November 2021

RE: Food Standard Authority (FSA) Novel Food applications for cannabidiol; Implications for replicate toxicity testing in animals

DevelRx Ltd and The Canna Consultants are concerned over what we consider to be the scientifically unjustified, and ethically unacceptable, replicate toxicity testing of Cannabidiol (CBD) that is being proposed/demanded by the Food Standards Agency (FSA), acting under guidance provided to them by the Committee on Toxicology (COT).

The Regulatory Position

For the past 2-3 years CBD, a cannabinoid compound that is purified from hemp plants, has been added to a growing number of food products (e.g., oils, tinctures, or confectionary). These products were brought to the market in the UK and the European Union and were not considered to be subject to regulation, however, in January 2019 extracted and purified CBD was classed as a Novel Food by the EU (and hence the UK).

Under a regime introduced by the FSA in February 2020, manufacturers of food products containing CBD were asked to submit a Novel Food application to the FSA for Authorisation of their CBD ingredient and products manufactured therefrom. This Authorisation process is designed to ensure the ingredient and products manufactured therefrom have been through a thorough and independent safety assessment.

We fully endorse this approach to protecting public safety and it is something which we demanded of the regulator and market participants in advance of the announcement of the FSA decision - a Position Paper entitled "The Road to a Better Future" was provided to Stakeholders by The Canna Consultants in October 2019 and any consideration of the document will identify it as the blueprint which was adopted by the FSA in its later announcement 4 months later. The document is hyperlinked above and available at: https://www.thecannaconsultants.co.uk/wp-content/uploads/2020/02/The-Road-to-a-Better-Future.pdf.

Our Issues of Concern

Issue 1

The first issue of concern is the assessment of the safety and toxicity risks of CBD that has been conducted by the Committee on Toxicity is superficial, scientifically flawed and has placed reliance in part on a biased data-source that was clearly part of a pharmaceutical company's lobbying campaign to the US government to restrict the non-medical use of CBD by the US public.

Based on this flawed assessment, COT has recommended that CBD needs to undergo additional and extensive toxicity and safety testing in animals before it is safe for human consumption.

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The approach to Novel Food applications that has been adopted by the FSA, under guidance from COT, is to treat CBD in the same way as a potential food contaminant (e.g., a pesticide or heavy metal). They are demanding that every manufacturing company which is making an application for CBD in a food product (or products) conducts an extended 96-day, repeat dosing, rat toxicity study (Organisation for Economic Co-operation and Development; OECD-408 study) on their individual CBD ingredient to evaluate their CBD's safety and toxicity. Furthermore, in the early feedback from the FSA on Novel Food applications, there have also been demands for justification in not conducting genotoxicity studies and other "Tier 2" toxicity studies (e.g., reprotoxicity) in animals.

Issue 2

Secondly, in its role as the approving body for every application for the use of CBD as a Novel Food, the FSA is not only mandating that every CBD ingredient undergoes additional safety and toxicity testing, but also failing to treat CBD ingredients which have virtually the same chemical composition as being Substantially Equivalent to each other, thus forcing every manufacturer of every ingredient and every user of that ingredient to pursue this 96-day repeat dosing, rat toxicity studies on what are, by any scientific assessment, the same ingredients. We acknowledge that the parameters of substantial equivalence demand limits from the mean to be identified, in order to ensure that two ingredients are actually *substantially equivalent*, but the insistence on separate studies for every ingredient will involve large scale, replicate animal toxicity testing.

The Origin of Our Concerns

Part of this approach might be justified if it were not for that fact that in 2018-2019, CBD was approved as a medicine (Epidyolex; GW Pharmaceuticals) to treat resistant forms of epilepsy in patients 1-2 years of age and above by the European Medicines Agency (EMA), the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the US Food and Drug Administration (FDA). The FDA has also recently approved Epidyolex to treat tuberous sclerosis complex in children of over 1 year of age.

To gain approval of CBD for medical use in humans, GW Pharmaceuticals performed the "full regulatory package" of safety pharmacology testing *in vitro*, in animals and in humans, together with a full programme of toxicity testing, including genotoxicity, reproductive toxicity and general toxicity testing in animals.

