EU regulatory perspective on ZKV for emergency vaccines

Geneva, 7 June 2016
Approval pathways for vaccines

• **Full approval** based on efficacy (e.g. rotavirus vaccines) or immunological data (e.g. MenB vaccine)

• **Conditional marketing approval** (e.g. H5N1 LAIV vaccine for use in a declared pandemic)

• **Approval under exceptional circumstances** (e.g. smallpox vaccine)

• **Art. 58 Scientific Opinion** for use outside of EU (e.g. malaria vaccine)
Conditional Marketing Authorisation

Products for which the applicant can demonstrate the positive benefit/risk balance, based for example on early evidence of effects that are expected to predict the clinical outcome from an ultimately comprehensive development, might be authorised under a conditional marketing authorisation (Article 14(8) of Regulation (EC) No 726/2004).

This temporary authorisation is not intended to remain conditional. It is reviewed once a year and may be renewed and, once the data required for confirming the positive benefit/risk relationship are provided (a “full dossier”), it can become a “normal” marketing authorisation.
Conditional Marketing Authorisation

On the basis of less comprehensive data and subject to specific obligations

**Scope** (at least one):
- for **seriously debilitating diseases or life-threatening diseases**;
- to be used in **emergency situations**;
- **orphan** medicinal products.

**Criteria** (all):
- the **risk-benefit balance is positive**;
- it is likely that the applicant **will be in a position to provide comprehensive clinical data**;
- **unmet medical needs** will be fulfilled;
- the **benefit** to public health of the **immediate availability** on the market of the medicinal product concerned **outweighs the risk** inherent in the fact that additional data are still required.

‘**unmet medical needs**’ means a condition for which there exists no satisfactory method of diagnosis, prevention or treatment authorised in the Community or, even if such a method exists, in relation to which the medicinal product concerned will be of major therapeutic advantage to those affected.
B/R balance in absence of comprehensive data

Risks identified in the studies conducted + risks related to the absence of some of the data

Benefits demonstrated with the available data

Disproportionate from the public health perspective to delay the approval of the medicinal product could potentially be based on intermediate endpoints that are reasonably likely to translate into clinical benefit, but do not directly measure the clinical benefit
### Missing elements* of comprehensive data**

<table>
<thead>
<tr>
<th>Data at the time of CMA</th>
<th>Data generated through specific obligations</th>
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</thead>
<tbody>
<tr>
<td>Data based on an intermediate endpoint (e.g. overall response rate)</td>
<td>Data on clinically most relevant efficacy endpoint (e.g. survival data)</td>
</tr>
<tr>
<td>Data from limited study/-ies</td>
<td>Data from a larger database or for longer duration, with the same endpoint(s) (e.g. response rate at a later time cut-off)</td>
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<tr>
<td>Data in overall population</td>
<td>Further data in important sub-populations (e.g. in patients with resistance or a particular biomarker)</td>
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<tr>
<td>Data on certain endpoints</td>
<td>Further data on additional endpoints / specific issues identified</td>
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<tr>
<td>Data in a certain combination therapy</td>
<td>Data with other co-medication for combination therapies</td>
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<tr>
<td><strong>Immunogenicity data</strong></td>
<td><strong>Vaccine effectiveness data</strong></td>
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* justified based on the strength of available results and taking into account the requirement for a positive B/R balance  
** data requirements laid down in Annex I of Directive 2001/83/EC, including confirmatory studies normally required in the particular indication for respective type of the medicinal product
Marketing authorisation under exceptional circumstances

- **Article 14 (8) of Regulation (EC) No 726/2004**: In exceptional circumstances and following consultation with the applicant, the marketing authorisation may be granted **subject to certain conditions**, in particular relating to the safety of the medicinal product, notification to the competent authorities of any incident relating to its use, and action to be taken. The marketing authorisation may be granted only when the applicant can **show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use**, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I to Directive 2001/83/EC. Continuation of the marketing authorisation shall be linked to the **annual reassessment** of these conditions.


