#### Hearing of 13/12/2024

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for ANMV: L.Baduel, B.Leroux, C.Guitarist, L.Fabry, E.Begon. Excused: N.Bridoux

#### Reminder of the responsibility for the comments expressed during the hearing and reported in this report:

- The identification of therapeutic gaps (and details of the situations expressed and the alternatives envisaged) is the responsibility of the representatives of the veterinary profession
- The ANMV provides additional information or answers to the technical-regulatory questions addressed. These supplements are systematically preceded by "<u>ANMV</u> Info:..." to distinguish the origin of the comments expressed.

#### **General remarks:**

- 1. Application (as from 08 08 2026) of Implementing Act 2024/1973 of 18 07 2024 concerning antimicrobials not authorized through the "cascade": concerns raised regarding strict application of this regulation, which would prohibit uses and/or certain current SNGTV recommendations relating to antibiotics whose MAs do not mention the species or indication concerned (e.g. only respiratory indications for florfenicol) and/or already restricted use (e.g. colistin)
- 2. Anaesthetic needs during castration: more a political problem than linked to therapeutic gaps
- 3. Vaccines lack of efficacy often underreported via pharmacovigilance declarations: it would be useful to complete the analysis of lack of efficacy by identifying applications for autogenous vaccines due to lack of efficacy of existing vaccines.

Changes in gaps since the last hearing in November 2022: see p8

### Hearing of 13/12/2024

Table summarising the comments of representatives of the veterinary profession (new elements since the last hearing – in blue):

O VMP (Absence of appropriate veterinary medicinal products) is highlighted in yellow, when requesting a VMP with a MA for the species and indication concerned

		VV.	hen requesting a vivir with a MA for the species and indication concerned	
Pathology	Problem encountered by the sector*:  PhV: Pharmacovigilance (efficacy or safety perceived by the sector as unsatisfactory)  Disp: Availability, shortages  Reg: Regulatory (cascade application, waiting time, restricted access)  0 VMP: Absence of appropriate VMPs  0 TS: Absence of therapeutic solution	*Problem type PhV Disp Reg 0 VMP 0 TS	Alternatives identified	PRIORITIES  Major:M minor: m
Influenza	Major public health issues.  Current vaccines perceived as ± effective.  Underreporting as known to all => important to continue reporting  Dominant pathology in fattening pigs with insufficient efficacy in these animals. Inadequate vaccination schedule and problem of interference with maternal immunity. Evolution of strains in the field => importance of Resavip monitoring and data on vaccine status.  ANMV Info*: 4 reports of lack of efficacy since Nov 2022 (3 cases with detection of H1avN2, 1 case with H1avN2 and H1avN1) * see footnote p5. The impact of epidemiological data on the serotypes encountered is taken into account in the assessment of declarations.  On the other hand, the vaccine status of the animals concerned is often unknown.	PhV	RESPIPORC FLU3®, FLUPAN H1N1®  Updating influenza vaccines in light of new identified genotypes is easier with Reg Eu 2019/6 due to the possibility of using the multi-strain approach for the vaccine, but this remains dependent on the interest of the MAHs. The evolution of genotypes has been published.  ANMV Info: no new marketing authorisations or variations to date  HIPRA GRIPORK® vaccine with MA in Spain: possible import ANMV Info: 1 request in 2024	MAJOR n° 1
Neonatal	Enterococcus: the drastic reduction of antibiotic therapy did not reduce its	0 VMP	Use of auto-vaccines, efficacy difficult to assess.	MAJOR
diarrhoea due to	prevalence and involvement in diarrhoea.	(vaccine)	ANMV Info: no request since end-2023	n° 2 or 3
enterococci				
or rotavirus	Rotaviruses are a major problem.  SUIGEN Rota Coli® (MA dated 28/06/22) emulsion for injection for pigs (Virbac): 1st porcine vaccine against E.coli and porcine rotavirus. Inactivated adjuvanted vaccine for vaccination of sows to protect piglets from neonatal diarrhoea. Rotavirus type A (predominant in the field), but what about crossprotection on type C sometimes encountered?  Lack of protection against serotype C is not mentioned in the SmPC.  ANMV Info: Cross-protection has not been demonstrated by specific studies but the relevance of the vaccine strain and the tested strain in clinical studies has been positively assessed.  ANMV Info*: 11 reports of lack of efficacy against rotavirus (9 O and 2 B). Serotype C identified in 6 cases and serotype A in 3 cases.	PhV	SUIGEN Rota Coli® (MA dated 28/06/22) – see opposite  ANMV Info: Vaccine now marketed.  Recent update of the positive list (JO 14/08/24) with the addition of vaccines with the porcine rotavirus valence: bivalent Suigen® Rota-Coli® and trivalent Suigen® Entero 3® vaccines (with the Clostridium perfringens valence).  Note: A live vaccine is authorised in North America (Merck ProSystem RCE available in the US) against Rotavirus (type A only) /Coli/Clostridium. 3 import applications in 2021: all refused by ANMV (2 live rotavirus strains, no safety data). Rq: Authorised in Spain.	

