

## Therapeutic gaps in the poultry sector

### Meeting of 07/10/2022

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#### Changes in deficiencies since the last meeting in July 2020:

	Meeting of 28/07/20	Meeting of 07/10/22
<b>MAJOR priority</b>	<ol style="list-style-type: none"> <li>1. Fight against the effects of viral passages (infectious bronchitis, SIGT, etc.) - laying hens</li> <li>2. Histomonosis - turkeys, guinea fowl, label poultry and laying hens</li> <li>3. Pain management for "convenience" procedures: topping, guinea fowl removal</li> </ol>	<ol style="list-style-type: none"> <li>1. Fight against the effects of viral passages (infectious bronchitis, SIGT, etc.) - laying hens</li> <li>2. Histomonosis - turkeys, guinea fowl, label poultry and laying hens</li> <li>3. Aspergillosis - turkeys</li> <li>4. Teniasis (cestodes) - ground laying hens and breeding hens</li> <li>5. Pain management for "convenience" procedures: capping, guinea fowl removal</li> </ol>
<b>Minor priority</b>	<ul style="list-style-type: none"> <li>• Colibacillosis - laying hens</li> <li>• Coccidiosis - standard broilers</li> <li>• Teniasis (cestodes) - ground laying hens and breeding hens</li> <li>• Aspergillosis - turkeys</li> </ul>	<ul style="list-style-type: none"> <li>+ Colibacilliose - broilers</li> <li>• Candidosis - turkeys</li> <li>+ Coccidiosis - turkeys and guinea fowl</li> <li>+ Hemorrhagic enteritis – turkeys and pheasants</li> </ul>
<b>Resolution in progress</b>	<ul style="list-style-type: none"> <li>➤ Candidosis – turkeys (thanks to NVR – WP ≥1d)</li> <li>➤ Adenovirus (breeders), Reovirus (depending on strains), viral pancreatitis – guinea fowl (thanks to auto-vaccines)</li> </ul>	<ul style="list-style-type: none"> <li>➤ Colibacillosis - laying hens (thanks to MA variation and auto-vaccines)</li> <li>➤ Coccidiosis - standard broilers (thanks to future vaccines)</li> <li>+ Highly pathogenic avian influenza (health policy and future vaccines)</li> </ul>
<b>Existing solution</b>		<ul style="list-style-type: none"> <li>☑ Adenovirus (repros), Reovirus (depending on strains), viral pancreatitis – guinea fowl (thanks to auto-vaccines and ATU)</li> </ul>

#### General remarks:

1. **The deficiency in antipyretics (MAJOR Gap no. 1)** has a very significant economic impact in the poultry sector due to its consequences on laying performance, and is also detrimental to animal welfare, as well as the absence of local anaesthetics.
2. **The sector is penalised by the absence of MRLs for at least 3 active substances (paracetamol, praziquantel and enilconazole):** how to mobilise the MA holders concerned or otherwise, identify other holders /sponsoring with the support of the sector?
3. **The Turkey sector is particularly affected by therapeutic deficiencies**, which do not seem to affect other producing countries as much (e.g Poland, Turkey).
4. **The New Veterinary Regulation (NVR) on medicated feeds** leads to disinvestment of the concerned manufacturers, and risks causing new therapeutic deficiencies (e.g. lack of parconazole premix for turkey candidosis).
5. **Alternative breeding practices and "bio" requirements promote the development of certain diseases** (e.g. teniasis, histomonosis) and sometimes go against animal welfare.
6. **The use of auto-vaccines** allows for a quicker response to the appearance of new strains than existing vaccines (e.g. colibacillosis), but the need to submit pharmacovigilance declarations should not be "too blocking" for their approval. Indeed, this would otherwise require vaccinating/sacrificing animals with a vaccine that is known to be of limited interest. The value of pharmacovigilance declarations was however recalled and shared. The interest in publications of epidemiological surveillance data was also highlighted to enable the updating of knowledge on the circulation of strains in farms.

