The Director General

Maisons-Alfort, 24 November 2017

OPINION
of the French Agency for Food, Environmental and Occupational Health & Safety

relating to Request No 2016-SA-0177 - Disposition of food producing animals participating in non-clinical studies on veterinary medicinal products

ANSES undertakes independent and pluralistic scientific expert assessments.
ANSES primarily ensures environmental, occupational and food safety as well as assessing the potential health risks they may entail.
It also contributes to the protection of the health and welfare of animals, the protection of plant health and the evaluation of the nutritional characteristics of food.

It provides the competent authorities with all necessary information concerning these risks as well as the requisite expertise and scientific and technical support for drafting legislative and statutory provisions and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are published on its website.

On 8 August 2016, ANSES received a formal request from the Directorate General for Food and the Directorate General for Health to conduct an expert appraisal on the disposition of food producing animals participating in non-clinical studies on veterinary medicinal products.

1. BACKGROUND AND PURPOSE OF THE REQUEST

A clinical trial or study on veterinary medicinal products is one undertaken to assess the safety and/or efficacy of a veterinary medicinal product, under normal farming conditions called 'field' conditions, in animals belonging to the target species of the veterinary medicinal product with the goal of obtaining a marketing authorisation.

Trials other than clinical trials, called non-clinical trials, are conducted under experimental conditions in facilities authorised to use animals for scientific purposes. All studies belonging to the category of non-clinical trials are specified in the report in Annex 2.

The regulations in force (Article L. 234-2 of the French Rural and Maritime Fishing Code) state that "the placing on the market of foodstuffs from animals that have been subject to trials on medicinal products is prohibited, except in the case of clinical trials on veterinary medicinal products". They also prohibit the use in human food of foodstuffs from animals that are or have been subject to non-clinical trials unless a consumer risk assessment has been undertaken. Some European Union (EU) Member States have legislation that allows for case-by-case decisions.

In France, according to the results of a consumer risk assessment, greater harmonisation of the applicable rules would help reduce food waste and improve the competitiveness of companies developing veterinary medicinal products. In this case, the principle of the 3Rs (Replace/Reduce/Refine), which is a fundamental research principle underlying the requirements of Directive 2010/63/EU[1], would be applied. To make use of food-producing animals used for scientific purposes, one option would be to incorporate them into the human food chain.

There are other biosafety aspects related to the introduction of animals on a farm, as well as *ad hoc* rules (fallow periods, serological testing, etc.), but these were not included in this formal request.

The examination of this request relied on various components:

- Regulatory background information was analysed to shed light on potential differences between the situation in France and in other EU Member States. The various French and European regulatory texts (food, animal testing, veterinary medicinal products, etc.) were summarised, and the economic context was presented based on information provided by manufacturers regarding the number of animals involved, the impact on trial costs and the sector's position on the European market.
- Social, cultural and political dynamics related to this request were addressed. The experts briefly described some issues related to the 'careers' of these animals (health crises and risks related to food, welfare of animals used for scientific purposes, consumption of meat, etc.) as well as social questions and criticism that could be raised by their availability for consumption.
- The public health risk from foodstuffs derived from animals subject to non-clinical studies on veterinary medicinal products, and recommendations on the regulation and notification of their use in human food were assessed.

A matrix breakdown was used for the appraisal of this request based on the status of the animals (untreated or treated), the type of treatment received, and the trial conditions. The scope of this expert appraisal included chemical and immunological medicinal treatments. A total of six scenarios were studied:

- Scenario 1: animals not having received any treatment,
- Scenario 2: animals having received a placebo or excipient,
- Scenario 3: animals having received a pharmaceutical product with a marketing authorisation (MA) in France or an EU MA,
- Scenario 4: animals having received a treatment with no MA in France or in Europe,
- Scenario 5: animals having received a vaccine with an MA,
- Scenario 6: animals having received a vaccine with no MA.

[1] This rule, recently transposed into French law, requires that testing facilities: 1) systematically choose, whenever possible, solutions not using animals, for example *in vitro* testing methods or *in silico* mathematical and bio-computing models (Replace), which also have economic advantages in terms of cost reduction; 2) use the fewest possible animals when their total replacement cannot achieve reliable results (Reduce); 3) optimise testing methods to minimise suffering and make optimum use of results (Refine).