Streptococcus suis septicemia, meningitis and arthritis	Highly antibiotics consuming disease.  No commercial vaccine. Difficult characterization of antigens.  ANMV Info: no new MAs since the last hearing (11/2022), neither in the Eu nor outside the Eu.  Autovaccines ± satisfactory.  Many circulating serotypes (not only serotype 9 tested as part of the EcoAntibio project – see opposite).  Anses Info: The REASAPATH data show that S.suis is ranked 2 <sup>nd</sup> most frequently susceptibility-tested bacteria in pigs, with a very high rate of resistance to tetracycline (83%) and to macrolides-lincosamides (63-67%) but low to amoxicillin (1%) (see Report 2022).  The recent work carried out from a diverse collection of strains (including clinical and non-clinical isolates), confirmed these high levels of resistance, but also revealed the presence of antibiotic resistance genes, mainly located on mobile genetic elements and at a higher frequency in non-clinical strains, isolated from tonsils. The presence of these "mobile" antibiotic resistance genes represents a major risk of spread of antibiotic resistance, not only in the pig environment, but also in its commensal flora or in pathogenic bacteria sharing the same ecological niche as S.suis, such as those of the Porcine Respiratory Complex.	O VMP (vaccine)	Autovaccines (S.suis = the most frequent request) ± satisfactory ANMV Info: no new requests since the last hearing (11/2022) but autovaccines are still widely used.  Antibiotics: βLactams (mainly amoxicillin). In 2022, sales of premix with amoxicillin declined sharply until they disappeared, but their use continued until 2022.  ANMV Info: according to sales monitoring, there are many Penicillins (especially amoxicillin, but also ampicillin and benzylpenicillin): - 6% in exposure in 2023 compared to 2021 (+19% in 1 year, but this increase probably not representative of the field). The increasing use of penicillins is linked to Streptococci (main disease found in pigs).  EcoAntibio project on immunisation by the mother Info Anses: New Biovac formula (Suiboost) for serotype 9 used in this EcoAntbio project: the experimental studies carried out have shown excellent protection in piglets derived solely from sows infected with S.suis (serotype 9) before the reproductive cycle, then vaccinated during pregnancy against the same bacterial strain (homologous autovaccine). Studies are continuing to understand the underlying biological mechanisms.	MAJOR n° 3 or 4
Brachyspira hyodysenteriae and pilosicoli	No commercial vaccine (complex development - no isolation possible - PCR identification)  ANMV Info: no new MA since last hearing (11/2022)  The sensitivity of Brachyspira strains must be monitored (as it is done in other countries such as DE, NL, DK, SP where strains are highly pathogenic with resistance development) => remain very vigilant, particularly with regard to the situation in Belgium and Italy, where the disease is much more present than in Brittany.	0 VMP (vaccine)	Macrolides  ANMV Info: reduction of 9% in exposure in 2023 vs 2021  Limited use of autovaccines (no strains to offer in Fr because bacteria are too difficult to isolate). Autovaccines a priori used in Spain.  ANMV Info: no request since last hearing (11/2022)  ATU Brachy RB Porcs (Ceva-Biovac) since 20/06/2022.  ANMV Info: ATU renewed – valid until 21/06/25	MAJOR n° 4 or 5
Post-weaning colibacillosis	Problem remains frequent => priority changes from minor to MAJOR n° 2 or 5 (see priority ranking p 7).  As a reminder:  Commercial vaccines (according to the SPC) are used on sows to prevent neonatal diarrhoea and are without action on post-weaning colibacillosis diarrhoea.  COLIPROTEC F4/F18® vaccine but for pigs of at least 18 days of age: risk of infection between the end of immunity transmitted by the mother and that induced by vaccination after 18 days of age (weaning at 21 days of age and diarrhoea possible from the following days). Results not systematic. Problem especially for acute diarrhoea related to F4-positive enterotoxigenic E coli.F4/F18, wich correspond to 60-70% of the isolates => problem for the other 30%.	PhV	Antibiotics (colistin)  ANMV Info: awaiting Calypso data for the pig sector (mainly colistin, in young piglets and oral use).  COLIPROTEC F4/F18® vaccine but for pigs of at least 18 days of age (see opposite).	MAJOR n° 2 or 5

