Dossier requirements for EU – P2 Quality

Part 2 – Quality

Chapters		Source information	Responsibility*
2.A. Qualitative and quantitative particulars of the constituents	1. – Qualitative particulars 2. – "Usual terminology" 3. – Quantitative particulars	TPP/MMI/BMI/BOM	R&D + Manufacturing
	2.A.4 – Product development	POC	R&D
2.B Description of the manufacturing process	2.B.1 – Introduction		RA
	2.B.2 – Flowchart of the production process and quality control procedures 2.B.3 – Detailed description of the production steps	MMI/BMI	Manufacturing site
	2.B.4 – Validation	Validation reports	R&D + Manufacturing
2.C. Production and control of starting materials	1. – Starting materials listed in Pharmacopoeia 2. – Starting materials not listed in Pharmacopoeia 3. – Preparation of solutions and media	MMI/BMI/BOM/CoA	R&D + Manufacturing
	2.C.4 – Specific measures to minimize TSE transmission	MMI/BMI/BOM	RA
2.D. In-process control tests		MMI/BMI	R&D + Manufacturing
2.E. Finished product control tests		MMI/BMI	R&D + Manufacturing
2.F. Batch-to-batch consistency		Batch CoA	Manufacturing
2.G. Stability	1. – Stability of the finished product 2. – Stability of the antigen 3. – In-use shelf life	Stability data	R&D + Manufacturing
Other information	Stand-alone module on the solvent, if applicable	MMI/BMI/BOM	R&D + Manufacturing

**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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DIRECTIVE(S)/VICH	
Directive 2009/9/EC	*Annex II – "Requirements for Immunological veterinary medicinal products"*, Part II, Quality
VICH GL1	*"Validation of Analytical Procedures: Definition and Terminology"*
VICH GL2	"*Validation of Analytical Procedures: Methodology*"
VICH GL17	*"Stability testing of biotechnological/biological veterinary medicinal products"*
VICH GL25	"*Testing of residual formaldehyde*"
VICH GL26	*"Testing of residual moisture"*
VICH GL34	*"Testing for the detection of Mycoplasma contamination"*
VICH GL40	*"Test procedures and acceptance criteria for new biotechnological/biological veterinary medicinal products"*

EP MONOGRAPHS	
Ph. Eur. 0062	"*Vaccines for Veterinary Use*" – section 2-2-1
Ph. Eur 0784	*"Products of recombinant DNA technology"*
Ph. Eur. xxxx	*Product-specific EP monograph*
Ph. Eur. 2.6.1	*"Sterility"*
Ph. Eur. 2.6.7	*"Mycoplasma"*
Ph. Eur. 2.4.18	*"Free formaldehyde"*
Ph. Eur. 3.2	*"Containers"*
Ph. Eur. 5.1.1	*"Methods of preparation of sterile products"*
Ph. Eur. 5.1.3	*"Efficacy of antimicrobial preservation"*
Ph. Eur. 5.1.7	"*Viral safety*"
Ph. Eur. 5.2.2	*"Chicken flocks free from specified pathogens for the production and control of vaccines"*
Ph. Eur. 5.2.4	*"Cell cultures for the production of vaccines for veterinary use"*
Ph. Eur. 5.2.5	*"Management of extraneous agents in IVMPs"*
Ph. Eur. 5.2.8	*"Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicines"*

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EMA GUIDELINES	
EMA/CVMP/IWP/206555/2010	*"Requirements for the production and control of immunological veterinary medicinal products"*
EMA/CVMP/IWP/315887/2017	"*Guideline on the use of adjuvanted veterinary vaccines*"
EMA/CVMP/038/97	*"Position paper on batch potency testing of IVMPs" (live/inac/RP)*
EMEA/CVMP/004/04	"*Guideline on live recombinant vector vaccines for veterinary use*"
EMEA/CVMP/743/00	*"Requirements and controls applied to bovine serum used in the production of immunological veterinary medicinal products"*
EMEA/CVMP/IWP/250147/2008	*"Data requirements to support in-use stability claims for veterinary vaccines"*

Consistency *versus* Flexibility

"What you see is what you get"

Transparency

Part 2 – Quality

2.A. Qualitative and quantitative particulars of the constituents

Composition before freeze-drying (per vial)

Name of substance	Quantity	Function	Reference
Active substances[1]: - Live attenuated virus strain x - Live attenuated virus strain x	x ml total volume	induction of immunity	2.C.2.1
Excipients: - x - x - Water for injections to	x mg x mg x ml	Stabiliser Buffer Solvent	EP EP EP

[1]Allantoic fluid constituents and gentamicin sulphate are present in the vaccine as remnants of the production of the antigen.

