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Expanding the regulatory decision making from relying on pre-approval individual efficacy data to post-approval evidence of population benefit

Elements from the EU regulatory landscape

Frank Vandendriessche
Pharmacist, PhD

Consultant at PhaRA
Pharmaceutical Regulatory Affairs Consultancy
www.phara-consulting.be

Outline of presentation

- EU regulatory framework & some vaccine specifics
- What if efficacy cannot be shown ?

  What beyond efficacy ?
  - Current case examples
  - Future case examples
- EU Adaptive Pathways and vaccines ?
- Overall conclusions

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EU Regulatory Framework

- Basis of licensure of medicinal products:
  potential risks outweighed by therapeutic efficacy

- RCT considered ‘golden standard’ for efficacy

- Allows for
  - Mandatory post-authorisation efficacy studies (PAES)
    to complement or verify initial evidence e.g
  - Approval under Exceptional Circumstances
  - Conditional Approval

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Some Vaccine Specifics *

PAES studies may be required to complement initial evidence or verify it e.g. efficacy in real life use

Protective efficacy not necessary and/or feasible for all types of vaccines.

Whether or not protective efficacy is assessed pre-authorization, attempts should be made to estimate vaccine effectiveness post-authorization.

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Conclusion

FOR THE BENEFIT-RISK ASSESSMENT OF VACCINES

THE EU REGULATORY FRAMEWORK ALLOWS (PARTLY) RELYING ON

(POST-APPROVAL) EVIDENCE OF (POPULATION) BENEFIT

***IN LIEU* OF**

PRE-APPROVAL EFFICACY

……BUT HOW MUCH ???

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Current case examples

- ✓ Meningitis C, ACWY and B vaccines
- ✓ Pneumococcal vaccines
- ✓ Rotaviral vaccines
- ✓ Human papillomavirus vaccines
- ✓ (Pre)pandemic influenza vaccines

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Current case examples

Conclusions

- ***EU vaccines have been approved in absence of vaccine specific efficacy data***
- ***Effectiveness and vaccine impact data have typically been typically post-approval commitments***
- ***Such data have been included in label updates***
- ***Exceptionally, such data have partly been used at time of approval***

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Future case examples

- ✓ Novel, non PS-conjugate vaccines
- ✓ Group B streptococcal vaccines
- ✓ Transmission blocking malaria vaccines
- ✓ Novel TBC vaccines
- ✓ HIV vaccines
- ✓ Dengue vaccines
- ✓ Ebola vaccines

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Future case examples

Conclusions

- ***As in the past,***
  - ***future vaccines may have to be approved in absence of efficacy data***
    Relying on surrogate markers of protection ?
  - ***Effectiveness and vaccine impact data will be asked as typical post-approval commitments***
  - ***Such data will (have to) be included in label updates***
- ***Are there more needs/options for alternative regulatory approaches for novel vaccines under development ?***

  Can the EU Adaptive Pathways be useful ?

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EU Adaptive Pathways Pilot

(See also M. Cavaleri – DIA Paris 2015)

// Support the selection of pathway of product development and (potential) earlier access to medicines through early dialogue involving all stakeholders (regulators, HTAs, payers, patients, learned societies…)

// **Criteria for candidate selection**

1. An iterative development plan
   a/ start in a well-defined subpopulation and expand

   b/ Conditional Marketing Authorisation (surrogate endpoints and confirm)

2. Real World Data (safety and efficacy) to supplement Clinical Trials
3. Input of all stakeholders, particularly HTAs, is fundamental
4. Unmet medical need

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EU Adaptive Pathways Pilot (*ctd.*)

(See also M. Cavaleri – DIA Paris 2015)

- Positive Benefit/Risk required for approval.
- Only uses existing regulatory tools.
- Discussion is non binding, safe-harbour brainstorming.
- Request for parallel EMA/HTA advice expected to follow, to discuss in depth and get formal advice letter.
- Acceptance/rejection in pilot has no inference about approval potential.

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EU Adaptive Pathways

Vaccines ?

- Real-life data dependent on recommendations
- Need to engage with public health authorities and vaccine recommendations committees

- Define subpopulations that would be most in urgent need of access to new vaccines ?

- Develop regulatory science tools to help in understanding immunogenicity and ultimately predict protection.

- Vaccine recommending EU bodies ??

- Quid vaccines mainly for outside EU ??
  (Art. 58 Opinion – no HTA ?)

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Conclusions

- EU regulatory framework allows for
  - approvals in absence of vaccine specific efficacy data
  - considering effectiveness data and vaccine impact data (post-approval)
- Effectiveness/vaccine impact data generally come after vaccine approval and may be used to update product labeling, in support of recommendations.
- Future cases will include those where vaccine efficacy can not easily be shown and effectiveness/vaccine impact data are important to consider pre- and/or post approval.

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Conclusions (*ctd.*)

- Whether a given data set will result in a positive benefit/risk assessment, is a scientific and medical assessment made (by CHMP) at time of vaccine licensing.
- Mechanism are in place for early dialogue with EU regulators, including the EMA pilot on Adaptive Pathways.
- EMA pilot on Adaptive Pathways could be used but may need identification and involvement of **all** relevant stakeholders, including payers/funders and/or vaccine recommending bodies.
- If the vaccine is not (mainly) intended for the EU, regulatory processes and options exist for EU Authorities/EMA to make available their vaccine assessment experience.

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Thank you for your attention