Neonatal diarrhoea due to <i>E.coli</i>	Commercially available vaccines rarely cross with strains isolated from the field and are weakly effective.  Vaccines ± recent: SUISENG COLI /C® (AMM 07/2020) and SUIGEN Rota Coli® (AMM 06/2022) cover only a small proportion of neonatal diarrhoea because they contain components against which sows are already vaccinated.  ANMV Info*: 1 case received for Suiseng coli/C (imputed O), 3 cases for Suigen rota coli (1 A and 2 O).* see footnote p5.  Multifactorial etiology of diarrhoea (virus + bacteria), complex to identify. Today, we have the possibility of sequencing the genome of E coli: it is mainly a question of cost, but the tools are available. The issue of updating treatment regimens and oral treatments for diarrhoea under the mother. The absence of injectable aminoglycosides with practicable withdrawal periods is problematic.  Risk with regard to antibiotic resistance given the high consumption of antibiotics (and orally) in these indications.  Inappropriate treatment regimens  ANMV Info: see survey and plans to update the doses of old ATBs, currently underway at European level.	(0) MV Reg	Auto-vaccines regularly requested for lack of efficacy (but difficulties in identifying pathogenic strains).  ANMV Info: 11 requests recorded at ANMV in 2022 and 20 requests since then. An import application for 300 vials of 100 mL at the end of 2023 to cover the breakdown of the FR SUIGEN ROTA COLI® vaccine  Antibiotics (see risks opposite).  The SNGTV good practice guidelines sometimes indicate antibiotics of category B (Restrict) according to the AMEG classification (e.g. colistin), which may no longer be prescribed without additional examinations or VMPs that do not have the MA for pigs or for the intended indications (e.g. florfenicol only for respiratory indications). Such use may be prohibited in the future (from 08 08 2026) in the event of (strict) application of IE 2024/1973 of 18 07 2024 relating to antimicrobials not authorised under the "cascade".  => wish MA's extensions for the concerned target species and/or indications (e.g. florfenicol)  Vaccines - MAs ± recent: SUISENG COLI /C® and SUIGEN Rota Coli® (see comments opposite).	
Anaesthesia for castration	The majority (60 to 70%) of French pigs are castrated. The recommendations well governed by the law: lidocaine for intra-testicular injection authorised, but not very effective and with frequent post-injection haemorrhages (declared to IFIP)  ANMV Info: no PhV declarations relating to bleeding, reported to the ANMV to date.  SC injection (infiltration) of PROCAMIDOR® or PRONESTESIC® (procaine + epinephrine) is also possible (MA for pigs), but procaine is almost not used in the field because it is not validated by the IFIP protocols (see CASTRABEA Resource Centre - IFIP) accepted by the authorities.  Any other off-label prescription exposes the responsibility of the veterinarian. No practical anaesthetics, with quick and safe effect, e.g. gel. Practical difficulty related to the speed of processing action, synchronization of the operation and users' safety during processing.  New VMP presented as a gel is still wished.  The issue is primarily political: the percentage of non castrated males farms has increased slightly, representing 30 to 40% of farms, but a saturation threshold has been reached at slaughterhouses. It is therefore not possible to do without castration. The provision by a MAH of a simple-to-use and	PhV?	<ul> <li>SC injection (infiltration) of PROCAMIDOR® or PRONESTESIC® (procaine + epinephrine) with MA for pigs (see opposite)</li> <li>Isoflurane (ISOFLUVET®) authorised in piglets (see SPC (anses.fr), reserved for veterinarians</li> <li>IMPROVAC®: possible alternative but which poses difficulties downstream (reorganisation of the slaughtering chains, installation of "noses" on the slaughtering chains, etc.).</li> <li>Non castrated males breeding = wished by the majority of French veterinarians. — see comment opposite</li> </ul>	minor (n° 1)

