ANALYSIS OF AGENDA ITEMS IN PREPARATION FOR THE 25th SESSION OF CODEX COMMITTEE ON RESIDUES OF VETERINARY DRUGS IN FOOD (CCRVDF25)

12 – 16 and 20 July 2021 Virtual Meeting

Substances/MRLs Submitted for Approval

AGENDA ITEM 6.2: Zilpaterol hydrochloride (cattle fat, kidney, liver, muscle) retained at Step 4

Objectives

This document offers an analysis of agenda items to support participation to the 25th session of the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF25), taking place virtually in July 2021. The document is intended for possible use by the Codex communities of practice promoted by GFoRSS and PARERA, as part of their contribution to enhancing awareness and supporting effective participation in international food standard setting meetings (Codex meetings) by representatives from members and observers, in particular in **the Middle East and North Africa.**

The analysis provided in this document offers a factual review of agenda items, their background and a discussion of some considerations. This analysis is indicative in nature and does not represent an official position of the organizations mentioned above (PARERA and GFoRSS), their membership or their management.

This analysis is prepared as part of the **Codex Initiative for the Middle East and North Africa**: ***MENA Codex Initiative***, implemented by PARERA and GFoRSS and funded by the US Codex Office, US Department of Agriculture.

**It is important to note that experts – members of the Expert Working Group (EWG) – do not represent the organizations and / or jurisdictions to which they are affiliated. The selection and participation in the EWG proceedings is based on each expert's own credentials and experience which should not be misconstrued as the country's / delegation's / organization's position to which they belong.*

Agenda Item 6.2: Maximum residue limits for zilpaterol hydrochloride (cattle fat, kidney, liver, muscle) (JECFA81 and JECFA85) retained at Step 4

Documents: REP18/RVDF-App. III and CX/RVDF 21/25/7 (*)

** Proposed MRLs for zilpaterol hydrochloride (cattle fat, kidney, liver, muscle) (JECFA81 and JECFA85) - CCRVDF24 agreed to retain these MRLs at Step 4 for further consideration at CCRVDF25 therefore no further comments are requested on this MRL. Document CX/RVDF 21/25/7 provides consolidated information of the outcomes of the JECFA81 and JECFA85 evaluations as well as the discussions at CCRVDF and CAC on this compound to facilitate discussion at CCRVDF25.*

Background

Zilpaterol hydrochloride has been assessed by JECFA at its 78th (2014) and 81st (2015) meetings at the request of the 21st and 22nd Sessions of the CCRVDF, respectively.

The 81st meeting of JECFA established an **ARfD of 0.04 µg/kg bw** and a proposed draft MRLs for zilpaterol hydrochloride in **cattle** kidney, liver, and muscle. 3.3 µg/kg in kidney, 3.5 µg/kg in liver and 0.5 µg/kg in muscle.

CCRVDF23 (2016) agreed to hold the proposed draft MRLs for cattle tissues to allow the sponsor to develop and provide additional data on the bioavailability of incurred residues for re-evaluation by JECFA. The new data developed by the sponsor did not show a difference in bioavailability of zilpaterol hydrochloride residues, but were submitted in full, for consideration by the 85th JECFA (2017). The 85th JECFA evaluated the new data provided and **reconfirmed the 81st JECFA's recommended MRLs.**

CCRVDF24 (2018) agreed that JECFA had conducted a robust scientific evaluation and that **there were no scientific or public health concerns** regarding the proposed draft MRLs for zilpaterol hydrochloride. There was extensive support from Member Countries to advance the proposed draft MRLs to the Codex Alimentarius Commission **for adoption at Step 5** (allowing for another round of comment and consideration by the Committee) or Step 5/8 (final adoption). However, some delegations objected to advancing the MRLs based on concerns outside the mandate of the Committee and Codex, including national legislation, animal welfare, and general opposition to "non-therapeutic" uses of animal drugs. As there was no consensus on advancement of the proposed draft MRLs for zilpaterol hydrochloride they were held at Step 4 and not forwarded to the CAC for consideration.

Review of Safety Assessments

Zilpaterol hydrochloride (trade name Zilmax), CAS no. 119520-06-8), is a β2-adrenoreceptor agonist that is used to **increase the rate of body weight gain**, improve feed efficiency and increase carcass muscle ratio in **cattle fed in confinement** before slaughter. Zilpaterol, by activation of protein kinase A, increases protein synthesis in skeletal muscle fibers, as well as reduces lipogenesis and increases lipolysis in adipose tissues.

The 78th meeting of JECFA, at the request of the 21st session of CCRVDF, evaluated zilpaterol hydrochloride and established **an ADI of 0–0.04 µg/kg bw** on the basis of a LOAEL of 0.76 ug/kg bw for a slight increase of tremor in humans in a single-dose study and an UF of 20.