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## Post-meeting comments/clarifications (in blue)

Disease	<b>Problem encountered*:</b> <b>PhV:</b> Pharmacovigilance (unsatisfactory efficacy or safety) <b>Disp:</b> Availability, shortage <b>Reg:</b> Regulatory (cascade application, waiting period, restricted access) <b>0 VMP:</b> No appropriate veterinary medicinal products <b>0 TS:</b> No therapeutic solution	<b>*Problem type</b> <b>PhV</b> <b>Disp</b> <b>Reg</b> <b>0 VMP</b> <b>0 TS</b>	<b>Alternatives identified</b>	<b>PRIORITIES</b> <b>Major: M</b> <b>minor: m</b>
<b>Fight against the effects of viral passages (infectious bronchitis, SIGT, etc.)</b> <u>Laying hens</u>	Need to be able to use an antipyretic in laying hens to limit the clinical, economic impact (laying fall from 10% to 70% during viral passages) and welfare concerns. Note that this impact is increased tenfold in alternative farms. <b>Absence of aspirin MRL for eggs and paracetamol MRL for eggs and meat in poultry.</b> => Treatments used and effective in breeding hen farms but sorted eggs must be withdrawn from consumption (human and animal). <b>Reminder:</b> for substances listed in Table 1 => cascade is possible with specific WP - see NVR Art. 115. <b>BUT for acetyl salicylic acid (= "aspirin"), sodium acetylsalicylate and sodium salicylate, it is specified: "Do not use in animals producing milk or eggs intended for human consumption" (see details below)</b> - <b>Aspirin</b> (acetyl salicylic acid): no MRL required for all species except fish but <b>prohibited in laying hens</b> (see above) Sodium salicylate: MRL Meat & offal defined for turkeys (=> 96% ADI) and "Do not use in animals producing eggs for human consumption". No MRLs required for oral use in pigs and cattle (and "Do not use in animals that produce milk for human consumption). Topical route: no MRL required for all species except fish. - <b>Paracetamol:</b> since 1999, no MRL required for pigs when oral administration (=> 42% ADI). No residue studies were provided for cattle and poultry => <b>With NVR, possible cascade with meat WP ≥ 1day and egg WP ≥ 10 days.</b>	<b>Reg</b>	<ul style="list-style-type: none"> <li>• <b>Oxytetracycline</b> (medicated feed or via drinking water) in the absence of anti-inflammatory or anti-pyretic VMPs that can be used in laying hens. A better response is usually achieved via food rather than drinking water. However, with NVR, several companies will stop the manufacturing of medicated feed.</li> <li>• <b>Plant extracts</b> (e.g. sanguinarine)</li> <li>• <b>Administration of acids, probiotics</b></li> </ul>	<b>M</b> <b>n° 1</b>
<b>Histomonosis</b> <u>Turkey</u> <u>+ guinea fowl</u>	<b>Very important issue for the turkey sector:</b> "orphan disease for an orphan sector".	<b>0 VMP</b>	<b>No effective alternatives.</b> <b>Combination of antibiotics</b> for digestive purposes. Apramycin off-label.	<b>M</b> <b>n°2</b>

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<p><b>+ label poultry and laying hens</b></p>	<p>Disease difficult to control once established. Evolution, impact and outcome varies according to age of occurrence, sex (most affected males) and batches. Euthanasia or early slaughter is applied, depending on the age of the animals. Distress +++ over several days: major impact in terms of animal welfare. Prevalence of about 2 to 6 cases for 400 batches per year - remains low, so low that it is difficult to test the efficacy of possible treatments. <b>Much higher prevalence in outdoor farming.</b> Microbiota impact and immune factors still to be explored.</p>		<p>Reminder: the cascade is not applicable with paromomycin for calves and pigs as it is contra-indicated in turkey due to the risk of developing resistance. Use of ATB or azoles (carcinogens) in other countries (US and? Eu). Ronidazole with marketing authorisation for pigeons, but prohibited for animals whose meat and products are intended for human consumption. <b>Phytotherapy:</b> very random efficacy. <b>Biosecurity.</b> Water hygiene <b>Future vaccines?</b> recently published work (see attachment below) on live attenuated vaccines by Austrian (Prof. Hess – encouraging results) and American (insufficient results) teams.</p> <p> </p> <p>2021-Mitra-Vaccination against the prot 2022-Hatfaludi-Experimental reproduct</p> <p></p> <p>2022-Beer-Evaluation of live-attenuated</p>	
<p><b>Aspergillosis Turkey</b></p>	<p><b>Off-label aerosol spraying use of Imaveral® in the presence of animals with a 28-days WP.</b> The MA is for the treatment of ringworm <b>for external use (local application or spraying)</b> in cattle, horses, dogs and cats, with a meat and milk WP of 0 day for cattle and horses. Currently, <b>MRL for enilconazole (IMAVERAL) exists for cattle (total residues &lt; 11% ADI) and horses but only for topical use.</b> <b>With NVR, the “cascade” WP for topical use could now be ≥ 1 day.</b> For information, a study conducted by Jansen (see opposite) showed that the quantities of enilconazole residues found in the skin and meat the day after 2 mists per day at 20 mg/m<sup>3</sup> for 3 consecutive days were 7 times lower than ADI. But <b>one single study may not be sufficient to cover veterinarians on a WP applied for a route of administration which is not the route indicated in the SPC.</b></p>	<p>0 VMP</p>	<p><b>Phytotherapy Treatment of the atmosphere.</b></p> <p>Published residue data during spray treatment:</p> <p> </p> <p>Poster Résidus enilconazole SNGTVpilote Résultats étude résidus enilco</p>	<p><b>M n° 3</b></p>