Neonatal diarrhoea with <i>Clostridium</i>	ANIMV Info: No PhV declarations to date => under-declaration?  Major risk with regard to antibiotic resistance given the high consumption of antibiotics (and orally) in these indications.	PNV	Vaccines including SUISENG DIFF/A® (AMM 12/2021) and ENTEROPORC AC® (AMM 12/2020) launched in spring 2022  Antibiotics (see risks opposite)	minor
Genital infections of sows	Off-label local administration of injectable or intramammary ATB treatments for which no suitable dosing regimen is available.  Unusual and irrelevant practice: to stop.  ANMV Info: see publication following the work of the CSMV, in La Dépêche Technique No. 207 of Sept 2023 (p8-11)  Vaccines perceived ± effective (problem of "multipathogenic" etiology)	0 VMP	Injectable ATBs (amoxicillin, colistin, ampicillin). <u>ANMV Info</u> : Sustained return of Clamoxyl® intrauterine tablet on 07/08/2024 but MA only for cattle and size not suitable for sows.  CENTRAUREO® was discontinued on 05/2023.  Abandon of the MA for Auréomycin notified on 30/11/22.	minor
Glaesserella parasuis (formerly "Haemophilus parasuis")	effective medicinal product would facilitate the maintenance of surgical castration in the medium term.  Problem of farms practicing castration and not the IMPROVAC® vaccination = majority of French pigs, including outdoors farming, particularly during late slaughter imposed by the specifications.  For memory: castration without anesthesia (legally possible until the end of 2021) prohibited since January 2022.  Commercial vaccines perceived ± effective (PORCILIS GLASSER® -MA 2004 and SUVAXYN M HYO PARASUIS® - MA 2008) and not always available. SUVAXYN shortages since 2018.  ANMV Info: No PhV declarations since Nov 2022  The issue of strain typing remains problematic. No cross-protection between different serotypes. Problem of strain typing because analysis laboratories do not seem to use the same techniques, hence difficulties in validating the lack of interest of commercial vaccines (type 4 for one of them or type 4 and type 5 for the second, which also includes Mycoplasma valence)  Molecular serotyping and the search for known and assumed virulence factors is available through sequencing. But this is not always enough to judge the value or not of trying a commercial vaccine.  Anses Info: Great variety of strains. Serotyping strains would probably help. Molecular serotyping is possible but does not appear to be performed in diagnostic laboratories.	PhV (0 VMP)	Import of SUVAXYN Respifend® (MA in the US) but little use because of a complex supply chain (import) and disease that is not very recurrent.  ANMV Info: 3 requests recorded at ANMV since 2018.  Possible supply directly from Zoétis: in 2021, import by Zoétis, storage and distribution by Serviphar.  A MA in Eu would be preferred rather than the use of import.  ANMV Info: Import application for 20,000 vials of 100 ml (50 doses) exp.  09/23 of SUVAXYN RESPIFEND MH HPS®.  2 import applications accepted in 2024 for FIXR HP ERY®, MA in Belgium.  Autovaccines: Widely used, despite possible difficulties in drafting the justifications requested due to the availability of marketed vaccines.	minor

