Europe IFAH
Representing the European Animal Health Industry

Industry perspective on challenges meeting the requirements for authorisation of vaccines in the EU

IFAH-Europe Biologicals Working Party

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Industry perspective on requirements for vaccines

- Some figures (IFAH benchmark)
- Where are the problems
  - Regulatory texts (Reg, Dir, monograph, GL, …)
  - Some examples
- Proposals for improvement
  - Regulatory level
  - Guidelines level
  - People level
- Conclusion

IFAH benchmark survey report 2011 Key elements

- Vaccines are key: « In terms of technology and innovation, companies in Europe and the USA are looking to replace (or supplement) disease treatment products with disease prevention via vaccine technologies and biotechnology.”

IFAH benchmark survey report 2011
Key elements

Companies report being able to get to market with a new biological 12-24 months earlier in USA than in Europe.

Time and costs for product development and registration

The average length of time to gain registration for a major new product for major livestock species in USA, in years [C9]	*major livestock species*	*companion animals*	*minor species*
Pharmaceuticals	9.4 yrs	6.4 yrs	6.0 yrs
New conventional vaccine, new Master Seed	4.3 yrs	4.1 yrs	5.5 yrs
New conventional vaccine, combination of licensed products	3.6 yrs	2.8 yrs	3.0 yrs
GMO products requiring NEPA RA/FONSI	5.4 yrs	5.0 yrs	6.0 yrs
Biologic Conditional License	2.8 yrs	2.9 yrs	3.5 yrs

- Comment: differences may be due to absence of repetition (e.g. pivotal efficacy), shorter studies (e.g. DoI) and absence of final registration process (15+ months).

IFAH benchmark survey report 2011
Key elements

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Development costs are higher in EU.

The approximate cost of developing a recent new FAP	AUSTRALIA A$M	CANADA C$M	EUROPE €M	JAPAN ¥100M	USA US$M
Pharmaceutical product with new active ingredient	52	1.27	21.6	1.4	38.8
New biological product	84	0.003	15.1	1.18	10.8
				9.5 €	8.8 €

3-4 US products for only 2 EU products!

The approximate cost of developing a recent new CAP	AUSTRALIA A$M	CANADA C$M	EUROPE €M	JAPAN ¥100M	USA US$M
Pharmaceutical product with new active ingredient	37	0.26	12.0	1.48	21.6
New biological product	26	0.003	13.8	1.03	11.8
				8.2 €	9.7 €

- Comment: differences may be due to more studies, demanding standards, longer time, cost of manpower.

IFAH benchmark survey report 2011
Key elements

« MUMS » Vaccines exist both sides: development costs difference is even greater.

The approximate cost of developing a recent new [MU]MS product in US$M	AUSTRALIA	CANADA	EUROPE	JAPAN	USA
Pharmaceutical product with new active ingredient	-	-	11.7	0.7	8.0
New biological product	-	-	8.0	-	3.0

2.5 €

3-4 US products for only 1 EU product!

- Comment: differences may be due to pragmatic approach of 'reasonable expectation of efficacy' and acceptable information on quality and safety

IFAH Europe – observations

- IFAH Benchmark: “Industry has their specific US products and licenses, facilities and US antigens. European industry has given up on the idea that there are vaccines, antigens made in EU that should be freely available in US for use or research.”

- IFAH-Europe: EU Industry is facing increasing challenges in exporting EU-made products linked to several factors e.g. costs of production, time to markets, customs barriers,....)

Where are the problems?

- Regulation/Directives:
  - High level of flexibility allowing various approaches:
  - MA (CP, DCP..), Art 7, Art 8, MA under except circ.
  - Open wording: ‘when data suggest’, ‘in general’, ‘should be discussed’, ‘should be shown’ (≠ should be demonstrated; should ≠must), ‘a more flexible approach’, …

- but
  - Interpreted with local/personal input (-> GL)

Where are the problems?

- Guidelines:
  - Always allowing alternatives (but undefined or non-precised),
  - Managed by EMA (not EU Commission),
  - Trying to cover all situations (even exceptional, infrequent)
- but
  - Differences in interpretation
  - Unpredictable reading/interpretation
  - Taken as ‘compulsory’ or require heavy validation of alternative
  - EU mind-set of risk aversion (more theoretical science than pragmatism or B/R approach)

Where are the problems?