- **CHMP Guideline EMEA/357981/2005**
Criteria of MA under exceptional circumstances

Criteria as per Annex I to Directive 2001/83/EC:

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or

- in the present state of scientific knowledge, comprehensive information cannot be provided, or

- it would be contrary to generally accepted principles of medical ethics to collect such information.
Conditional MA

- Comprehensive data expected after authorisation
- To later switch to ‘full’ MA
- Valid for 1 year only
- Annual renewals
- Only in centralised procedure

MA under exceptional circumstances

- Comprehensive data not possible
- To remain such indefinitely
- Normal validity of MA
- Annual re-assessments
- Possible in all registration procedures
Article 58 of Regulation (EC) No. 726/2004

1. “The Agency may give a scientific opinion, in the context of cooperation with the World Health Organization, for the evaluation of certain medicinal products for human use intended exclusively for markets outside the Community. For this purpose, an application shall be submitted to the Agency in accordance with the provisions of Article 6. The Committee for Medicinal Products for Human Use may, after consulting the World Health Organisation, draw up a scientific opinion in accordance with the provisions of Articles 6 to 9. The provisions of Article 10 shall not apply.

2. The said Committee shall establish specific procedural rules for the implementation of paragraph 1, as well as for the provision of scientific advice.”
Article 58

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2. The said Committee shall establish specific procedures, rules and the implementation of paragraph 1, as well as for the provision of scientific advice.

Article 59

1. The Agency shall take care to ensure early identification of potential sources of conflict between its scientific opinions and those of other bodies established under Community law carrying out a similar task in relation to issues of common concern.

The alternates shall represent and vote for the members in their absence and may act as rapporteurs in accordance with Article 62. Members and alternates shall be chosen for their role and experience in the evaluation of medicinal products for human and veterinary use as appropriate and shall represent the competent national authorities.

2. The committee may co-opt a maximum of five additional members chosen on the basis of their specific scientific competence. These members shall be appointed for a term of three years, which may be renewed, and shall not have alternates.
Ad hoc expert group tasks

• Landscape analysis of potential investigational products for treatment or prevention of Zika virus infection based on current research platforms for flaviruses

• Early interaction with identified interested developers to explore options for regulatory support

• To identify the most appropriate regulatory approach to ensure that potential vaccines and/or treatments are progressed as swiftly as possible through drug development.

• Liaison and facilitation of scientific advice on questions from manufacturers on their development plans, endorsed by CHMP
Common topics discussed with ZKV vaccines developers

- Strain selection
- Toxicology package for Phase I
- Animal models of ZKV infection to be used as proof-of-concept and their timing within clinical development
- Other in vivo or in vitro studies to characterize immune response and risk of ADE, e.g. passive transfer studies etc
- Design and timing of reproductive toxicity studies
- Definition of doses for Phase I studies
- Establishment of immune marker that could be used as CoP
- Licensure pathways and feasibility of clinical trials with infection endpoints
TPP: Clinical illness prevention

- For prevention of clinical illness in women of child-bearing age:
  - definition of clinical illness
  - What is the evidence around symptomatic vs. asymptomatic ZKV infection and fetal malformations or GBS?
  - Importance of determining in efficacy trials the whole spectrum of prevention that the vaccines can achieve, including asymptomatic infection
TPP: Immune marker as primary endpoint

- **Use of neutralizing antibodies titer threshold:**
  - Which threshold? Based on which data?
  - Animal models?
  - Data from natural history of infection?
  - Human challenge studies?
  - Extrapolation from other flaviviruses? How?
  - Interplay among flaviviruses and risk of ADE
Difficult at this stage to define pathways:

- Reproductive toxicity studies, which should preferably be available also for Phase II studies in non-PWs, are a prerequisite but not necessarily sufficient per se to define potential risks.

- Essential to understand the potential to elicit adequate protective immunity in a rapid fashion with a single dose.

- The safety characterization should rely on both previous human data with the platform, if available, and any further evidence/ consideration on the potential risks associated with each type of construct and ZKV specificities.

- Would benefit from awaiting form clinical trials results in non-PWs.
The risk of GBS needs to be further characterized:

- It is still unclear whether the cases of GBS reported following ZKV infection have an autoimmune etiology or are a consequence of the direct effect of ZKV.

- If autoimmunity related, could impact all vaccines constructs and needs to be handled cautiously.

- Difficulties in envisaging robust investigations pre-approval.

- Post-authorisation safety studies will need to be conducted.

- Post-authorisation studies would be needed for estimating the impact on pregnancy and impact on other flaviviruses infections.
Conclusions

- Need for expedited regulatory pathways in front of an emergency
- Advancement in the understanding of ZKV disease and its clinical sequelae needed to inform regulatory strategies
- Various regulatory tools such as conditional marketing authorisation are available for licensure before or during an outbreak
- Definition of correlates of protection and assays validation/standardisation
- Vaccines construct specific aspects
- Handling of uncertainties and post-approval studies as needed
- EMA ready to contribute to international regulatory discussion
Thank you for your attention

Further information

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