Veterinary

Dossier requirements for EU – P3 Safety

Part 3 – Safety

DIRECTIVE(S)/EP MONOGRAPHS/VICH	
Directive 2009/9/EC	"*Title II - Requirements for Immunological veterinary medicinal products*", Part III, Safety Tests
Directive 2001/18/EC	*"Deliberate release into the environment of genetically modified organisms"*
Ph. Eur. 0062	"*Vaccines for Veterinary Use*" – section 2-2-1
Ph. Eur. 5.2.6	"*Evaluation of safety of veterinary vaccines and immunosera*"
Ph. Eur. xxxx	Product-specific EP monograph
VICH GL44	*"Guideline on target animal safety for veterinary live and inactivated vaccines"*
VICH GL41	*"Target Animal Safety: Examination of live veterinary vaccines in target animals for absence of reversion to virulence*"
VICH GL9	*"Guideline on Good Clinical Practises"*

EMA GUIDELINES	
EMEA/CVMP/552/02	"*Guideline on EU requirements for batches with maximum and minimum titre or batch potency for developmental safety and efficacy studies*"
EMA/CVMP/IWP/315887/2017	"*Guideline on the use of adjuvanted veterinary vaccines*"
EMEA/CVMP/004/04	"*Guideline on live recombinant vector vaccines for veterinary use*"
EMEA/CVMP/IWP/54533/2006	"*Guideline on user safety for immunological veterinary medicinal products*"
EMA/CVMP/IWP/594618/2010	"*Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products*"
EMEA/CVMP/852/99	"*Note for guidance – Field trials with veterinary vaccines*"
EMA/CVMP/074/95	*"Environmental risk assessment for immunological veterinary medicinal products"*
EMA/CVMP/EWP/81976/2010	*"Statistical principles for veterinary clinical trials"*

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Chapters	Condition	Applicable for		Source information	Responsibility*
		Live	Inac		
3.A. Introduction and general requirements		x	x		RA
3.B.1 Safety of the administration of one dose		x	x	Subject report(s)	R&D
3.B.2 Safety of the administration of an overdose		x		Subject report(s)	R&D
3.B.3 Safety of the repeated administration of one dose	Booster in primary vaccination course	x	x	Subject report(s)	R&D
3.B.4 Examination of reproductive performance	If vaccine shall be used in birds in lay	x	x	Subject report(s)	R&D
3.B.5 Examination of Immunological functions	If vaccine may affect immune response	x	x	Subject report(s)	R&D
6. Special requirements for live vaccines 1. – Spread 2. – Dissemination 3. – Reversion to virulence		x		Subject report(s)	R&D
3.B.7 User safety		x	x		RA+R&D
3.B.8 Study of residues		x	x	Subject report(s)	R&D
3.B.9 Interactions	If vaccine shall be mixed/administered concurrently with other IVMP	x	x	Subject report(s)	R&D
3.C Field studies		x	x	Subject report(s)	R&D
3.D Environmental risk assessment		x	x	All data	RA+R&D
3.E. GMO stand-alone module		x			RA+R&D

**Task assigned to the function providing the documents/data. The overall responsibility for the writing and compilation of the dossier lies with Regulatory Affairs.*

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3.A. Introduction and general requirements

KEY ELEMENTS	COMMENTS
• Describe aspects of the product (e.g. live or inac and formulation at variable- or fixed antigen content). • Provide evidence for the "validity" of methods used, as applicable • Multivalent vaccines: report safety of the largest combi for fall-out products (see EMA guidance on combined vaccines)	

3.B. Laboratory tests

KEY ELEMENTS	COMMENTS
General: • Studies performed according to GLP • Animals should be of youngest age recommended for vaccination • For chicken, use SPF birds • Dosage = the maximum virus titre (live) or maximum potency (inac) on the SPC • Vaccine batch(es)[1] manufactured in accordance with Part 2 of the dossier	[1]Type 5 batch protocol, released by R&D

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3.B.1 Safety of the administration of one dose[2,3]

KEY ELEMENTS	COMMENTS
Study group • One group of 8 SPF birds (10 birds - if younger than 3 weeks). • Test each species and animal category • Include group of control vaccinates, as applicable. • Include group for mixed-use/associated-use, as applicable (see Part 3.B.9) Dosage • Live R&D vaccine batch(es): MSV+1 or MSB+1 • Maximum titre (live) or maximum potency (inac)[4], unless justified[5] • Test each route of administration Follow-up • Observe and examine for signs of systemic and local reactions, daily, for at least 14 days. • Detailed post-mortem macroscopic and microscopic examinations of the injection site. • Measure other performance criteria, as relevant. Results No animal shows abnormal local or systemic reactions or signs of disease or dies from causes attributable to the vaccine.	[2]Live vaccine - study not needed if the results of the overdose study revealed no signs of systemic or local reactions. [3]This study may be part of the repeated dose study (see part 3.B.3). [4]For inac vaccines formulated at fixed antigen content, the batch used should correspond to the maximum limit of the potency range stated on the SPC. [5]In case blending of a multivalent live vaccine with all antigens at max titre is difficult, we can use different batches where each batch holds a maximum titre or potency of at least one -different- antigen.