Calculation needed!

Composition per ml of solvent

Name of substance	Quantity	Function	Reference
Patent Blue V (E131) Water for injections to	x mg x ml	colouring agent diluent	Ph. Fr. EP

Active components after freeze-drying

Active ingredient	Quantity (per dose)
Live attenuated virus strain x	6.0-7.5 $\log_{10}$ EID_{50}
Live attenuated virus strain x	3.0-7.7 $\log_{10}$ EID_{50}

Min-Max titres on the SPC/artwork

Efficacy studies - min titre guaranteed at the end of shelf life
Safety studies

Container (vaccine + solvent)

Type	Material	Requirements	Sterilisation method
Container	glass	EP 3.2.1.	EP 5.1
Container	polyethylene	EP 3.1.4.	EP 5.1
Stopper	Rubber	EP 3.2.9.	EP 5.1
Cap	Aluminium	not applicable	not applicable

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2.B Description of the manufacturing process

Flowchart Antigen Production

Step	Production steps	Control tests
A01	Pre-incubation of SPF eggs	
A02	Preparation of eggs	
A03	Preparation of inoculum	
A04	Inoculation of eggs	
A05	Post-incubation	
A06	Cooling of eggs	
A07	Harvest of the amnion allantoic fluid	
A08		IPC

Flowchart Final product

Step	Production steps	Control tests
B09	Preparation of stabiliser	
B10	Preparation of vaccine suspension	
B11	Filling of vials	FPC
B12	Freezing	
B13	Freeze drying	FPC
B14	Securing of bungs with aluminium cap	
B15	Storage at 20°C	
		Quality control of final product
B16		FPC
B17		FPC
B18		Release
B19	Removal from -20°C storage	
B20		Final inspection
B21	Shipment	

Description vaccine manufacturing

- Flowchart steps A+B
- Lead times/storage between different manufacturing steps and subsequent quality control steps.
- Culturing conditions: medium, batch size, temperature, pH, timelines
- Emulsification process: process scale and size, *equipment*, temperature, timelines, speed, pH
- Harvest process, inactivation method, purification, storage of antigen
- Final product formulation and storage
- All information on the solvent

Validation (vaccine and solvent)

- **Three GMP production batches (1 full scale, 2 pilot scale)**
- **Released by the QP → batch CoA**

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2.B. Description of the manufacturing process – Key validations

Inactivation control test

- Test performed immediately after inactivation
- Determine the level of detection of residual live virus/bacteria:
  - Spike inactivated cultures with different titres of live antigen
  - Bacterial vaccines: at least 2 passages in suitable liquid/solid medium.
  - Viral vaccines: at least 2 passages in embryonated eggs or cells (add 1 ml inactivated harvest to 150 cm^2 monolayers).

Inactivation kinetics

- *Sets the maximum titre limit prior to inactivation of routine antigen production*
- Extrapolation is not allowed.
- Collect samples at regular intervals and analyse by the validated inactivation control test.
- If the inactivation kinetic study shows that inactivation is completed after 60 minutes, the minimum inactivation time is set for 90 minutes (67% rule).

Antigen content

- Method validated according to VICH GL1 and GL2
  - Live bacterial count or virus titre
  - A suitable *in vitro* method (e.g. ELISA), performed before or after inactivation
- Serves as basis for vaccine formulation

Batch potency test

- Method validated according to VICH GL1 and GL2
- See specific EP monograph, if applicable
- Live vaccine: bacterial count or virus titre:
  - Each batch: between min and max titre
  - Min titre: end of shelf life
- Inac vaccine:
  - The test must discriminate between potent and sub-potent batches
  - Fixed- versus variable antigen formulation

