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Perspective of veterinary SMEs on challenges meeting the requirements for authorisation of vaccines in the EU

Dr Rhona Banks

Veterinary Biologicals Consultant

Objective

– Particular challenges faced by SMEs in authorising products at EU and National level

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Challenges Faced by SMEs

- EC wants to promote innovation and development of new medicinal products by SMEs
  - 'Think small first'
  - SMEs in Commission Recommendation 2003/361/EC
  - Financial awards are available
  - Have to be registered – form to complete (EMA has a guide to the New SME definition – 52 pages)

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Challenges Faced by SMEs

- Once Registered at the EMA there is a lot of assistance
  - SME Office
  - News bulletins
  - SME Workshop (annual)
  - EMA personnel are well prepared to meet with SMEs
  - Access to Innovation Task Force
  - Financial incentives (scientific advice, admin assistance re translations, fee deferral and other items)

- This seems a lot ..... However....

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Challenges Faced by SMEs

- SMEs are very varied
  - Research institutions
  - Universities
  - Start up companies (often Spin-offs)
  - Contract organisations
- R+D concerns involved with novel technologies
  - Main intent seems to be demonstration of ‘Proof of Principle’ only
  - Path from this to actual Development of a Product seems to be less than clear

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SME Understanding of Regulations

- Seldom anyone with a Regulatory background who understands (or has even read) the requirements
- General idea that ‘Regulations are important’
- Virtually no consideration on how to use the regulations to actually develop a product
- Rarely prepare a draft Summary of Product Characteristics which could be used as a:
  - Target to work towards the claims for the product
  - Baseline for the development team to understand
  - Checklist for what needs to be achieved
  - Reference document to monitor development

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What effect does this have?

- Starting materials used may not be in line with requirements
- Seed materials may not have been prepared correctly (often little history either)
- Method for preparation of the biological product not described well
  - Difference in how batches have been prepared
  - No real SOPs in place
  - Method creep
- Little consideration on how to scale up from R+D level to pilot scale or commercial scale

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What effect does this have?

- Safety and Efficacy studies not set up in line with Ph Eur methods (may forget to consider specific or closely related monographs)
- Challenge methods not sufficiently well set up (lack of effect on Control group)
- Too few animals in each group (can't show statistical relevance)
- Or: Very large number of animals in each group (in desperation to show statistical relevance)
- Frequently have to start whole development again (wastes animals, time, money)

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What effect does this have?

- Even getting registered as an SME takes time and is not always simple
- SMEs often not well prepared for discussions with regulators
- Do not know the most useful questions to ask for Scientific Advice (or how to present them)
- Reluctant to use Joint Scientific Advice with EMA/FDA
- May not understand the regulators explanations
- Frequently stop interaction with regulators so that they can get additional finance

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Suggestion

- There is little training on Regulatory aspects in either Scientific degree courses or in Veterinarian qualifications
- Understanding of many SMEs is that financial funds available are for demonstration of safety and efficacy in animals or for production of the vaccine
- Financial awards do not appear to be considered as usable for Regulatory advice or training
- There should be a real Outreach in Regulatory training at a more basic level

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English

- Joined the Veterinary Medicines Directorate (UK) in 1996
- Carried out QA/QC inspections at vaccine production sites all over the EU
- Wrap up sessions
- Realised many people did not understand me
- Developed my own ‘Simple English’

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Why Use Simple English?

- It is not because I cannot write very complicated sentences with double negatives and diabolical grammar, not forgetting subclauses, all of which are indicative of a confused mind and which leave the reader almost completely unable to understand the issues being discussed or to remember how the sentence started.
- It is not because I consider my readers or listeners to be unintelligent.
- It is for clarity.

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Why Not Use Simple English?

- The Directives, Regulations, Guidelines, Lists of Questions are often written in a complex way.
- It is not unusual to find sentences containing >50 words
- This may be stated as ‘custom and practice’ or ‘for legal reasons’
- However, it must be possible to simplify the wording so that everything is easier to understand
- This would certainly aid SME companies ….

  and large companies and regulators too

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How to Demonstrate Efficacy?

- Back in 1996 – at the VMD
- Training for assessment of Vaccines
  - Quality and Safety must be thoroughly assessed
  - Efficacy should have ‘reasonable evidence’ but do not expect it to be fully proven…this would be established in the field.
  - Shocked!

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How to Demonstrate Efficacy?

- Since 1996 - ever increasing emphasis on demonstration of efficacy particularly to include statistical significance
  - Not easy: vaccines are rarely 100% effective
  - Challenge models: balance is difficult, variability between animals
  - Ph Eur monographs generally recommend use of relatively few animals to establish immunogenicity
  - Highly likely that some studies based on these would not reach statistical significance (but there would be a good difference)
  - No monograph – greater expectations

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How to Demonstrate Efficacy?

- There are now many more questions focused on the Efficacy part of the dossier
- May be time for a little more pragmatism
- Historical evidence shows many vaccinations induce ‘Herd immunity’ even if not 100% effective
- Benefit : Risk assessment very important particularly for unmet animal health issues
- Vaccination can reduce antibiotic usage

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How to Demonstrate Efficacy?

- May be sufficient to accept a ‘Reasonable evidence of efficacy’ for a new vaccine
- Provided:
  - Quality and Safety have been well established
  - Pharmacovigilance monitoring for SLEE
- Vet market is very small and paid for by the users and profit margins are low. If Vets, farmers or owners do not see a value to a vaccine then they will not use it.

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Regulatory work is tough for Biologicals!

Thank you for listening

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