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3.B.2 Safety of the administration of an overdose[6]

KEY ELEMENTS	COMMENTS
Study group • One group of 8 SPF birds (10 birds - if younger than 3 weeks) • Test most sensitive species or animal category Dosage • Live R&D vaccine batch(es): MSV+1 • 10x maximum live titre[7] • Test most sensitive route of administration Follow-up • Observe and examine for signs of systemic and local reactions, daily, for at least 14 days. • Measure other performance criteria, as relevant. Results No animal shows abnormal local or systemic reactions or signs of disease or dies from causes attributable to the vaccine.	[6]For live vaccines only [7]In case blending of a multivalent live vaccine with all antigens at 10x max titre is difficult, we can use different batches where each batch holds a 10x maximum titre of at least one -different- antigen.

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3.B.3 Safety of the repeated administration of one dose[8]

KEY ELEMENTS	COMMENTS
Study group • One group of 8 SPF birds (10 birds - if younger than 3 weeks). • Test most sensitive species or animal category • Include group for mixed-use/associated-use, as applicable (see Part 3.B.9) Dosage • Live R&D vaccine batch(es): MSV+1 or MSB+1 • Maximum titre (live) or maximum potency (inac), unless justified • Test each route of administration Follow-up • Observe and examine for signs of systemic and local reactions, daily, for at least 14 days. • Measure other performance criteria, as relevant. Results No animal shows abnormal local or systemic reactions or signs of disease or dies from causes attributable to the vaccine.	[8]Study only needed if the vaccine is administered more than once as part of the standard vaccination scheme. (See also part 3.B.1)

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3.B.4 Examination of reproductive performance[9, 10]

KEY ELEMENTS	COMMENTS
Study group • One group of 8 SPF birds at the recommended age of gestation. • Include group for mixed-use/associated-use, as applicable (see Part 3.B.9) Dosage • Live R&D vaccine batch(es): MSV+1 or MSB+1 • Maximum titre (live) or maximum potency (inac), unless justified • Test most sensitive route of administration Follow-up • Observe and examine for signs of systemic and local reactions, daily, until 1 day after birth. • Evaluate reproductive performance and effects on progeny, as applicable Results No animal shows abnormal local or systemic reactions or signs of disease or dies from causes attributable to the vaccine.	[9]Study only needed if the vaccine is recommended for laying birds [10]Study can be part of the lab safety studies or the field studies

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3.B.5 Examination of Immunological functions[11]

KEY ELEMENTS	COMMENTS
See product-specific EP monograph for details, e.g. Gumboro	[11]Study required in case the vaccine may affect the immune response of the vaccinated animal or progeny

3.B.6 Special requirements for live vaccines

KEY ELEMENTS	COMMENTS
1. – Spread of the vaccine strain • Antigen strain: MSV+1 or MSB+1 • From vaccinated to unvaccinated target animal • Route of administration most likely causing spread • Include spread to non-target species as relevant[12,13] • Transmission of vaccinated target animal to humans[14]	[12]Vector vaccines; relevant species sharing the same ecosystem as vaccinated animals and focussing on species known to be susceptible to the vector, in particular the natural host species of the parental vector. A risk analysis concerning the extent of the exposure should be performed. [13]Non-target species highly susceptible to the vaccine [14]Vector vaccines only; requires risk analysis and comparison between vaccine and parent strain if spread to humans is possible.

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3.B.6 Special requirements for live vaccines - *continued*

KEY ELEMENTS	COMMENTS
3.B.6.2 – Dissemination in the vaccinated animal[15] • Antigen strain: MSV+1 or MSB+1 • Test secretion routes, e.g. faeces, eggs, oral, nasal as applicable • Test organs as applicable • Persistence at injection site[16]	[15]Vector vaccines; comparison needed between vaccine and parent strain. Requires sensitive validated detection system for the vector vaccine. [16]Only for vaccines against zoonotic disease for food-producing animals [17]Use of MSV+1 or MSB+1 allowed in case master seed is not available in sufficient quantities
3.B.6.3 – Reversion to virulence of attenuated strains[15] • Antigen strain: MSV or MSB[17] • *See details in the product-specific monograph* • Five serial passages • Use 5 birds each for passage 1-4; use 10 birds for passage 5 • *In vitro* propagation cannot be used to expand passage inoculum • Clinical observations during the study, the last passage is monitored for 21 days • At each passage, the presence of live vaccine is shown – if no recovery found, repeat in 10 animals using material from the former passage. If the vaccine is not recovered again, the test proves no increase in virulence. Otherwise, perform safety test using 1st and 5th passage in each 10 birds.	