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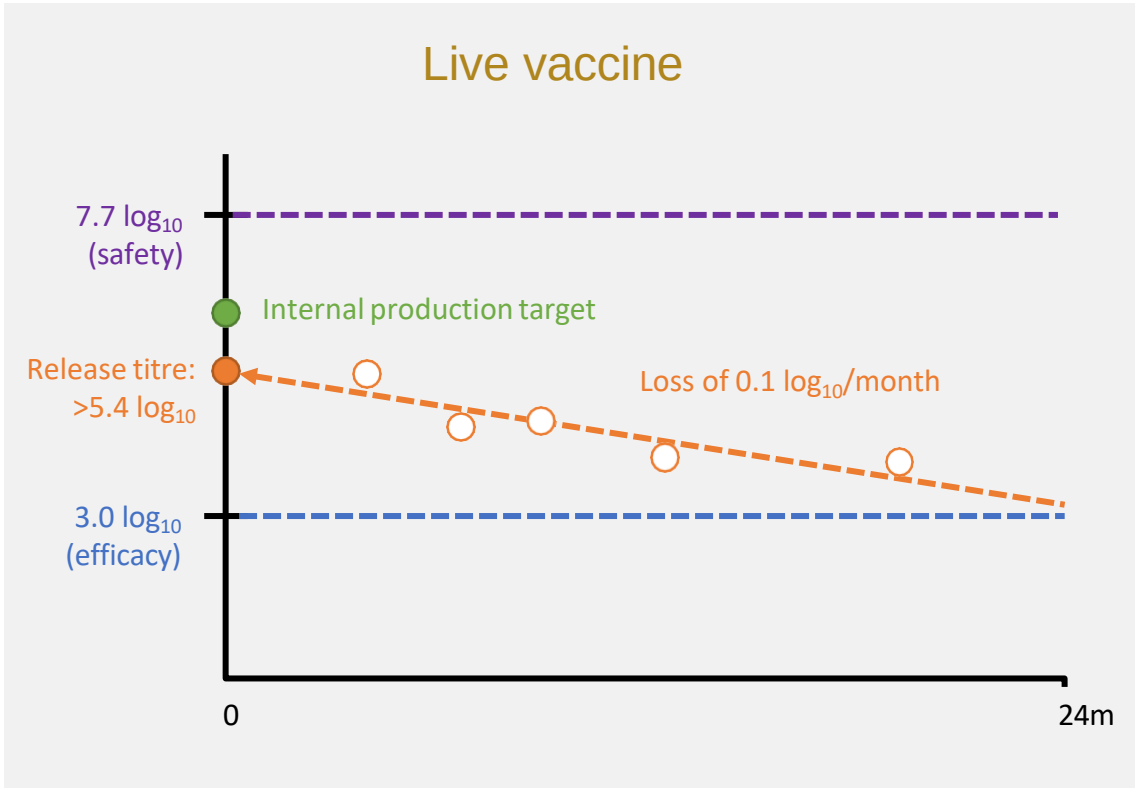
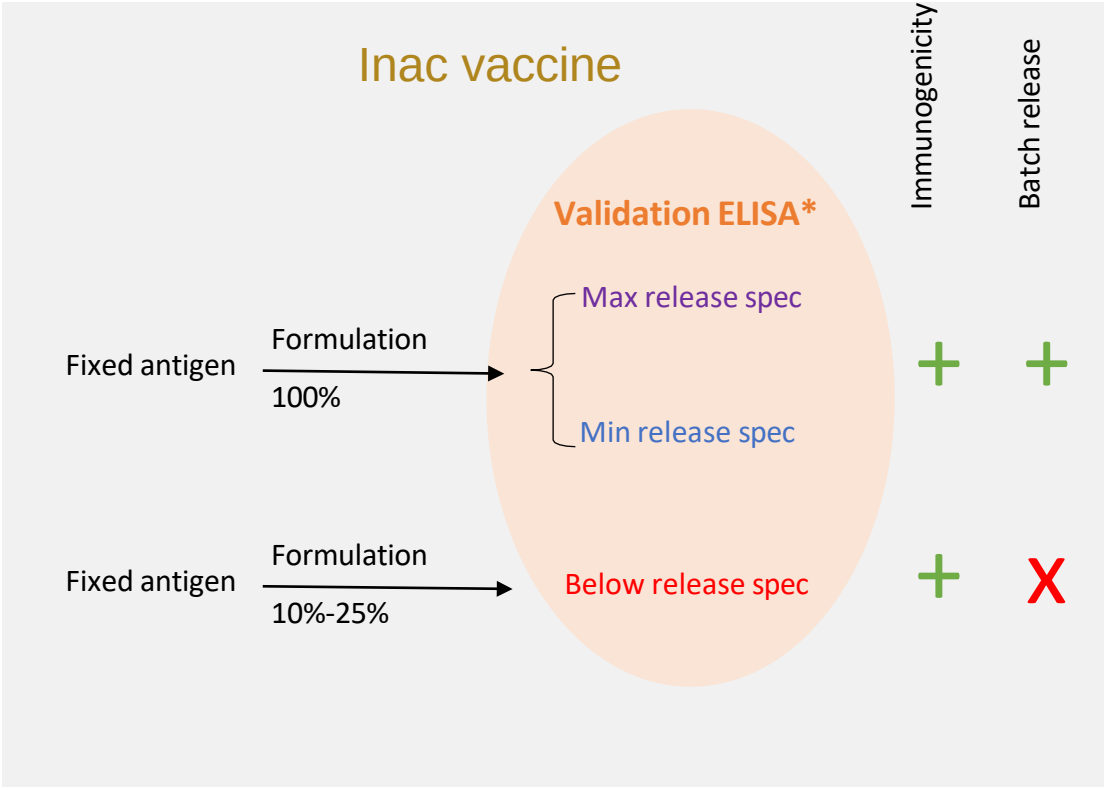
2.B. Description of the manufacturing process – Batch potency test