- Monographs:
  - Should target vaccine quality
  - Compulsory only for identified parts,
  - Covering more and more diseases (not only major threats)
- but
  - Taken as ‘compulsory’ especially the ‘development part’ or asking heavy validation of alternative
  - Challenge design sometimes too strict/unique/not validated
  - Taken as a tool for assessment (in or not in… MA or not MA)
  - Sometimes old,
  - Slow update

Compliance to regulatory texts: where are the problems?

- Everything is doable but needs time and resources (animals, money, equipment, …)
- Especially true when departing from GL (justification has a cost)
- Ph.Eur. monographs: more concerns as ‘compulsory’ or felt ‘compulsory’
  - Confusing
  - Too complex
  - Too strict

Compliance to text / guidelines: where are the problems? Concrete examples:

- (Re-)use MRP:
  - clearly re-assessment of entire dossier,
  - even sometimes assessment of (recent) registered product
- Combination guidelines:
  - asking for all data
    - whatever existing knowledge
    - all claims
  - Giving (apparently) flexibility:
    - If a threshold … recognized as a correlate of protection… has been established … the challenge … can be omitted
    - mixing of IVMPs does not negatively affect the onset and duration of immunity
- GRIMV
  - If an antibiotic not listed in table 1 of the annex to Regulation 37/2010 is used, then the applicant should address the consumer safety implications

Compliance to monographs: where are the problems? Concrete examples:

- Some further details on monographs:
  - Confusing: *Salmonella Enteritidis*: immunogenicity test (222): how to do direct plating of fresh faeces samples and at the same time establish a number of live Salmonella?
  - Too complex (challenge design): *Actinobacillus pleuropneumoniae*, Coccidiosis
  - Too strict (for some vaccine, whereas there are no criteria for the same types of vaccines): infectious bronchitis inactivated vaccine for layers; fixed challenge route

Proposal for improvement: on GLs, on process

- IFAH Europe developed a long list of ideas for discussion ()

BWP list

- Not easy as often case-by-case or specific situation
- Could consider:
  - At Regulation level (incl. Ph.Eur.)
  - At Guideline level
  - At people level

Starting point / mindset

- MA should set a minimum level supporting a minimum SPC wording with acceptable R/B.
- Absence of knowledge is acceptable if transparency is ensured with end user
- Detailed claims will have to be supported by data, but detailed claims should not be required:
  - DoI, 1-shot revaccination schedule validation,
- To increase product availability, a reduction in costs/resources is essential
- Minor uses or diseases may never be covered as not economically viable, (cost of development/production/labelling/etc)

Proposal for improvement: on GLs, on process?

At Regulation level:

- if we cannot do less, can we do it more efficiently (quicker and/or cheaper)?
  - Clinical field trial? On-going stability? GxP level? 2-phase-filing, (repeat use and sunset clause)
  - Ph.Eur.: development part, sterility test removal for oral vaccine (all species) or web-wing administration, restricted extrapolation of maximum titer before inactivation

Proposal for improvement: on GLs, on process?

At GL level:

- Can we globally accept a pragmatic way to develop (based on successful history)?
  - Route of administration in poultry, serology as surrogate in some instances, update of vaccine strain(s), antibiotic residues in vaccine dose, (replacement of cell line)

Proposal for improvement: on GLs, on process?

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At people level:

- Key is common interpretation/understanding:
  - training (common to regulators and industry, (eg. TAIEX type) can support this
- Collaborative approach is always better :
  - antibiotic residues in vaccine dose, RD114, Bio MUMS disease list

Proposal for improvement: on GLs, on process?

At people level

(to apply more than academic/theoretical knowledge):

- QP declaration for active same for pharma and human, GMP questions during assessment, use of PV data, day-old chick from both layer and broiler for field test.
- B/R including absence of data, MUMS having less data (no on-going development),

Conclusion

- If more product availability is expected it should come with incentives and new ways
- Today context/environment is not favourable to such trend except when political wish is present
- Risk sharing: common choices allow common decisions
- Categorize: reduce scope to a manageable size:
- Historical data: a lot of information is already available and assessed, use it with confidence

Conclusion

- **Next steps**
  - Be pro-active and innovative during afternoon session
  - Preliminary list of IFAH Europe is available for your review and use
  - Need collaborative work with all stakeholders representatives (small working groups)

IFAH-Europe Contact Details

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Thank You!

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