Furthermore, as part of that assessment process, the pharmacokinetics (including drug-drug interaction studies), tolerability and safety of CBD were also extensively explored in human subjects. The Epidyolex database consists of 15 clinical pharmacology and double-blind, placebo-controlled clinical trials. This pharmacokinetic, safety and toxicity evidence has been reviewed by experts from the MHRA, EMA and the FDA in the US and the data and their detailed assessments are publicly available[2,3].

COT have published their assessment[1] on the safety of CBD using the publicly available review information from the Epidyolex European[2] and US[3] regulatory submissions and also from other scientific research studies. It is COT's review of the Epidyolex safety and toxicity findings which has led to the demands by the FSA for toxicity studies to be performed on

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every one of the individual CBD ingredients by each CBD manufacturer that has submitted a Novel Food application.

Authors' Involvement in the Issue

DevelRx Ltd (Professor David Heal, Dr Sharon Smith and Dr Christopher Atterwill) (https://develrx.com) were approached by The Canna Consultants (Mr Stephen Oliver and Mr Matthew Lawson) (https://www.thecannaconsultants.co.uk) and asked to advise on the issue, the latter believing that the FSA/COT's position to be scientifically and ethically unjustified.

DevelRx are experts in central nervous system (CNS)-active drugs, and safety pharmacology assessments in drug discovery and development. The Canna Consultants provide policy and legislation consultancy to governments and regulators on medicinal cannabis and the cannabinoid industry.

DevelRx and The Canna Consultants have made a full evaluation of the COT safety assessment of CBD and consider that the COT analysis and conclusions are deeply flawed for reasons detailed in Annex A.

The Canna Consultants have been discussing this issue with the FSA for over 18 months, through written correspondence, videoed Q&A sessions and on-line discussions with the Regulated Products Team (Annex B).

We are of the strong opinion that the request by the FSA for multiple toxicity testing on the same Novel Food product, CBD:

1. is unnecessary because this testing has already been conducted by GW Pharmaceuticals;

2. is unethical because animals are being used as surrogates when the question has already been answered by studies in the relevant species, humans;

3. is unscientific because no guidance has been provided by COT / FSA on how the findings will be interpreted or the implications arising from them; and,

4. is contrary to the principles of the 3Rs (reduction, replacement, and refinement) to avoid unnecessary use of animals in experiments.

Signed,

Professor David Heal, BSc, MSc. PhD, DSc FRSC, FBPhS (DevelRx Ltd)
Dr Sharon Smith, BSc, PhD (DevelRx Ltd)
Dr Christopher Atterwill, BPharm, PhD, FRPharmS, FIBiol, FRCPath (DevelRx Ltd)
Mr Stephen Oliver, LLB (The Canna Consultants)
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Annex A The Flaws in the COT Advice to the FSA over the Safety Profile of Cannabidiol (CBD)

DevelRx and Canna Consultants have had several virtual meetings with senior members of the FSA (see also Annex B) and very clearly pointed out that what COT is proposing is:

(i) Scientifically invalid;

A fair and objective scientific assessment is totally reliant on using evidence that is free of bias. Many of the statements in the COT background document are lifted directly from a lobbying submission by GW Pharmaceuticals to the FDA with the stated aim to restrict or prevent public access to CBD products and the unrestricted use of cannabis for medicinal purposes. COT has not reviewed the data (none is presented to FDA), has taken GW Pharmaceuticals statements at face value and treated a lobbying piece designed to protect the commercial interests of the pharmaceutical industry as being neutral and objective.

GW Pharmaceuticals statements unequivocally reveal the commercial position that the company is attempting to defend:

"*Since our founding in 1998, GW Pharmaceuticals has been singularly focused on unlocking the potential of cannabinoids as medicines to address serious medical conditions*…"
"*In opening the door for consumer-market CBD products, FDA risks further diminishing the likelihood that more cannabis-derived product will be developed into proven medicines for these patients.*"
"*Due to a variety of factors—including competition from unapproved products—incentives to develop and drive competition among FDA-approved cannabis medicines are weakened to begin with*."