*A number of (R&D) final product batches is needed to set the release requirements for the potency test

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2.C. Production and control of starting materials

Listed in the Pharmacopoeia

- European Pharmacopoeia, or if not available, US Pharmacopoeia (e.g. NZ amine), or other Pharmacopoeia
- Non-biological or biological origin (e.g. SPF eggs, gelatin)
- Required: Certificate of analysis (CoA) from supplier
- Required: EDQM Certificate of Suitability (CEP) from supplier (TSE compliance)

Not listed in the Pharmacopoeia - Non-biological origin

- Certificate of analysis (CoA) from supplier
- Description, function, method of identification
- Treatment (e.g. sterilization)
- Storage
- Shelf life

Not listed in the Pharmacopoeia - Biological origin

- Description, function, source, origin, geographical region, history
- Processing, purification, inactivation and validated control measures
- Test for contamination (EP 5.1.1 or EP 5.2.5 through risk assessment)
- Required: Certificate of analysis (CoA) from supplier or internally (see master seeds)
- Required: EDQM Certificate of Suitability (CEP) or milk statement from supplier (TSE compliance)

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2.C. Production and control of starting materials - *continued*

Master Seed Virus

- Handled by a seed lot system
- Vaccine production maximally passage 5 from the MSV
- Certificate of analysis (Qualified Person):
  - Test for Identity
  - Test for bacteria and fungi (EP 2.6.1)
  - Test for mycoplasma (EP 2.6.7)
  - Test for absence of extraneous agents (EP 5.2.5)
- EP 0062: In the tests on the master seed lot, the material tested is not more than 5 passages from the master seed lot at the start of the tests, unless otherwise indicated.
- Storage condition

Safety studies: MSV/MSV+1, max label titre
Safety studies: Final product MSV+1, max label titre
Efficacy studies: Final product MSV+5, min label titre

Substrate for vaccine production

- Cell lines or primary cells: EP 5.2.4
- SPF eggs: EP 5.2.2

Master Seed Bacteria

- Handled by a seed lot system
- Define min-max passages before start production stage
- Genus, species, method of preparation, titer, culture medium, culture conditions and harvest
- Characteristics of seed material (dissociation or antigenicity) maintained during subculturing
- Certificate of analysis (Qualified Person):
  - Bacterial titre
  - Test for identity
  - Test for purity
- Storage conditions

Solutions and media

- Media is considered as one starting material.
- Qualitative and quantitative composition
- Preparation processes, including sterilisation procedures, storage and shelf life.
- Compliance with EP 5.2.5 as applicable

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2.D. In-process Quality Control Tests

	Live vaccine	Inactivated vaccine
IPC 01	Antigen titre	Antigen titre (before or after inactivation)
IPC 02		Purity[1]
IPC 03		Inactivation
IPC 04	Sterility[2]	Sterility[2]

[1]Bioburden test for antigen harvest for inactivated vaccines produced on eggs (see paragraph 2.5 of link)
[2]According to EP 2.6.1

	Antigen batches		
	Batch 1 (100%)	Batch 2 (10%)	Batch 3 (10%)
IPC 01			
IPC 02			
etc			

For all QC tests:
- Validation report – VICH GL1 and VICH GL2
- Signed SOP in the English language

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2.E. Final Product Quality Control Tests

	Live vaccine	Inactivated vaccine
FPC 01	Antigen titre(s): min-max, release limit*	Batch potency test (on bulk): min-max, release limit*
FPC 02	Identification	Identification
FPC 03	• Mycoplasma – EP 2.6.7 • Residual moisture • Check on freeze-drying	• Preservative (on bulk) – EP 5.1.3: min-max, release limit* • Free formaldehyde (on bulk) – EP 2.4.18 • Viscosity: min-max limit • Emulsion stability
FPC 04	Extraneous agents – EP 5.2.5**	Extraneous agents – EP 5.2.5**
FPC 05	Bacteria/fungi (sterility) – membrane filtration (EP 0062/ EP 2.6.1)***	Bacteria/fungi (sterility) – membrane filtration (EP 0062/ EP 2.6.1)
FPC 06	Filling volume	Filling volume
FPC 07	Visual appearance (before and after reconstitution)	Visual appearance