The Health Based Guidance Value (HBGV) was established based on a review of available **acute oral studies (n=4)** performed in adult human volunteers (total of 16 healthy and 23 asthmatic volunteers) where various effects (blood pressure, heart rate, clinical chemistry parameters, tremor and bronchodilatation) were measured. Effects observed were described as slight and transitory and typically related to the β2-adrenergic agonist activity of zilpaterol HCl.

Considering all the human data, the LOAEL for zilpaterol HCl was **0.05 mg/person** (equal to 0.76 g/ kg bw). An overall NOAEL could not be identified for this effect while the NOAEL for cardiovascular and bronchodilation effects ranged from 0.05-0.25 mg/person.

At the 81st JECFA meeting, the **same ADI value of 0.04 ug/kg bw was set as the ARfD based** on the existing study.

JECFA considered a refined assessment with one-sided 95% confidence interval over the 95th percentile of residue concentrations derived at 77 hours post-dose: 3.3 µg/kg in kidney, 3.5 µg/kg in liver and 0.5 µg/kg in muscle.

There were no measurable residues detected in fat. These values would result in acute dietary exposure (GEADE) of **1.9 µg/day for the general population (80% of the ARfD)** and **0.57 µg/day for children (94% of the ARfD).**

It is noted that the time point at which the MRLs are calculated (77 hours) is consistent with currently approved withdrawal times (GVP). Previously, JECFA had considered a 72-hour withdrawal time following dosing but the resulting 95th% residues resulted in children exceeding the ADI (117%).

The analytical methodology reviewed by JECFA at its 81st meeting **was a validated LC-MS/MS method. F**or all bovine tissues, the LOQ was 0.25 µg/kg with calculated LODs of 0.048, 0.067 and 0.045 µg/kg for liver, muscle and kidney, respectively.

Situation in Other Jurisdictions

While the process used by JECFA to establish HBGVs and recommend MRLs for cattle is consistent with the usual process (GVP), there will likely be continued debate as to whether consensus can be reached by CCRVDF.

The EC requested that EFSA review the decision by the 81st JECFA to set an ADI/ARfD and recommend MRLs for zilpaterol hydrochloride in cattle.

EFSA (2016) noted that the ADI/ARfD of 0.04 µg/kg bw proposed by JECFA **is sufficiently protective for the establishment of MRLs and safe exposure levels for humans.** While originally referring to the JECFA risk assessment for zilpaterol hydrochloride as "comprehensible", this was modified in the published EFSA opinion to **"scientifically robust**". EFSA did note that only a withdrawal period of more than 3 days resulted in residue levels for which the corresponding acute dietary exposure was below the JECFA ARfD. As the range of withdrawal periods for currently approved zilpaterol formulations is indicated as 2-4 days, EFSA stated that withdrawal periods <3 days may be insufficient to protect consumers.

Directive 96/22/EC prohibits the use of β-agonists in food-producing animals except for therapeutic use, under direct veterinary supervision, in cows and horses. Likewise, meat and meat products obtained from animals treated with β-agonist for growth promoting purposes are banned in the European Union. The prohibition applies equally to domestic products and meat imported from third countries. As such, it will be expected that all EU member states will not agree to advance the proposed MRLs beyond step 4. Various other countries where zilpaterol is not approved for use will also likely express an objection to advancing the proposed MRLs.

As of October 2017, zilpaterol hydrochloride the US, Canada, South Africa, South Korea, the Ukraine and Brazil while, as of 2013, its use had not been approved in China, Taiwan, Russia, and many countries in the European Union.

Discussion of the EWG Possible Scenario at CCRVDF25

Should there be opposition for moving the proposed MRLs forward further in the Codex Step procedure, such opposition and concerns would not be associated with a health rationale, nor with a rationale that is considered as part of the mandate of Codex (to protect consumer's health and enable fair practices in the food trade).

Beyond the scientific considerations and the details of the scientific assessment for this substance, the EWG discussed the overall direction that Codex Committees and the Commission would adopt in situations where there is likelihood of polarization of positions, related to differences in national policies that are beyond the mandate of Codex.

Previous situations, where opposition to a standard would lead to obstructing the adoption of the standard due to the lack of consensus, were mostly driven by trade considerations and by the assumption that the adoption of a standard by Codex would offer ammunition to a possible trade dispute. More recent experience, including subsequent to the adoption of the standard related to Ractopamine MRLs have not led to such disputes. Moreover, if national policies are well substantiated by the same level of standard of protection over time, this would support the country's right to maintain such level of protection, even if it is not consistent with Codex decisions.

A standard adopted at Codex for substances that were fully evaluated and that were deemed safe and fulfilling Codex conditions for adoption, would offer guidance to countries, where the sole source of regulatory decisions comes from Codex proceedings and would not deprive such jurisdictions (producers, regulators) from access to such safe products used in conjunction with food production.