Human safety data always takes precedence over animal data. The Epidyolex database (GW Pharmaceuticals) consists of 15 clinical pharmacology and patient double-blind, randomised clinical trials, or double-blind clinical trials. It includes 10 completed trials in healthy subjects (trials with a pharmacokinetic element), 2 supporting trials looking at the effects of Epidyolex on sleep and drug withdrawal symptoms, 2 trials in specific populations (renal-impaired or hepatic-impaired patients) and 5 trials in patients with epilepsy.

What the FSA / COT proposes is to re-initiate safety testing of CBD in animals, while ignoring the large clinical trials database that is publicly available from GW Pharmaceuticals development of Epidyolex. Safety testing data are valid whether CBD is under evaluation as a medicine or a Novel Food product. This is important because the safety and toxicity of CBD in Epidiolex was tested in animals and humans at doses that were many times higher than the daily intake of CBD as a novel food product that is recommended by the FSA / COT. Hence the safety margins are large for the consumption of CBD as a novel food product.

Epidyolex is a highly purified CBD preparation (>98%) with minor amounts of psychotropic and non-psychotropic cannabinoids. The CBD isolates / distillates which are the subject of novel food applications by our clients are of similar or greater purity than CBD in Epidyolex From a safety perspective, there is no biologically relevant difference between Epidyolex and the novel food CBD isolates / distillates in these FSA Novel Food applications.

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(ii) Unethical from an animal welfare perspective; and,

(iii) Potentially in contravention of the Animals Scientific Procedures Act which precludes replicate testing without good reason.

If there is substantial evidence that unnecessary animal testing of CBD has been demanded by two government bodies, i.e. COT and FSA, it would contravene the government's commitment to the 3R's in animal testing, undermine the case for the use of animals in medical research and could present a major problem in respect of public opinion.

Based on the publicly available EMA[2] and FDA[3] clinical and non-clinical assessment of CBD, we prepared an extensive analysis of the toxicity and safety risks posed by CBD scaled from the maximum therapeutic Epidyolex oral dose (20 mg/kg/day) to the FSA recommended maximum daily CBD novel food consumption (1 mg/kg/day). That document has been made available to the FSA in various CBD Novel Food applications.

As stated in our letter, the analysis and reasoning in the COT document[1] are deficient. Some examples of why are given below:

1. For drugs in clinical development, there is an accepted weighting hierarchy for evidence when evaluating their ADME (absorption, distribution, metabolism and excretion), safety and toxicity. Precedence is always given to safety studies performed in human subjects. By demanding new toxicity testing to be performed in animals, while discounting the large clinical database from Epidyolex and other clinical trials of CBD, COT has failed to adhere to the accepted weighting that applies to safety and efficacy outcomes;

Strength of evidence		
Level	**Evidence source**	**Evidence strength**
Level 1	Systematic review and meta-analysis of DBRCTs; clinical guidelines based on systematic reviews or meta-analyses	Very strong
Level 2	One or more DBRCT	Strong
Level 3	DBCT with no randomisation	Moderate
Level 4	Case-control or cohort study	Limited
Level 5	Systematic review of descriptive and qualitative studies	Insufficient
Level 6	Single descriptive or qualitative study	Weak
Level 7	Experiments performed in mammalian species	Weak
Level 8	Experiments performed in non-mammalian species	Very weak
Level 9	Experiments performed in vitro	Extremely weak / ignore

DBRCT = Double-blind, placebo-controlled, randomised clinical trial.
DBCT = Double-blind, placebo-controlled, clinical trial.

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This point is clearly stated. Section 2.10.6 of the EFSA guidance document (Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283) clearly sets out what human data should be taken into consideration (see below):

"2.10.6. Human data
Human studies, if available, should be provided if they contain information relevant for the safety assessment, such as physical examination, blood chemistry, haematology, urine analysis, blood pressure and organ function tests and/or monitoring of adverse reactions. Relevant data may be derived from the use of the novel food for medical purposes or from epidemiological studies.
Additional human studies may be needed to investigate further potentially adverse effects, e.g. to address adverse effects observed in toxicological studies. In those cases where the novel food may exert pharmacodynamic effects, specific studies may be required to demonstrate that the proposed consumption and use of the novel food do not raise safety concerns.
The data from intervention studies and observational studies in humans should be organised according to a hierarchy of study designs and research questions, reflecting the relative strength of evidence which may be obtained from different types of studies. Studies with the highest level of scientific evidence should be presented first."

