EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

What's new in Annex II

Scientific developments

Veterinary Medicines Info Day 2021

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BACKGROUND

- Annex (I and) II of Reg (EU) 2019/6 contain administrative and technical details that need to be submitted
- (Annex I : List of most of the administrative information required for part 1 of a dossier)
- Annex II was not updated at the time of adoption of Reg (EU) 2019/6 (transfer of Annex to Dir 2001/82/EC); updated by delegated act
- Main changes relate to: update requirements to scientific and technical progress, new sections in relation to biological and novel therapy VMPs
- Still awaiting finalisation by EC

SECTION I: GENERAL PRINCIPLES

- Restructured, but not much change in regard to the actual contents
- Legal references updated
- Applicant to confirm that all submitted data relevant to the quality, safety and efficacy, including data publicly available, are not subject to protection
- Justification for applications for VMPs with non-prescription status *
- Compliance with Ph Eur applicable to all relevant parts of Annex II
- Part 2: If dossier is CTD: Use the Quality Overall Summary (QOS) for critical expert report (CER)
- Tabulated summary of all technical data: no longer required for part 2 *

* *"New"*

SECTION II: REQUIREMENTS FOR VMPS OTHER THAN BIOLOGICAL VMPS ('PHARMACEUTICALS')

QUALITY

- Manufacturers of active substance and finished product not required in Part 2*
- Product development: Justification of proposed pack size - route of administration, posology, target species* - for all VMPs not only antimicrobials
- Stability AS: No retest period and storage conditions needed when AS is fully retested immediately before its use in the manufacture of the FP* - acceptable now for all AS
- Others: Justification of sterilisation method/aseptic processing; definition of batch size + ranges accepted; justification of specifications; batch data: in general 3 batches from the proposed manufacturing site; immediate packaging (AS, FP and intermediates) and devices: explicit reference to materials and specification; intermediates storage conditions

SECTION II: REQUIREMENTS FOR VMPS OTHER THAN BIOLOGICAL VMPS ('PHARMACEUTICALS')

SAFETY

- Objective of safety data: Assess the safety for target animal, user and environment. Consumer safety handled in MRL procedures*
- No systematic difference between food-producing and non-food producing*
- Possibility to use EPMARs instead of safety studies*
- Reproductive toxicity studies required for use in breeding animals*
- Definition of novel excipient aligned with definition in quality part*

SECTION II: REQUIREMENTS FOR VMPS OTHER THAN BIOLOGICAL VMPS ('PHARMACEUTICALS')

- Deleted section on microbiological properties of residues* (effects on human gut flora, industrial food processing)
- Expanded section on development of resistance and related risk in humans
- ERA: GMO moved to Section IIIA, new section on PBT or vPvB substances*
- Reference to VICH and other GLs (also in other sections)

RESIDUES

- Deleted section on pharmacokinetics in target animal*
- Report MRL status of constituents

SECTION II: REQUIREMENTS FOR VMPS OTHER THAN BIOLOGICAL VMPS ('PHARMACEUTICALS')

EFFICACY

- Mostly editorial, addition of details/clarifications on existing data requirements
- Moved to Section IV: information re fixed combinations
- Moved to PK section: information re bioavailability
- Expanded: section on development of resistance (risk to animals)
- New section: Dose determination and confirmation *
- Reference to VICH and other GLs (rather than listing individual details)

SECTION IIIA: REQUIREMENTS FOR BIOLOGICAL VMPS OTHER THAN IMMUNOLOGICALS ('BIOLOGICALS')*

- Mostly according to requirements in Section II. Note that some current GLs only address pharmaceuticals but the same principles may also apply to biologicals
- Specific Quality requirements may apply depending on the type of product
- Safety: Environmental risk assessment of veterinary medicinal products containing or consisting of genetically modified organisms Directive 2001/18/EC

SECTION IIIB: REQUIREMENTS FOR IMMUNOLOGICAL VMPS

QUALITY

- Product development: justification of preservative, pack size,
- Requirement for novel excipients – provide details supporting safety data*
- Live attenuated vaccines – confirmation of stability of attenuation of the seed*
- Demonstration of absence of EAs according to Ph. Eur. - Risk-based approach
- Possibility of max. bioburden limit instead sterility - non-liquid, non-parenteral VMPs*
- Consistency data from combined products can be used for related products
- Stability tests: AS, FP and solvent, intermediate products, at least 3 representative batches, in-use shelf life for multi-dose containers

SECTION IIIB: REQUIREMENTS FOR IMMUNOLOGICAL VMPS

SAFETY

- General requirements explained: target animal, consumer, user and environment
- Pre-clinical studies shall be GLP-compliant, exception possible for certain studies
- Spread of the vaccine strain – Assessment of likely no. of animal-to-animal passages*
- For vaccines containing GMOs – risk of changing the tropism or virulence of strain*
- ERA for DNA vaccines – risk of DNA integration in germ line cells*
- Residue tests - determination of residual organisms at the injection site for live vaccines for zoonotic diseases may be required*

SECTION IIIB: REQUIREMENTS FOR IMMUNOLOGICAL VMPS

EFFICACY

- Mostly addition of details/clarifications on existing data requirements
- General requirements - Clinical efficacy trials not required when SPC claims are fully supported by pre-clinical data*
- Revision of current guidance on field studies and indications for veterinary vaccines initiated - Concept paper published for consultation until 31 March 2021

SECTION IV: REQUIREMENTS FOR SPECIFIC MAA

- GENERICS
- HYBRIDS
- FIXED COMBINATIONS
- INFORMED CONSENT
- BIBLIOGRAPHIC
- LIMITED MARKETS
- EXCEPTIONAL CIRCUMSTANCES