2. ORGANISATION OF THE EXPERT APPRAISAL

The expert appraisal was carried out in accordance with French Standard NF X 50-110 "Quality in Expert Appraisals – General Requirements of Competence for Expert Appraisals (May 2003)".

ANSES entrusted examination of this request to a group of expert rapporteurs reporting to the Expert Committee on Assessment of the physico-chemical risks in foods (CES ERCA). The group of expert rapporteurs met several times in 2017 and interviewed representatives from the veterinary medicinal products industry and service providers, as well as the information centre on the social impacts of livestock and meat (CIV). Its expert appraisal work was regularly submitted to the CES ERCA. The CES ERCA's summaries and conclusions rely on the collective expert appraisal report prepared by the group of expert rapporteurs and were validated in its meeting of 13 September 2017. This work was therefore conducted by a group of experts with a wide range of complementary skills.

All of the participants in this expert appraisal are listed in Annex 1.

The group of expert rapporteurs produced a collective expert appraisal report available in Annex 2.

ANSES analyses interests declared by experts before they are appointed and throughout their work in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals.

The experts' declarations of interests are made public via the ANSES website (www.anses.fr).

3. ANALYSIS AND CONCLUSIONS OF THE CES ERCA

In light of the collective expert appraisal report prepared by the group of expert rapporteurs, the CES ERCA is issuing the following conclusions.

The background analysis provided an overview of the various European regulatory positions as to authorising the reintroduction in the food chain of animals from non-clinical trials, for the various possible scenarios. It also reviewed the foundations of the dichotomy between clinical trials and non-clinical trials on veterinary medicinal products. It provided grounds for revisiting French positions based on considerations related to animal ethics, the reduction of food waste, and economic competitiveness.

Specifically, the analysis of social, cultural and political dynamics related to this request provided further insight. It demonstrated a lack of social knowledge and human and social sciences (HSS) studies dealing strictly with the subject matter of the request. The conclusions relating to HSS had no predictive power but still provided overall perspective. They covered various known and studied generic challenges: behaviours, perceptions, criticisms and social controversies related to animals, food (especially meat) and food safety. They raised the possibility, which cannot a priori be verified, of social responses (questions, doubts, misgivings, etc.) following the publication of this opinion. The analysis also highlighted uncertainty regarding the social conditions in which the opinion will be received (by which stakeholders(s)?, how?). Moreover, the consumer risk assessment undertaken in the context of this work, for chemical medicinal products on the one hand and for immunological medicinal products on the other hand, led to standardised conclusions for certain medicinal products (e.g. MAs) and/or animal groups (e.g. placebo, untreated) but to a case-by-case approach for other medicinal products and/or animal groups.

The HSS component, the consumer risk assessment, and a pragmatic approach aiming to make clear recommendations led to the recommendations put forward by the group of rapporteurs being simplified and certain options deemed difficult to standardise and requiring assessment on a case-by-case basis being abandoned.

In the end, the following recommendations have been proposed for the three identified situations:

- **Systematic use in human food (with a withdrawal period of zero):**
  - for untreated animals, with no risk of possible contamination through licking or contact with treated animals,

- for animals having received a placebo or excipients appearing in Table 1 of Commission Regulation (EU) No 37/2010[2] on MRLs, or included in the 'out of scope' list[3],
- for animals having received a substance appearing in Table 1 of Commission Regulation (EU) No 37/2010 on MRLs, for which an Acceptable Daily Intake (ADI) and a Maximum Residue Limit (MRL) are not required, or a substance included in the 'out of scope' list,
- for animals having received an immunological medicinal product that does not contain any zoonotic agents but contains excipients appearing in Table 1 of Commission Regulation (EU) No 37/2010 on MRLs, or included in the 'out of scope' list.