In addition to employing biased evidence, placing reliance on evidence in Levels 6 to 9 and failing to classify systematically the findings according to accepted evidential rankings, the assessment reported by the FSA and conducted by its advisors in COT[1] is deeply flawed and an unreliable assessment of CBD's safety and toxicity.

2. An assessment of adverse event signals for a novel drug must be compared against the background incidence in the placebo group in clinical trials to determine the magnitude of the signal. This has frequently been overlooked in the COT review.

3. When conducting safety assessments of drugs for clinical use, it is essential to characterise the doses which produce adverse events. It is especially important because COT is attempting assess the safety of CBD as a food whereas the clinically effective doses of Epidyolex are 10x to 20x higher than the recommended daily CBD consumption.

4. The COT document fails to consider that Epidyolex is being used to treat two severe forms of epilepsy (Dravet Syndrome and Lennox Gastaut Syndrome) in children and adults. The confounding impact of epilepsy on the adverse event profile of Epidyolex has not been factored into the COT document.

5. The contribution of co-administered anti-epileptic drugs to adverse events ascribed to Epidyolex has not been taken into consideration in the COT briefing document.

6. There are numerous statements in the COT document that are highly misleading, e.g., on liver toxicity. There is no description of the magnitude of changes, whether they were clinically significant, of the relevant data in the placebo control group for comparison.

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7. There are numerous statements in the COT document that are contradicted by the data they present.

8. COT has failed to differentiate between coincidence and causality.

9. Lack of objectivity in their assessment, e.g., COT focussed on findings in 5 subjects in a very small, short-term Phase 1 clinical study of 12 subjects, whilst ignoring the findings from a larger study of 64 patients receiving Epidyolex for 14 weeks. This entry was lifted directly from the lobby document that GW Pharmaceuticals sent to the FDA.

10. The COT assessment of CBD's safety and toxicity focuses on adverse event frequency but ignores the transitory nature of many of CBD's adverse events, particularly with regard to central nervous system side-effects, e.g. sedation. It also ignores their severity, which is of much greater relevance.

The misleading and negative opinion by COT of the potential safety and toxicity risks posed by CBD (Epidyolex) contrasts with the view of EMA in their Assessment Report (2019)[2] and the FDA in their Drug Approval Package (2018)[3].

Currently, the FSA adheres to the guidance for Novel Food applications set out by the European Food Standards Agency (EFSA)[4]. The tiered approach set out in the EFSA Guidance requires:

"*The Panel notes that all relevant knowledge on the novel food should be considered in order to make decisions on whether and which toxicity studies are necessary. Important elements include:*

- *the identity, chemical structure, composition and physico-chemical properties of the novel food.*
- *available information on previous human consumption of the novel food and its source.*
- *anticipated use(s), maximum use levels and the resulting intakes.*
- *available pharmacokinetic data.*
- *available toxicological data on the novel food or its constituents.*
- *available human studies.*
- *available relevant information on non-food uses (e.g., cosmetics, chemicals, pharmaceuticals)."*

All of this required information has been provided to the FSA in the CBD Novel Food applications submitted on behalf of our CBD manufacturing clients. The safety data that we have evaluated in our Novel Food application documents to the FSA derive not only from Epidyolex *in vitro*, animal and clinical studies, but also from other clinical studies using Pharmaceutical grade CBD from other sources, CBD with other cannabinoids including delta 9-tetrahydrocannabinol, tetrahydrocannabivarin, cannabigerol and CBD-rich botanical extracts containing terpenoids, flavonoids and sterols. The findings support the safety of CBD as a novel food.