<sup>\*</sup>the number of declarations recorded by the ANMV is only one element of the monitoring of veterinary medicinal products, which should be correlated with the following information: the date of the start of marketing of the medicinal product, the number of animals that have actually been treated with this medicinal product, the assessment of the causal relationship according to the ABON method between the symptoms or lack of efficacy described and the administration of the medicinal product, the fact that these declarations concern animals whose health status may vary widely and/or who have received several medicinal products at the same time, the completeness of the national database (does not contain declarations before 2008 neither all non-serious cases).

Pathology: being resolved with existing solution	Initial problem of the sector	Problem type	Solution / Alternatives Reason for: Resolution in progress / Elimination of therapeutic gap	GAP initially Major:M minor: m
Post-partum	Marketing withdrawal of SERGOTONINE® in 2020 by the only supplier. Impact +++: piglets stillbirths and milk losses from sows => economic + subsequent fertility damages, need for ATBs necessary in case of problems.	Disp	Import (from Spain or Poland) of HEMOGEN® (ergometrine alone without serotonin). Very satisfactory recourse.  Several import applications in 2021. Use of this VMP is currently increasing (problem of hyperprolificity that increases concerns)  TUA (temporary use authorisation) since 07/2022, renewed until 26/06/2025.  Essential awaiting the MA.	Under resolution
Actinobacillosis	Commercial vaccine perceived ± effective => auto-vaccines spontaneously preferred  Vaccine (PORCILIS ACTINOPORC® - MA dated 1996).  Very limited sales. 16 PhV declarations in 2014.  ANMV/Anses info*: 1 case in Nov 2022, imputed N because of noncompliance with the 4 weeks between 2 injections. *see footnote p5  Variability in the effectiveness of the commercial vaccine probably linked to the great diversity of strains and serotypes (molecular serotypes possible for a short time but this method seems to be little practiced by the labs) and to be linked to Mycoplasma hyopneumoniae COGLAPIX® (Ceva) has a MA in Eu, not in Fr.	PhV	ANMV Info: New national MA dated June 2023: Suigen® App® 2, 9, 11 (Virbac). 2nd porcine vaccine against Actinobacillus pleuropneumoniae. Like Porcilis® ActinoPorc, Suigen® App 2, 9, 11 is an inactivated vaccine for vaccination of pigs from 6 weeks of age. However, its antigenic composition is different. Available in the field for about a year and not yet everywhere, as autovaccines have been considered generally satisfactory for several years. Autovaccines (frequent) ANMV Info: One request late 2023. 16 waiver requests in 2024-25 with the APP B1S2 and/or 1/9/11 strains Satisfactory ATB treatments (tetracyclines, sulphonamides) in case of clinical emergency.	Under resolution
Leptospirosis (sows)	2 vaccines: PORCILIS ERY+PARVO+LEPTO® (MA 2016 but only available since 2019) and SUIGEN PARVO L6 (MA 07/2024) not yet marketed.  Difficulties with diagnosis.  Helped to reduce the use of tetracyclines in sows	PhV	For the sector, vaccines are available with good efficacy against leptospirosis, but more limited against parvovirosis (like other parvo only vaccines) => potential risks on the control of leptospirosis if this led to a reduction in the use of this vaccine.  For memory: for illustration purposes*, a dozen statements of lack of efficacy with a potential causal link were recorded at the ANMV before the previous 2022 hearing for PORCILIS ERY+PARVO+LEPTO, half of which clearly refer to a lack of efficacy with regard to parvovirosis.  *see footnote of p5  => Pharmacovigilance follow-up to be continued. Antibiotics	Under resolution