- **Use in human food with a withdrawal period equal to that in the MA for the pharmaceutical product under study:**
  - for animals having received a pharmaceutical product with an MA in France according to the recommendations in this MA,
  - for animals having received a pharmaceutical product with an MA in France under conditions different from the recommendations in this MA, if exposure is less than or equal to that obtained in application of the MA's recommendations. This situation is encountered when the only difference compared to the conditions of the MA is: either a dose below the recommended dose, or a new minor target species for which the product has a known MRL status identical to that of a major species and the dose is less than or equal to the recommended dose for the major species (unless it is an injectable formulation, topical product or transdermal product).
- **No use in human food:**
  - for animals having received a chemical or immunological product containing a substance with no MRL status,
  - for (vaccinated and control) animals having been challenged with a zoonotic agent,
  - in all other situations where the medicinal product is used under conditions different from those stipulated in the MA: in specific situations when permitted by the available data (and also for animals that receive a product that has no MA in Europe but contains a substance with a MRL listed in Table 1 and has an established MRL or ADI), the French Agency for Veterinary Medicinal Products (ANMV) could determine a specific withdrawal period (WP), as is currently performed for animals from clinical trials. However, for the reasons mentioned above (to avoid case-by-case decisions) and considering that knowledge of the medicinal products used is less complete in this stage of development, the experts recommend not using these animals in human food.

These recommendations may help risk managers in their review of the French legislation, by focusing on changes in the draft European regulation on veterinary medicinal products, which will ultimately be the only applicable regulation in the European Union. These same risk managers may, if they see fit, interview consumers and their organised representatives, in order to draw attention to the replacement of animals subject to trials and open the topic up for discussion. France's national consultation on the food sector (*Etats Généraux de l'Alimentation*), planned to last until the end of 2017, could be a window of opportunity to address these points. The same is true for the meetings

[2] Commission Regulation (EU) No 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin

[3] Substances considered as not falling within the scope of Regulation (EC) No 470/2009, with regard to residues of veterinary medicinal products in foodstuffs of animal origin. EMA/CVMP/519714/2009 - Rev.33

of the French National Food Council (CNA). During this process of informing the public, it is essential to clarify and explain situations involving animals subject to testing and used in human food.

Minority opinions

Three CES ERCA experts (Alain-Claude Roudot, Pierre-Marie Badot and César Mattéi) expressed a dissenting opinion regarding the use of marketing authorisations (MAs) for risk assessments involving the sale and consumption of healthy animals exposed to veterinary medicinal products in the trial phase.

An MA is an authorisation given based on a benefit/risk analysis. This means the medicinal product is administered to a sick animal to treat it, and the risk incurred is considered negligible in relation to the expected benefit. In the framework of this formal request, the medicinal product is administered to healthy animals, with no direct benefits for the exposed animal or indirect benefits for consumers: it is therefore a situation in which a food is contaminated by chemical products, for which the risk should be assessed as is, and not in relation to a possible benefit.

Therefore, in the specific framework of this request, i.e. with no expected health benefits, the use of an MA to assess the possible placing on the market of a healthy animal exposed to a veterinary medicinal product in the trial phase is inappropriate and cannot be considered to be a criterion ultimately ensuring consumer protection.

4. AGENCY CONCLUSIONS AND RECOMMENDATIONS

The French Agency for Food, Environmental and Occupational Health & Safety endorses the CES ERCA's conclusions.

The Agency reiterates that the establishment of an MA includes a safety assessment stage for veterinary drug residues in relation to consumer exposure through food. Moreover, the benefit-risk assessment for animals is undertaken at a later stage separate from the safety assessment, which is a mandatory prerequisite. In order to protect consumers, prescriptive Maximum Residue Levels are established. These standard levels also exist internationally in the *Codex alimentarius* and are recognised by countries as the basis for import controls for foodstuffs.

Lastly, the Agency notes that the use in human food of animals used for scientific purposes raises an ethical issue that lies outside its sphere of competence, and insists on the CES ERCA's recommendations regarding drawing attention to the placing on the market of animals subject to trials and opening the topic up for discussion among consumers.

The French Agency for Food, Environmental and Occupational Health & Safety recommends, in a single market authorising the circulation of foodstuffs between Member States, the development of European harmonisation regulating the disposition of animals included in both clinical and non-clinical trials on veterinary medicinal products in the framework of the draft European regulation relating to veterinary medicinal products.

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KEYWORDS

Résidus médicaments vétérinaires, consommation animaux, essais non cliniques
Veterinary drug residues, consumption of animals, non-clinical studies.