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Annex B The Background to the Novel Food Application Process for Cannabidiol (CBD)

The Canna Consultants (TCC) - Matt Lawson and Steve Oliver - have been in dialogue with the FSA over this issue since February 2020 and have engaged in written correspondence, videoed Q&A sessions and on-line discussions with members of the Regulated products team: Head of Radiological, GM and Novel Foods, Novel Food Chemical Risk Assessment Team and Policy. Agreed minutes have been produced for private discussions and the Q&A recordings are publicly available on The Canna Consultants website (www.thecannaconsultants.co.uk).

The essence of these discussions has been the FSA's insistence that:

- an extended OECD-408 study in rodents is required for a CBD Novel Food application;
- a failure to accept existing safety margins for CBD as the medicine, Epidyolex, as a sound basis for assessing the safety of novel foods containing cannabinoids of equivalent / similar purity levels with regard to existing human data;
- a failure to provide a policy on Substantial Equivalence;
- justification of "gaps in safety data" position promoted by the COT, FSA and the ACNFP *(*Advisory Committee on Novel Foods and Processes*)*; and,
- their failure to recognise the ethical imperative against replicate animal testing, the legal obstacles to such testing - especially in the context of the absence of scientific need for it when set against a tiered approach (see Annex A).

The requirement by the FSA for the *in vivo* studies has created confusion in the industry and also with expert toxicologists in pharmaceutical human safety evaluation. This is at odds with the formal EFSA/FSA Guidance[4], which requires a tiered approach and further animal testing only where it is necessary.

The Canna Consultants' Position

The position of The Canna Consultants has consistently been that, if a full analysis of the data is carried out and applied to the subject Novel Food then, in circumstances where there is Substantial Equivalence between the compounds which are the subject of the publicly available scientific data[2,3] and the subject of Novel Food, then it is not only unnecessary and entirely unjustified, but also unlawful.

Guidance was sought as to whether the FSA had a policy on collegiate applications and the parameters for Substantial Equivalence across ingredients, directed to highly purified extracts which resulted in end products that contained no more than 1mg of combined controlled cannabinoids (with the later ideal being that such composition would be verified by laboratories which demonstrated their technical abilities under "blind" conditions in the UK Government-commissioned Ring Trial study of laboratories[6]).

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Discussions and requests for engagement resulted in a recording session with the FSA, where pre-agreed questions were posed and the sessions recorded for later public release. The videos were provided to the FSA ahead of publication and an opportunity for editing afforded them.

The salient points are as follows:

The FSA reiterated that the COT assessment of Cannabidiol from the Epidiolex and other available data identified the following gaps which needed to be addressed:

- Adverse effects on the liver;
- Reproductive effects;
- That the long-term effects of CBD were unknown;
- Drug metabolism - reference Cytochrome P450 enzymes;
- Somnolence and the potential effects on driving; and,
- Immunotoxicity / Allergenicity.

The FSA's position was, and still is, that these cannot be addressed without *in vivo* studies. When asked why they held these concerns in the context of a maximum daily dose of 1mg per kg in adults and where vulnerable groups were excluded, the position stated was that "adverse effects in the liver were observed at 1mg per kg of CBD".

When pressed on providing a policy on the use of animal testing and guidance on the areas to be addressed, the FSA stated that they would consider this and would seek to provide further guidance by September/October 2020. Despite now being over 12 months beyond that point, no policy or guidance has been forthcoming in any context.

The FSA stated that in order to be Validated, an applicant must either have either completed an OECD-408 toxicity study, commenced such a study or have made arrangements for the commencement of such a study.

The Canna Consultants' concerns were shared with DevelRx and an examination of the COT meeting minutes discussing CBD were examined along with the resulting Position Statement which informs the FSA's current stance.

The FSA's position was further challenged during a meeting with them on Friday 29th January 2021, attended by DevelRx and The Canna Consultants. The following questions and answers were provided in agreed minutes:

Question 1: **Does the FSA accept the Sponsor's position that its CBD isolate (>98.7%) purity is chemically identical and of a directly comparable purity to the CBD in Epidyolex (>98.0% purity)?**

FSA response: They could not offer an opinion on the lack of difference between the Always Pure Organics CBD Isolate and CBD in Epidyolex. They

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stated that the FSA does not have full access to GW Pharmaceutical's Epidyolex data as it is confidential. Therefore, it is not possible to determine what impurities may be present in Epidyolex.