SECTION IV: REQUIREMENTS FOR SPECIFIC MAA

GENERICS (ART 18)

- Part 1 and 2: complete – clarification added re expert report
- Part 3 and 4: Reference to already existing data of a reference product, but:
- - User safety risk assessment in CER (URA)*
  - Environmental risk assessment (ERA) (where relevant*),
  - For certain VMPs (sc, im, transdermal): TAS and residue data
  - BE data, if applicable
  - Information about antimicrobial/antiparasitic resistance * (bibliographic data)
-

SECTION IV: REQUIREMENTS FOR SPECIFIC MAA

HYBRIDS (ART 19)

Similar to a reference veterinary medicinal product, but which do not meet the conditions in the definition of a generic medicinal product

- Part 1 and 2: complete
- Part 3 and 4: reference to already existing data of a reference product plus new data, as needed (should include new URA, ERA, resistance, where relevant*),
- Any deviation/missing data need to be provided or their absence justified.
- Reference product can be third country for pre-clinical and clinical studies, but reassurance needed that the RP was authorised in line with EU requirements *

SECTION IV: REQUIREMENTS FOR SPECIFIC MAA

FIXED COMBINATIONS (ART 20)

- Clarification: Only "known" active substances (fixed combi with new API -> Art 8)
- Sound justification for the combination needed
- Part 1, 2, 3 and 4: complete for the fixed combination
- Data on individual substances: generally not required
  BUT: They can replace certain studies with the fixed combination
- URA, ERA, residue depletion, TAS and clinical study: fixed combination data

SECTION IV: REQUIREMENTS FOR SPECIFIC MAA

INFORMED CONSENT (ART 21)

- Part 1: complete (including consent form)
- Part 2, 3, 4: not required
- Clarification on data requirements (no new requirements)

BIBLIOGRAPHIC APPLICATIONS (ART 22)

- VMPs that are “well-established”
- Part 1, 2, 3, 4: complete; but part 3 and 4 can use bibliographic data
- Clarification of “well-established” and data requirements (e.g. EPMAR)

SECTION IV: REQUIREMENTS FOR SPECIFIC MAA

LIMITED MARKETS (ART 23) *

- Part 1 and 2: complete
- Part 3 and 4: some data may be omitted, if it is confirmed that the VMP is LM AND that the benefit of having the VMP on the market outweighs the risk of missing data
- MA is limited to 5 years (renewable)
- Must be a stand-alone product (e.g. addition of a LM target species or indication to an existing product is no longer possible)
- New guidance on Part 3 and 4 requirements currently under development by CVMP and new CVMP reflection paper on eligibility for LM status also under development (both currently published for consultation until 15 May 2021)

SECTION IV: REQUIREMENTS FOR SPECIFIC MAA

- **EXCEPTIONAL CIRCUMSTANCES (ART 25)**
- Part 1: complete plus justification that immediate availability on the market outweighs the risk of lack of certain documentation (positive benefit-risk balance) - (to be confirmed by CVMP)
- Part 2, 3 and 4: certain data can be missing at the time of submission
- Authorisation subject to specific obligations, conditions and/or restrictions (e.g. conduct of post-authorisation studies)
- CVMP guideline on data requirements for authorisation of IVMPs under exceptional circumstances under development (Concept paper published for consultation until 31 March 2021)

SECTION V: REQUIREMENTS FOR MAA FOR PARTICULAR VMPS

- **Novel therapies veterinary medicinal products**
- **Vaccine Antigen Master File**
- **Multi-strain dossier**
- **Vaccine platform technology**
- **Authorised homeopathic veterinary medicinal products -** *unchanged*

SECTION V: REQUIREMENTS FOR MAA FOR PARTICULAR VMPS

- **Novel therapies veterinary medicinal products***
- Could fall under: veterinary medicinal products other than biological; biological veterinary medicinal products other than immunological; immunological veterinary medicinal products
- Overall follow requirements described in Section II or III
- Deviations may be possible when justified
- Additional requirements may be relevant for particular types of products
- Risk analysis may be needed for specific types of products
- Specific data requirements for particular types of products will be developed by CVMP

SECTION V: REQUIREMENTS FOR MAA FOR PARTICULAR VMPS

Vaccine Antigen Master File (VAMF)

- Principles, content and certification outlined*. Use is optional
- Data requirements: Part 1 (summary of the dossier) and Part 2 (quality)
- VAMF certificates will apply throughout the EU
- Procedural guidance will be developed by the Agency
- Guideline on data requirements for authorisation of VAMF under discussion - Concept paper published for consultation until 31 March 2021

SECTION V: REQUIREMENTS FOR MAA FOR PARTICULAR VMPS

Multi-strain dossier

- Scope widened* to all inactivated vaccines against antigenically variable viruses or bacteria for which rapid or frequent change in the strains in the final product is needed to ensure efficacy in regard to the epidemiological situation in the field
- Each dossier applicable only to one virus species, bacteria genus or vector
- Eligibility for the multi-strain dossier will be confirmed by the Agency before submission of the application
- Revision of the existing guideline on data requirements initiated - Concept paper published for consultation until 31 March 2021

SECTION V: REQUIREMENTS FOR MAA FOR PARTICULAR VMPS

Vaccine platform technology*

- Basic principles and evaluation/certification briefly outlined
- Full MAA dossier required for 1st product using the platform for a target species
- Data requirements will depend on the type of platform
- PTMF certificates will apply throughout the EU. Reduced data requirements for further MAA dossiers based on the same platform
- Procedural guidance will be developed by the Agency
- Guideline on data requirements for authorisation of PTMF in development - Concept paper published for consultation until 31 March 2021

Any questions?

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