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	<p><b>Very insecure supply of the market with only 1 VMP</b> sold by an equine market-oriented MAH.</p> <p><b>Removal of CLINAFARM biocide</b> (imizalil) from Elanco: reason? Its use is no longer possible, including in hatching units =&gt; <b>risks and concerns +++</b> with a possible increase of aspergillosis on 1-day animals.</p> <p><b>What are the risks for the user in case of off-label spraying use?</b> Information from Anses Ploufragan: A thesis in Nantes - CHU is underway (Sophie Hartuis supervised by Patrice Le Pape) on the epidemiology of environmental resistance to Aspergillus azole. Animal thesis (<a href="https://tel.archives-ouvertes.fr/tel-01373927/file/TH2015PEST1183_archivage.pdf">https://tel.archives-ouvertes.fr/tel-01373927/file/TH2015PEST1183_archivage.pdf</a>) sent some time ago – no contact since.</p>			
<p><b>Teniasis (cestodes)</b> <b><u>laying hens</u></b> <b><u>breeding hens</u></b></p>	<p><b>Increasing prevalence.</b> <b>No egg MRL for praziquantel.</b> Praziquantel included in Table 1 with “no MRL required” for sheep (total residues &lt; 30% ADI) and horse. CESTOCUR meat WP (sheep) = 0 days. <b>=&gt; With NVR, possible cascade with meat WP ≥ 1 day and eggs WP ≥ 10 days.</b> <b>=&gt; To obtain MRL for eggs, data are needed on metabolism and residues in poultry.</b> According to Regulation 2017/880, no possible extrapolation of MRLs between unrelated species, or between tissues and eggs within the same species. It should be noted that the <b>NVR (Art 40.4)</b> reinforces this prohibition of use in the absence of data and <b>provides 5 years protection over the data submitted.</b> <b>Parasiticides not currently approved for this species and this indication and without evidence of efficacy.</b> <b><u>Nematodes parasitism (Ascaridia and Heterakis):</u></b> increasing problem, probably linked to the development of outdoor breeding, but not only, as confined farms are also affected. Following the change in regulation on the use of anthelmintics, particularly in organic farms, the sector is moving to alternatives with unproven (and probably low or nul) efficacy, and the prevalence and impact of these worms (Ascaridia) are increasing.</p>	<p><b>0 VMP</b></p>	<p>Unofficial recommendations without MA (for fenbendazole or flubendazole), at doses whose efficacy and safety have not been validated and whose WP is problematic in organic farms.</p>	<p><b>M</b> <b>n°4</b></p>