Question 2: If the FSA disagrees, what are the reasons?

FSA response: No answer was given but they reiterated that the FSA did not have full access to the Epidyolex data.

Chris Atterwill (DevelRx) pointed out that all Epidyolex toxicokinetic and safety data was in fact in the public domain by way of EMEA[2], FDA[3] & WHO[7] (World Health Organisation) reports/regulatory summary dossiers from which most of our data and conclusions had been extrapolated.

FSA response: These these were not the full (raw) data from GW Pharmacuticals.

Question 3: Absorption, distribution, metabolism and excretion (ADME). The Epidyolex ADME studies in human subjects were conducted to GCP standards using a wide range of doses in fasted and fed conditions. The analyses were GLP compliant and the results have been reviewed and accepted as valid by the MHRA and EMA. What reasons do the FSA have to believe that published research studies from inferior, research level sources will contribute to our knowledge on CBD?

FSA response: This request was an error in the FSA feedback document on a CBD Isolate Novel Food application. They said that the FSA believes that there are gaps in GW Pharmaceutical's Epidyolex data, but did not expand on this point. There was no time in this meeting to go into what gaps the FSA thinks should be filled by the applications for CBD in food products.

Question 4: What toxicological testing does the FSA propose is necessary?

FSA response: Their advice was "follow the EFSA guidance". It was the responsibility of the CBD manufacturers / suppliers to decide which toxicity studies they need to perform. The FSA could not give any specific advice in this regard.

Chris Atterwill (DevelRx) suggested that in view of the stance of the FSA on the requirement for toxicity testing, it would follow that there would also be a requirement by the FSA to conduct human testing of CBD as humans are the target species in this situation. The FSA stated that there would not be a requirement from them for human testing of CBD in food products. However, an extended OECD-408 toxicity study (3 month repeated oral dosing of CBD) in rodents would be required contrary to the well known and internationally documented "reliability question" around the ability of animal toxicological testing to predict accurately human safety.

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It is well known and accepted that animal toxicology studies to predict human safety and risk are not 'failsafe' and give varying degrees of reliability for pharmaceutical products entering the clinical trial phases to evaluate safety in human drug development. This was well highlighted in in 2006 for the Tegenero drug candidate, TGN1412, in healthy human volunteers when a clinical trial went drastically wrong following testing of the molecule in regulatory animal toxicity studies. There are many other cited examples around the unreliability and variability of animal toxicology to fully or correctly predict the safety of molecules administered to humans. Thus, the rationale for conducting additional toxicology studies in animals for a molecule such as CBD is highly questionable when thorough preclinical and clinical evaluation studies have already been conducted for a medically approved version of CBD in the form of Epidiolex. Furthermore, this internationally-approved regulatory package of studies was conducted under Good Laboratory Practice / Good Clinical Practice (GLP / GCP) compliance unlike the plethora of research toxicology publications for CBD often cited by the COT[5].

Question 5: What scientific justification is there for additional testing of the Sponsors CBD Isolate, which is of the same purity (>98%) as CBD in Epidyolex?

David Heal (DevelRx) raised the topic of the ethics and legality of repeated animal toxicity testing and informed the FSA representatives and that it would be a matter of great concern to the UK Home Office in terms of the adherence to the 3Rs (Replacement, Reduction and Refinement of animals in experiments). One consequence of the FSA requirement for Sponsors to conduct rodent toxicity testing on a wide range of CBD products could be to drive CBD manufacturers / suppliers to conduct inferior toxicity studies outside of the UK, which has some of the highest welfare standards on animal testing in the world. It was emphasised that the testing of CBD in the target species, humans, has already been conducted in numerous clinical trials, in thousands of subjects by GW Pharmaceuticals and at a ≥20-fold higher dose than the 1mg/kg/day CBD dose recommended by the FSA in food products.

FSA response: The FSA does not have full access to the Epidyolex database, but the data from development of a medicinal product would not be appropriate for assessment of the safety of a food product. In the former situation, subjects would be under medical supervision and the bioavailability of CBD could be different in a food product. However, they agreed that it was a responsible view to aim to keep toxicity studies in animals to a minimum and suggested that applicants could form a consortium to have their toxicity studies performed.

