerns about rising demands for maintenance and compliance, pharmacovigilance, increased Environmental Risk Assessment (ERA) costs and lack of harmonisation in procedures between national agencies

The regulatory environment and barriers to innovation



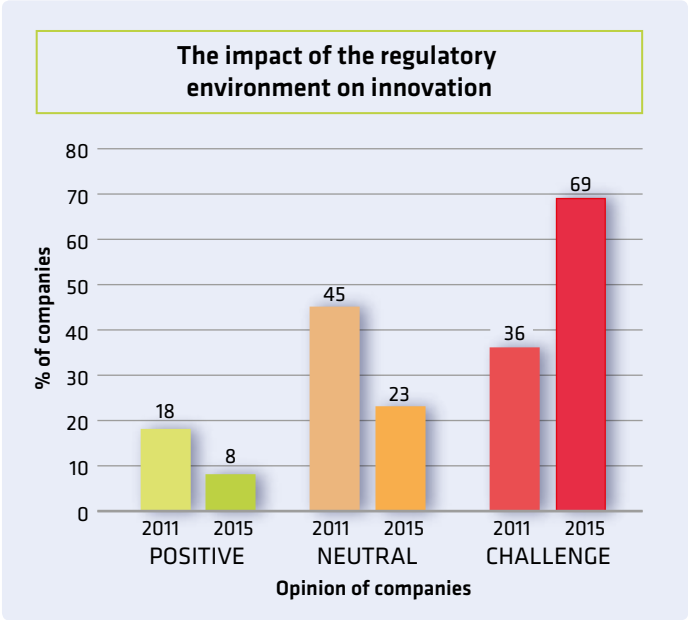
The impact of specific elements of regulations on the industry's ability to innovate

Top 4 positives	RHS
1. Centralised procedure	+85%
2. Decentralised procedure	+54%
3. Patent protection	+38%
4. Mutual recognition procedure	+23%

Top 4 challenges	RHS
1. Environmental risk assessments	-100%
2. Antimicrobial resistance requirements	-58%
3. Protection of technical documentation	-23%
4. Maximum residue limits data requirements	-23%

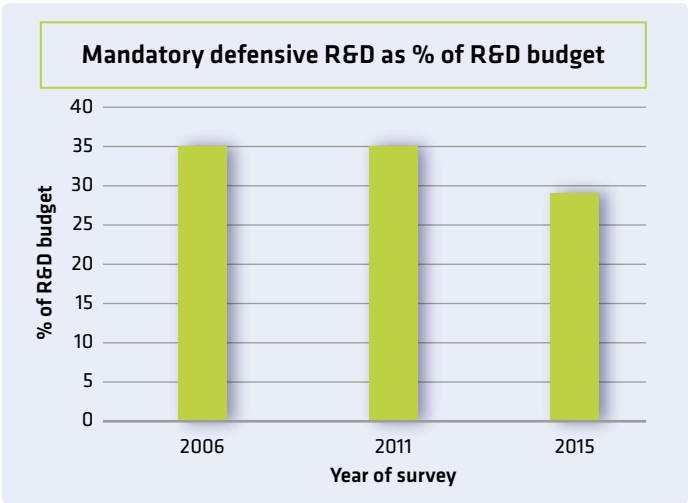
RHS (relative helpfulness scores) – total percentage of companies regarding a procedure or requirement as helpful or very helpful minus the total regarding it as unhelpful or very unhelpful

Trend: All the positive areas have increased their relative helpfulness scores (RHS) since 2011 while all the scores for the negative areas have become worse.



Mandatory Defensive R&D (MD-R&D)

- The average has declined to 29% of R&D budget from 35% in previous surveys
  - Individual companies ranged from 6% to 50%
  - The 5 top spenders averaged 45%
- No company has reported a decrease in MD-R&D spend since the 2006 survey
- The majority reported an increase in MD-R&D spend
  - 76% cited 'increased referrals' as a major cause of the increase



"We have reduced our company's MD-R&D expenditure from 30% in 2011 to 21% in 2014, not because the situation had improved, but because we decided to spend fewer resources in defence and maintenance of existing products."