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	The management of Heterakis is an important element to be compared with the control of histomonosis, a disease for which no treatment is available so far (Heterakis is a possible vector of Histomonas – no publications).			
Pain management for "convenience" procedures: topping, guinea fowl removal	<p>No anti-inflammatory drugs with MA for broilers, except aspirin (which has limited palatability and questioned compatibility with other products or biocides?).</p> <p>Immunocastration raises other questions: product efficacy, degraded meat quality, societal acceptability.</p> <p>Increase in <b>attacks between hens</b>, particularly on organic farms with difficulties in satisfying the amino-acid balance required for production and feathering (reduction in the use of synthetic amino acids which are considered as allopathic treatments).</p>	0 VMP	<p>Immunocastration (IMPROVAC)</p> <p><b>Ketoprofen:</b> Extension of MRLs to poultry (since <b>May 2022</b>) for this NSAID (<b>eggs excluded</b>) under the status "without MRL (quantitative) required" (see <a href="https://eur-lex.europa.eu/eli/reg/2022/1000/oj">Ketoprofen 003652-EXTN-0004 MRL Summary opinion (europa.eu)</a>).</p> <p>Under the same status, ketoprofen already has MRLs in cattle (meat and milk), pigs and horses =&gt; With NVR: Cascade WP ≥ 3 days (if prescribing KELAPROFEN 100 mg/mL or KETPROPIG 100 mg/mL), 4.5 days (if DINALGEN 300 mg/mL or LABIPROFEN 150 mg/mL) or 6 days (if prescribing other VMPs).</p> <p>But <b>ideally, these ketoprofen-based VMPs should apply for MA extension to "Chickens/Turkeys/Ducks"</b>.</p> <p><b>Paracetamol</b> can be used via the cascade (WP = 1 day) but with what efficacy?</p> <p><b>Wearing transfixing glasses</b> to limit attacks between hens is very effective (by limiting the field of vision to the lateral surroundings) but their placement (beak piercing) is considered an act of mutilation, which prohibits this practice.</p>	M n° 5
	<p>No local anaesthetics (sprays? gels?).</p> <p><b>Unauthorised and illegal use of alfaxalone</b> (see File "2022-03-25 FAQ MV AM" - penultimate Q/A p3): the prescription of ALFAXAN (alphaxalone) at a dose of 2mg/kg IV for anaesthetic of chickens before hatching with a fixed WP of 28 days <b>is not authorised</b> (non-compliance with Article 113 4) because <b>the substance is not listed in Table 1 of the MRL Regulation (no. 37/2010)</b>.</p> <p>Its use would fall under the definition of <b>illegal processing within the meaning of Regulation 2019/2090, with the related consequences (including destruction of the animals concerned)</b></p>	0 VMP	Work on anaesthesia of poultry with isoflurane – publication in progress (no recent information).	M n° 5
<u>Collibacillosis broiler chickens</u>	<p>Real problem not solved.</p> <p>The Poulvac E coli vaccine, the only one marketed, requires at least 2 weeks for immunity to be established and contains "only" O78,</p>	1 VMP	Autovaccines.	m

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	while recent publications confirm the diversity of strains and the limited efficacy on chick mortality. <b>Protection for chicks and against other APEC</b> (avian pathogenic Escherichia coli) <b>strains</b> remains an issue.			
<b>Candidosis</b> <u>Turkeys</u>	There is a parconazole-based premix allowed in guinea fowl with zero-day WP. <b>With the NVR, the “cascade” WP changes from 28 days to 1 day for turkey.</b> However, with NVR on medicated foods, manufacturers are disinvesting from this activity and <b>the single parconazole premix may soon no longer be manufactured.</b>	<b>1 VMP</b>	Premix Parconazole 6 guinea fowl (the “cascade” WP = 1 day for turkey with NVR). But stopping the production of this premix is likely. <a href="#">Alternatives exist with highly controversial copper products.</a> <a href="#">Research could be done on probiotics.</a>	<b>m</b>
<b>Coccidiosis</b> <u>Turkey and guinea fowl</u>	Future vaccines in ovo are only for Gallus	<b>0 VMP</b>		<b>m</b>
<b>Haemorrhagic enteritis</b> <u>Turkey and pheasants</u>	Shortage of DINDORAL, <b>the only vaccine on the market.</b>	<b>Disp</b>	No vaccine alternatives	<b>m</b>