Hearing of 13/12/2024

## **Prioritisation of identified gaps**

	Arnaud Lebret	Xavier Sauzéa	Claire Chauvin	Prioritisation of the previous hearing (18/11/22)
Neonatal diarrhoea due to Enterococci or rotavirus	MAJOR n°2 (Different approach and "investigations" to be carried out depending on the germ: no commercial vaccine for one, while for the other, existing commercial vaccine presumably only effective against Rotavirus A)	MAJOR n°3		MAJOR n°1
Influenza	MAJOR n°1 (public health issues)	MAJOR n°1 (public health issues)	public health issues +++	MAJOR n°2
Streptococcus suis septicemia, meningitis and arthritis	MAJOR n° 3	MAJOR n°4		MAJOR n°4
Brachyspira hyodysenteriae and pilosicoli	MAJOR n°4	MAJOR n° 5		MAJOR n°5
Post-weaning colibacillosis	MAJOR n°5	MAJOR n°2	MAJOR	minor
Neonatal diarrhoea due to <i>E.coli</i>	(but n° 1 or 2 upon application of IA)	(as soon as IA application)	(upon application of IA)	minor
Anaesthetics for castration	? minor	minor n°1		MAJOR n°3
Glaesserella (Haemophilus) parasuis	minor	minor		minor
Genital infections sows	minor	minor		minor
Neonatal diarrhoea with <i>Clostridium</i>	minor	minor		Under resolution
Post-partum sows	Under resolution	Under resolution		Under resolution
Actinobacillosis	Under resolution	Under resolution		Under resolution
Leptospirosis (sows)	Under resolution	Under resolution		Existing solution

#### Hearing of 13/12/2024

#### Changes in gaps since the last hearing in November 2022:

#### **Rather favorable trend for:**

- Rotavirus neonatal diarrhoea, thanks to the marketing of a new vaccine (also listed on the national "positive list" since August 2024)
- Anaesthesia for castration, gap considered to be "less major" as it is rather linked to "political" considerations

#### **Less favorable trend for:**

- Influenza, now considered the number one gap due to its major impact, with possible serious public health implications.
- Neonatal or post-weaning colibacillosis, due to tits multifactorial etiology, the difficulties in identifying pathogenic strains, the limited vaccines efficacy and the use of antibiotics outside of strict SPC recommendations or good practice
- Clostridium neonatal diarrhoea, despite recently marketed vaccines, due to "multipathogenic" etiology
- Leptospirosis, due to the need to maintain vigilance regarding the use of existing vaccines despite their limited efficacy against parvovirosis

	Hearing of 18/11/22	Hearing of 13/12/24
MAJOR	Neonatal diarrhoea due to enterococci or rotavirus	1. Influenza
priorities	2. Influenza	2. or 3. Neonatal diarrhoea due to enterococci or rotavirus
	3. Castration anaesthetics	3. or 4. Streptococcus suis septicemia, meningitis and arthritis
	4. Streptococcus suis	4. or 5. Brachyspira hyodysenteriae and pilosicoli
	5. Brachyspira	5. or 2. Neonatal or post-weaning colibacillosis
Minor	Post-weaning colibacillosis	Castration anaesthetics
priorities	Neonatal E.coli diarrhoea	Glaesserella (Haemophilus) parasuis
	Glaesserella (Haemophilus) parasuis	Genital infections in sows
	Genital infections in sows	Neonatal diarrhoea with <i>Clostridium</i>
Under	Post-partum in sows	Post-partum in sows (thanks to TUA renewal)
resolution	<ul><li>Actinobacillosis (thanks to autovaccines)</li></ul>	Actinobacillosis (thanks to new MAs and autovaccines)
	Neonatal diarrhoea with Clostridium (thanks to recent vaccines)	Leptospirosis (recent vaccines but their limited efficacy on parvovirosis needs to be
		monitored)
Existing	☑ Ileitis (thanks to new vaccines – MAs 2020 & 2019)	
solution	☑ Leptospirosis (thanks to a vaccine – MA 2016, available in 2019)	