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). Data was collected on the time needed for NPD and the cost of NPD and was compared to data from the 2011 benchmarking survey.

Time

The regulatory step: time from the dossier submission to when a MA is issued.

41 examples were provided, including
27 pharmaceuticals and 11 biologicals.

- On average the regulatory approval step for both types of product took 1½ years
- No significant change from the 2011 survey (some decreases of 1 or 2 months)

Changes in the total time for NPD, from the start of research until a MA is obtained

18 examples were provided, including
11 pharmaceuticals and 7 biologicals.

- The average NPD process has increased by 1 year for livestock species in 2015 (c.f. 2011)
- For companion animals and minor species the average increase in NPD time is ½ year

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.

Costs

New Product Development (NPD)

18 examples of costs of NPD were provided;
11 for pharma products and 7 for biologicals.

- Mixed picture compared with 2011; some product types have increased in NPD costs and some decreased (e.g. PAP pharma is down, while PAP biologicals is up)
- The cost to develop innovative ('high cost') products has increased to €49-62 M (c.f. 2011 €48-50 M)
- Other products cost around €10 M (little difference between pharma/bio and PAP/CAP)

Product extension

17 examples of pharma product extensions were given (9 PAPs, 6 CAPs and 2 MSP)

- The 2 MSP extensions had considerably reduced costs (-64%)
- The CAP and PAP extensions had increased costs of just over 10%
- A PAP extension costs approximately 35% of the original NPD cost on average

Overall little change in the cost of product extensions, except the 2 minor species product extensions cost much less.

"Many regulatory agencies have difficulties dealing with the uncertainties of innovative products, and may try to use human medicine guidelines on new developments such as biotech biologicals."

Stakeholders and their influence

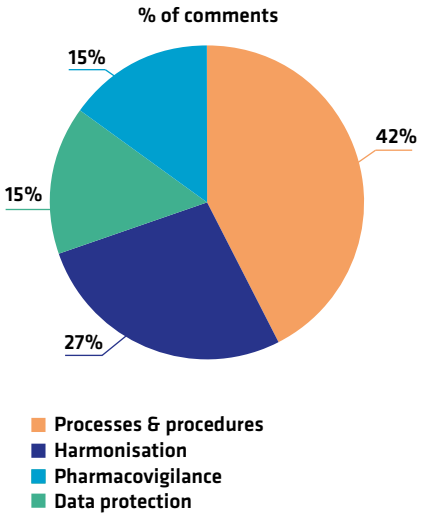
- Political and NGO involvement continues to impact regulatory process
- Socio-political interventions tend to push the regulatory framework away from science-based decision making towards risk adverse regulations
- Other EU bodies are perceived to influence regulatory process with an impact on veterinary medicines
- 'Specific interest bodies' command a loud voice, for issues such as ecotoxicology, antimicrobials and food safety, impacting regulatory cost & predictability
- National decisions impact VMPs, e.g. the French 'Loi d'avenir' concerning antibiotics, and in Germany where the ERA is done independent of any overall benefit: risk assessment
- Industry is concerned that decisions are sometimes taken in the absence of knowledge of the existing regulatory framework, and are based on non-scientific arguments

Regulatory changes still wanted for the future

Improvements to processes and procedures, particularly:

- A more determined effort for harmonisation, within the EU and internationally
- The specific areas of pharmacovigilance and data protection
- More dialogue with rapporteurs during scientific advice
- Risk-based approaches and science-based decisions
- Better SPC (Summary of Product Characteristics) harmonisation processes
- Involvement of industry in the implementing Acts for the new Regulation
- Single-dossier, single-process
- Risk-based pharmacovigilance, including removal of the periodic nature of safety reports
- Better data protection for antibiotics, to encourage continuing investment
- Better data protection for new species and for additional indications for existing species.