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Pathology: currently being resolved with existing solution	Initial problem	Type of problem	Solution / Alternatives Reason for: <b>Resolution in progress</b> / <b>Disappearance of the therapeutic gap</b>	Gap initially <b>Major: M</b> minor: m
<p><b>Colibacillosis</b> <u>Laying hens</u></p>	<p>During the laying period, POULVAC E Coli can now be used (since the acceptance of the <b>MA variation approved in 2021</b> –see opposite), but its effectiveness has not been demonstrated.</p> <p>However, the use of auto-vaccines remains essential in a large number of cases, particularly if the E Coli strain is different from that of the vaccine. Conditioning the auto-vaccines authorization to the submission of pharmacovigilance reports poses the problem of being forced to vaccinate/ “sacrifice” (at least one batch) with an ineffective vaccine.</p> <p>More than 90% of breeding hens for meat and egg production currently receive autovaccines with very good results. Auto-vaccines are used at the pullet stage to prevent disease in the egg-laying building.</p>	<p>Reg</p>	<ul style="list-style-type: none"> <li>• <b>POULVAC E Coli: removal of the initial "Contra-indication"</b> in § 4.7 of the SPC, for its use during laying period. <b>MA variation submitted on 01/03/21, accepted on 09/09/21 by the CVMP to amend the SPC §4.1 Indications "Chickens (meat chickens, <u>future laying/breeding chickens</u>) and turkeys" and §4.7 Use in pregnancy, lactation or laying</b> <i>"The safety of Poulvac E. coli has been demonstrated when given to hens during the laying period in one dose by nebulisation and by administration of drinking water. However, the effectiveness of Poulvac E. coli has not been demonstrated when given to hens during the laying period. The decision to use this vaccine in hens during the laying period should be made on a case-by-case basis.</i> <i>The safety of Poulvac E. coli has not been studied in turkeys during the laying period. Do not use in turkeys during the laying period and during the 6 weeks preceding the laying period."</i></li> <li>• <b>Autovaccines:</b> Extension of the use of autovaccines in case of epidemiological link (strains of the breeding of laying animals used during the breeding phase in the chick) <b>considered by the NVR.</b></li> <li>• Colistin with restriction</li> <li>• Phytotherapy</li> </ul>	<p>m</p>
<p><b>Coccidiosis</b> <u>standard broilers</u></p>	<p>Rather an economic issue: cost of vaccines (purchase / administration) + adaptation of the food formula. <b>The 3 available vaccines, for Gallus only and for short (meat) production, are more expensive than coccidiostatic additives and a slight drop in performance seems to occur around 14 days when using these vaccines.</b></p>	<p>PhV / Eco / Reg</p>	<p><b>Future vaccines in ovo at hatcheries</b>, for Gallus only. Vaccination possible at 1 day with live vaccines. <b>Three vaccines are available</b>, for Gallus only, and for short (meat) production. <b>Amongst treatments other than amproliums, sulphonamides have indications for coccidiosis, but are rarely used.</b></p>	<p>m</p>

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	<p>=&gt; <b>In ovo vaccination possible with future vaccines, but obligation to ask the customer to sign a discharge</b> because the majority of the SPCs of other vaccines in ovo mention "Do not mix".</p> <p>Amprolium available but not very effective. <b>Sulphonamides have indications for coccidiosis</b>, but are rarely used.</p> <p>Toltrazuril with WP of 18 days for broilers, when clinical signs occur at 25-28 days. Other molecules have WPs that are too important for the age at which clinical coccidiosis occurs.</p> <p>Other problems following vaccination: <b>impossibility of prescribing ATB treatments during the 3 weeks of vaccine immunity, which may lead to the use of fluoroquinolones, if the sulfonamides are not sufficient or if there are shortages in small presentations of flumequine. Other alternatives</b> (complex products composed of plant extracts or essential oils for the most part) <b>without any official claim and indications such as "contributes to the management of the risk associated with coccidia"</b>. Products used in drinking water, therefore equivalent to treatments. <b>No rigorous efficacy studies for these complex products.</b></p>		<p><b>Alternatives used in the field: complex products consisting of plant extracts or essential oils for the most part but without official claims neither rigorous efficacy studies.</b></p>	
<p><b>Highly pathogenic avian influenza (HPAI)</b></p>	<p><b>Use of vaccines:</b> candidates exist but the health policy should first be defined.</p> <p>Anses has already been requested urgently: 2 referrals (for Gallus and palmipeds) are being drafted. The impact is French and European and the economic impact is international.</p>		<p><b>New vaccines developed</b></p>	
<p><b>Adenovirus (breeders), Reovirus (depending on strains), Guinea fowl viral pancreatitis: needs for "viral auto-vaccines"</b></p>	<p>Production capacity still limited in France (under development).</p>		<p><b>Existing auto-vaccines</b> (but capacity still limited in France - under development). Annual renewal <b>ATU</b> for Filavac°Fit (Filavie). Inactivated avian vaccine against adenovirus and/or reovirus.</p>	