*Imposed by stability data
**Risk-based approach
***Bioburden test for live freeze-dried non-parenteral avian vaccines made on eggs (≤1 non-pathogenic micro-organism per dose)

For all QC tests:
- Validation report – VICH GL1 and VICH GL2
- Signed SOP in the English language

2.F. Batch-to-batch consistency

- Three GMP consistency final product batches, fully tested and released by the QP:
  - One full scale batch (100%)
  - Two batches at pilot scale (10%)
- These batches validate the production process (see 2.B.)
- Batch protocols (CoAs) according to the EDQM template (available within R&D)

2.G. Stability tests

- Shelf-life final product of x months at 4 °C is validated by d[illegible] of x+3 months
- Dossier submission:
  - Completed stability program with R&D final product batches
  - Ideally, first data from GMP consistency batches
- Live vaccines may require an internal storage at -20 °C after release.
- At t=0, product batches fully tested and released by R&D or QP (GMP).

Stable vaccine
Claimed shelf life ≠ stability data

Decline in stability
Claimed shelf life ≠ stability data

⇒ *Advice: a.s.a.p. prepare and align with manufacturing on a complete stability program with all batches, FPC tests and timepoints!*

2.G. Stability tests - *continued*

Live vaccines

Infectivity titre of [product] during storage at 2-8 °C

	Storage conditions during ... months							
	Initially at -20°C	Subsequently at 2-8°C						
		0	6	9	12	15	21	27
Batch FP1	0							
	15							
	27							
Batch FP2	0							
	15							
	27							
Batch FP3	0							
	15							
	27							

Residual moisture of [product] during storage at 2-8 °C

	Storage conditions during ... Months							
	Initially at -20°C	Subsequently at 2-8°C						
		0	6	9	12	15	21	27
Batch FP1	0							
	15							
	27							
Batch FP2	0							
	15							
	27							
Batch FP3	0							
	15							
	27							

At t=27 at 4 °C, include sterility test or alternative (e.g. integrity container/closure)

Infectivity titre of [product] at 30°C for 3 days

3 days storage condition	**Batch FP1**	**Batch FP2**	**Batch FP3**
T=0			
30°C ± 1°C			

In-use shelf life at RT *after reconstitution*

	Batch FP1	**Batch FP2**
T=0 hrs		
T=2 hrs		
T=4 hrs		

Storage of antigen (prior to freeze-drying)

	Batch A1	**Batch A2**	**Batch A3**
T=0			
12m at -20 °C			

2.G. Stability tests - *continued*

Inactivated vaccines

Potency test after storage at 2-8 °C

	Time at 2-8°C in months						
	0	6	9	12	15	21	27
Batch FP1							
Batch FP2							
Batch FP3							

Emulsion after storage at 2-8 °C

	Time at 2-8°C in months						
	0	6	9	12	15	21	27
Batch FP1							
Batch FP2							
Batch FP3							

Preservative after storage at 2-8 °C

	Time at 2-8°C in months						
	0	6	9	12	15	21	27
Batch FP1							
Batch FP2							
Batch FP3							

Viscosity after storage at 2-8 °C

	Time at 2-8°C in months						
	0	6	9	12	15	21	27
Batch FP1							
Batch FP2							
Batch FP3							

- At the end of the stability program, test for sterility or alternative (e.g. integrity container/closure)
- Antigen stability: formulate final product with aged antigen
- If in-use shelf life is less than one working day (maximum 10 hours) it is acceptable to omit the potency testing.
- Check EP 5.1.3 and EP 0062 (2-2-2) for efficacy of preservative in relation to in-use shelf life.

2.G. Stability tests - *continued*

Solvent

- Qualitative and quantitative particulars
- Description of the manufacturing process
- Production and control of starting materials (MRLs)
- Control tests during the manufacturing process and finished product
- Three consistency batches released by the QP (CoA)

Appearance after storage

	Time below 25°C in months						
	0	6	9	12	15	21	27
Batch 1							
Batch 2							
Batch 3							

Sterility after storage

	Time below 25°C in months						
	0	6	9	12	15	21	27
Batch 1							
Batch 2							
Batch 3							