Regulatory changes companies would like for the future by type



Most desired changes yet to be achieved:

- Base dossier reviews for existing products solely on pharmacovigilance data and other relevant progress in science
- Reduce the administrative burden as regards procedures and greater harmonisation between member states

Most impacted business decisions:

100% of surveyed companies said EU Regulations have had the most impact on:

- reduced product range in Europe
- reduced coverage of species in Europe

Global Benchmarking – all regions

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

KEY CONCLUSIONS

- **Regulatory regimes** can make or break the industry's ability to fulfil its function
- **Regulatory expectations** are conditioned by human pharmaceutical frameworks - guidelines or procedures are inappropriately applied to animal health products
- **Veterinary medicines market** is estimated at $24B in 2015, about 2.5% of the human health market
- Two main factors **impeding innovation** are: (a) investment required to ensure that data packages are valid for all parts of the world; (b) significant expense of maintaining products on the market (taking 15-39% R&D budgets)
- **Incompatibilities** in requirements between EU and USA
  - e.g. e-submissions, trial protocol approval in US, differences in statistical and validation methodology, absence of timetables in US and different approaches to data protection periods
- **Positive aspects** in the US include staged submissions and public acceptance of biotechnology (e.g. for vaccines), but are not necessarily compatible with other regions
- **Globally** there are some highlights of improvement but tremendous areas of concern remain, notably failure of harmonisation to make significant progress
- **Brazil and Australia** were seen as more conservative than the US towards innovation
- **Antibiotics** and pressure on use in animals pose the biggest external challenge;
  - this introduces tremendous strategic and financial uncertainty into the industry
  - companies will not risk investment in developments that might become banned
- **Innovation** planning remains difficult
  - Agencies lack staff with expertise in new technologies; staff lack supporting guidelines
  - Improve coordination of scientific advice between FDA and EMA, and globally
- Globally adopt **best practices**; fast-tracking innovative new products (e.g. Brazil) or offering provisional conditional licences
- **Business innovation** is increasingly coming from activities not formally regulated, such as diagnostics, business management support for practices, or nutraceutical products
- The **digital world** has arrived and is an opportunity (e.g. Big Data management, and opportunities arising from the internet)

> *"Regulatory regimes can make or break our ability to bring new solutions to market, important for the health and welfare of animals."*

CORE FINDINGS

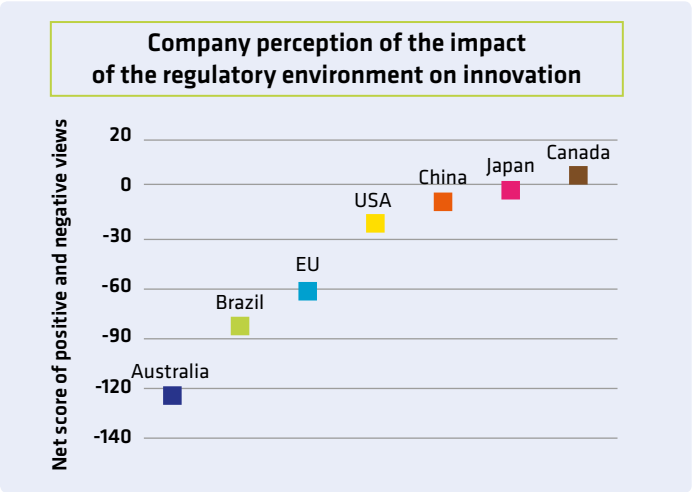
R&D

- R&D expenditure as a % of total sales varies from 6.2% in Canada to 9.3% in Australia
- Europe is 7.8%
- Most companies spend 7%-11%; average spend is 8%-9%

Regulations and innovation

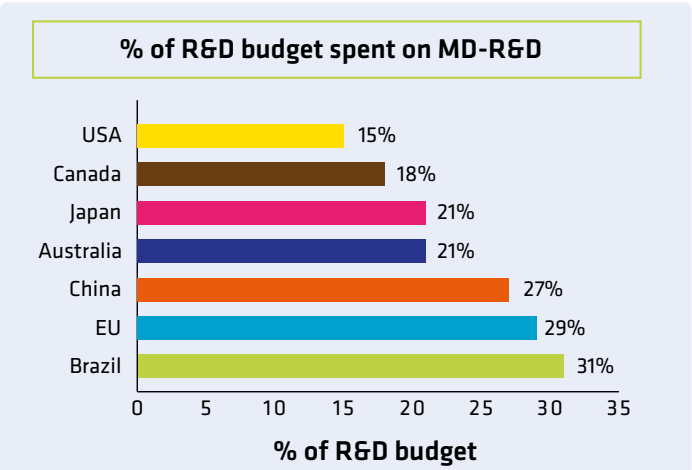
Considering impact of the regulatory environment on innovation:

- EU companies are very negative
- In Australia and Brazil opinion is worse, but these countries are currently undergoing major changes in their regulatory systems
- In Japan, China and USA opinion is moderate
- Only Canada reaches a positive score



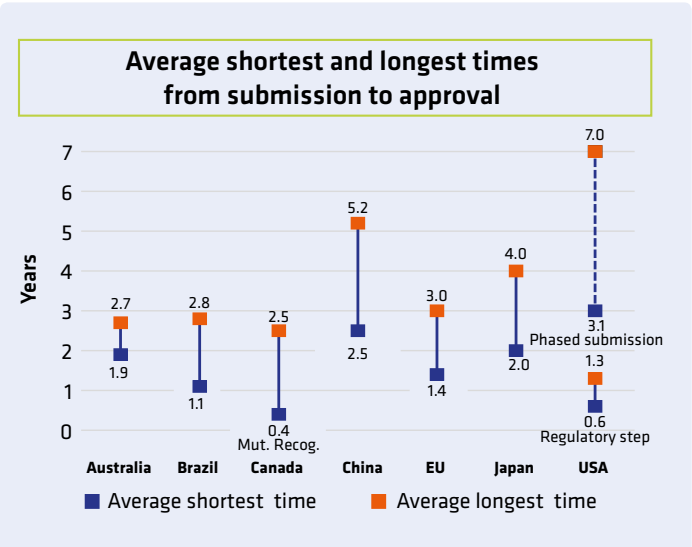
Mandatory Defensive R&D (MD-R&D)

- Large range between regions (15%-39% spent on MD-R&D as % of local R&D budget)
- EU is 29% versus 15% in USA
- Brazil: upgrading the regulatory system and product reviews has triggered a large increase
- All countries have seen an increase
- Overall <55% of companies report an increase
  - Increase in product review activities;
  - Acquisition of companies / products



Times-to-approval for new products: regulatory step

- China and Japan have the longest approval timelines
- USA: the prior staged submissions timelines are 3.7 to 7.2 or even 10 years
- Canada: mutual recognition agreement with USA can create short timelines
- China: has a wide range, possibly reflecting the level of local regulatory knowledge
- Approval time for biologicals is often shorter than pharmaceuticals
- Japan: long approval times caused by sequential involvement of 2 ministries
  - Changing this to a simultaneous review would have a big impact on times-to-approval



Trends in time for New Product Development (NPD)

- Increases in the time for NPD since 2011 range from 0.2 years to 3.5 years
- The increase in NPD time for CAPs tends to be smaller than that for PAPs

Costs of NPD

- Across the survey regions there is a complex mixture of:
  - large-scale full development activities
  - bridging or top-up studies needed to adapt a foreign dossier to local requirements
  - very low costs, e.g. for administrative fees for recognising an overseas license (Canada)
- Costs for a CAP were up to US$74M for a PAP up to US$75M
- 70% of respondents observed increases in NPD costs
- The highest costs were for pharmaceutical products in Europe, linked in part to increased costs related to environmental risk assessments and antimicrobial resistance (AMR)

Product extensions – costs

The regions fall into 2 groups for product extensions costs (adding a new species or claim):

- Less expensive: Australia, Brazil, China and Japan, (0.3 to 2.1 US$M)
- Higher cost: Canada, EU and USA (2.2 to 9.9 US$M)

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

- The Low Risk Products programme in Canada (https://www.lrvhp.ca)
- Regional collaboration on simultaneous assessments (e.g. joint US Center for Veterinary Medicine (CVM)-Canada's Veterinary Drugs Directorate (VDD) reviews)
- Work-sharing activities in the EU for review of post-approval variations
- Brazil's fast-track process for innovative products
- Animal Drug User Fee Act in USA and similar fee-for-service approaches
- E-submissions of applications, variations and pharmacovigilance reports in a standard format
- Streamlining of the review process for product and manufacturing-site variations
- Acceptance of foreign study reports and data if produced using VICH guidelines
- Mutual recognition of GMP and acceptance of foreign products made using recognised standards
- Acceptance of the MRLs recommended by Codex Alimentarius
- Use benefit:risk assessment and a flexible approach for product-specific risk analysis
- 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