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3.B.6 Special requirements for live vaccines - *continued*

KEY ELEMENTS	COMMENTS
3.B.6.4 – Biological properties of the vaccine strain • Determine intrinsic properties of the vaccine as relevant, e.g. neurotropism • Vector vaccines: discuss change in tropism or virulence compared to parent strain	
3.B.6.5 - Recombination or genomic reassortment of strains • The probability of recombination or genomic reassortment with field or other strains shall be discussed	

3.B.7 User safety[18,19]

KEY ELEMENTS	COMMENTS
• Hazard identification and characterisation • Exposure assessment • Assessment of the consequence of a hazard occurring • Risk characterisation • Risk management (selection and assignment of appropriate control measures) • Risk communication	[18]See explanation for each element in the specific EMA guideline [19]Depending on the risk assessment, appropriate warnings may end up on the SPC

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3.B.8 Study of residues

KEY ELEMENTS	COMMENTS

In-scope[20]	Out-of-scope[20]
Pharmacological active substances, e.g. adjuvants/preservatives*	• Active substances of biological origin intended to produce active or passive immunity • Non-active ingredients listed by EMA

**Preferably use substances for which an MRL has been defined[21] or published by EMA*

Biological substances, other than vaccines, can be either 'chemical-like' or chemical-unlike[22]:

- '*Chemical-like*' substances present similar concerns to chemical substances and are subject to a full MRL assessment.
- '*Chemical-unlike*' substances are more complex substances that may contain multiple chemical types whose residues can be cells, amino acids, lipids, carbohydrates, nucleic acids and their breakdown products. The CVMP decides on a case-by-case basis whether 'chemical-unlike' substances require a full MRL assessment.

[20] As defined in article 1(2) of Regulation (EC) No 470/2009

[21] Table 1 in the Annex of Regulation (EC) No 37/2010; substances listed in Table 2 are prohibited for use in veterinary medicinal products

[22] See EMA/CVMP/572629/2019

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3.B.9 Interactions[23]

KEY ELEMENTS	COMMENTS
• Lab studies: ○ Live R&D vaccine batch(es): MSV+1 or MSB+1 ○ Can be replaced by field safety studies if follow-up is the same compared to lab safety data of individual vaccines ○ Use most sensitive target animal using the most sensitive route of administration where interference might happen ○ Use both vaccines at maximum live titre or potency (inac) ○ In case of difference in minimum ages, use the oldest of the minimum ages ○ Compare results with the vaccines administered alone ○ Risk analysis needed in case of possible genetic reassortment of the vaccines • Field studies: ○ Standard vaccine production batches, safety and efficacy data combined ○ Can replace lab safety studies if follow-up is the same compared to lab safety data of individual vaccines	[23]Applicable when this vaccine can be mixed or used concurrently with another vaccine licensed by our company in the EU.

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3.C Field studies

KEY ELEMENTS	COMMENTS

• Two or more different geographical sites are recommended[24]
• Studies performed according to GCP
• Animals should be in age range and class intended for treatment
• Requires local authorization (i.e. special authorization for use of the product)[25]
• Can include both safety and efficacy:
  ○ Dosage: standard production batch
  ○ Trail shall be double blinded, placebo controlled
• Investigate local- and systemic reactions;
  ○ Broilers: weekly mortality, feed conversion ratio, age at slaughter and weight, downgrading and rejects at the processing plant
  ○ Layers: laying performance and hatchability
	[24]Non-EU is possible (See Gumbohatch)
	[25]The requirements for application of a field study in the EU are country-specific. Permits to allow field studies with a GMO are made publicly available, e.g. Buro GGO

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3.D Environmental risk assessment[25]

KEY ELEMENTS	COMMENTS
• Hazard identification; • Assessment of exposure to the hazard and the likelihood that the hazard will occur; • Assessment of the consequences of that exposure; • Assessment of the level of risk (by consideration of the severity of any adverse consequences and the likelihood that they will occur); • Selection and assignment of appropriate control measures (risk management), as far as possible	[25]See EMA guideline for details

3.E Assessment required for veterinary medicinal products containing or consisting of GMO[26]

KEY ELEMENTS	COMMENTS
• All elements listed in Annex III.A of Directive 2001/18/EC • Environmental risk assessment according to principles in Annex II of Directive 2001/18/EC • Include a copy of any written consent or consents of the competent authorities to the deliberate release into the environment of the GMOs for research and development purposes where provided for by Part B of Directive 2001/18/EC	[26]Stand-alone volume to be evaluated separately by CVMP and the national GMO authorities as part of the EU central registration procedure.