Companies would like to see the following improvements:

- Focus more on risk-based approaches, and product-appropriate benefit:risk analyses
- Enhance transparency, predictability, efficiency and flexibility of agencies
- Improve accessibility of agency staff for discussion and advice on new technologies
- Increase staffing and provide continuous training to become innovation-ready
- Expand e-submissions and inter-agency working
- Promote mutual recognition of good clinical practice (GCP), good manufacturing practice (GMP), high-quality foreign data and product approvals
- Streamline approval of minor changes to products and manufacturing
- Propose global adoption of regional best regulatory practices

POSITIVES

- National regulations keep dangerous products off markets and provide assurance about the safety and high quality of authorised products.
- Agencies base approvals on expert evaluation of all quality, safety and efficacy data.
- Foreign data produced according to good laboratory practice (GLP) or VICH* guidelines increasingly accepted.
- E-submissions with some concern about incompatibility of formats accepted.
- Satisfaction with the Centralised Procedure.
- Good experiences with the work-sharing and grouping processes for variations.
- Proposed new Veterinary Medicines Regulation, generally well-received; cautious welcome on aspects such as data protection, pharmacovigilance, labelling and variation simplification.
- The large regulatory authorities of North West Europe are perceived as open to dialogue, with efficient processes and reliable outcomes.

CHALLENGES

- Lack of pre-submission dialogues and advice on regulatory options, in many countries.
- Insufficient staff and inadequate training in some countries (e.g. for manufacturing inspections or dealing with new technology).
- In some countries, lack of transparency of the review and approval process.
- Failure of agencies to contact applicants about new changes in regulatory procedures.
- Manufacturing inspectors in many countries apply human medicines criteria and inspection timelines impacting dossier review timelines.
- No adaptation of regulatory approaches to type of product or their specific risk profiles.
- Quality or timeliness of assessments when multiple agencies are involved in licensing.
- Influence of a wide-range of stakeholders on the regulatory process.
- Serious concern about AMR and the impact on the development of antimicrobials and innovation in the EU, as well as the approach to antibiotics in the proposed Veterinary Medicines Regulation.
- Unanimity that application of requirements for environmental risk assessments (ERA) impacts both innovation and existing products.
- The costs currently involved in maintaining and defending products.
- The difficulties in ensuring veterinary medicines availability in small Member States markets (regulatory burden and costs).
- Member States imposing their own conditions, or begin referral processes despite majority agreement at European level on marketing authorisations and usage conditions and take too long to issue national approvals.
- The involvement of multiple EU agencies for procedures related to products for production animals (PAPs) creates slow timelines and unpredictability.

MARKET FACTORS

- Pet market is expanding, with veterinarians becoming more influential.
- Supply chain is consolidating; food retailers and producers are more influential.
- Swine and poultry markets are each consolidating; the bovine sector is growing.
- Consolidation of customer base such as integrated meat producers and processors creates market pressures
- Increased competition in emerging markets is generating overall market growth but there is pressure on profit margins, which customer consolidation is also contributing to.
- Emerging markets with fewer compliance requirements influence plant investment decisions.
- Up to 2013 market was flat, but from 2014 it has been more positive and economically dynamic.
- Slower organic growth, acquisitions are increasing to create broader portfolios.
- All companies now have generics, and are now competing in every segment.
- Growing interest in medicated pet-foods and animal nutraceuticals (with some regulatory difficulties).
- High consolidation in the market, with 3 companies commanding more than 50% of the market.

* International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

The 2015 Global Benchmarking report is the fifth in the series, based on a survey taking place every five years since 1996. The 2015 survey is the first to include China and Brazil, in addition to Australia, Canada, Europe, Japan and USA. The European report analyses data from 13 European companies, and compares it with the other regions.

The full Europe report and further information including an overview presentation is available from the IFAH-Europe website: **www.ifaheurope.org**

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