Question 6: If the Epidyolex database is acceptable for raising potential safety issues for CBD in the COT evaluation document, why isn't it acceptable for CBD Novel Food applications to use data from that same database to answer those same questions?

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FSA response: No answer to the first part of the question. They reiterated that the clinical data on Epidyolex could not be extrapolated to the use of CBD in food products, that the FSA does not have full access to the Epidyolex database and to "follow the EFSA guidance".

Stephen Oliver (Canna Consultants) stated that there was a need for much clearer guidance from the FSA and again raised the question whether applications based on the Epidyolex data could be validated if the gaps in the application that were identified in the FSA feedback of a CBD Novel Food application were now addressed.

FSA response: The answer was non-committal and repeated that Epidyolex data could not be extrapolated to assessing the safety of a food product.

Question 7: Since the CBD Isolate in a Novel Food application is >98% pure which is the same purity as CBD in Epidyolex (ACNFP/143/01), what bridging toxicity studies are necessary and what is the scientific justification for them?

FSA response: FSA conceded that a full justification rather than bridging studies may be acceptable.

Chris Atterwill (DevelRx) again pointed out that in an 'ideal world', additional preclinical toxicology studies on a product would need to be accompanied by human clinical data for the product in terms of toxicokinetics for a meaningful safety comparison to be made.

FSA response: For a Novel Food this was not applicable.

The Canna Consultants have continually challenged the Regulator's stated position, its lack of policy, its failure to address the matters from a scientific perspective and its failure to provide any credible explanation for its failure to apply the tiered approach which is required.

As a result, and in partnership with DevelRx, The Canna Consultants have conducted a through examination of:

- the events leading to the COT's position;
- the COT's consequent advice to the FSA (see Annex A); and,
- the FSA's subsequent implementation of what we believe to be a flawed examination and scientifically unjustifiable requirement for further animal testing.

There are ethical considerations against further duplicate animal testing of a substance as demanded by the FSA when the trend has been recently to modernise testing approaches

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for substances for human consumption and administration, and wherever possible to accommodate the 3R's principle. The FDA Modernisation Bill of 2021 goes somewhere along this line, recommending for example the need to use ' alternative adjunct' testing methods such as human cell technologies to more accurately predict human safety and risk. Many internationally approved bodies have evolved over the past decades to promote this approach, such as the UK NC3R's and ECVAM *(*European Centre for the Validation of Alternative Methods*)*. Furthermore, in the not too distant past, initiatives such as the EU Cosmetics Testing Amendments and REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) for industrial chemical human hazard and risk evaluation have proactively attempted to adhere to the principles of the 3R's in the need for animal testing for substances intended for, or accidently exposed to, humans. In the case of the FSA demanding additional duplicate testing under an OECD-408 study for cannabinoid products in Novel Foods, this is not in the spirit, ethically or scientifically, of the above initiatives.

There are still many Human Healthcare Products on the 'consumer shelves', such as herbal remedies, with little or no regulation at all (except for Product Labelling Requirements), but are still freely available for *ad libitum* consumption. This is entirely at odds with the FSA and COT approaches to the licensing of CBD in novel foods. A more balanced and better informed approach, in our opinion, is required where the Safety Evaluation parameters and safety margins for an 'equivalent' medical product such as Epidiolex is given preference over an unregulated 'mix' of random literature-based research data as requested of our Novel Food applicants by the FSA.

In summary, it is the firm view of The Canna Consultants that the FSA's slavish mantra to the COT's flawed analysis is morally, ethically and scientifically at odds with the government's policy position and threatens to undermine unrelated essential *in vivo* work which is justified from a safety perspective whether that be in food or medicine.

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References

[1] Committee on Toxicity (COT). CBD Update. TOX/2020/02.
https://cot.food.gov.uk/sites/default/files/tox202002cbd.pdf

[2] European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP). (Access to all EMA reviews of Epidyolex submission dossier).
https://www.ema.europa.eu/en/medicines/human/EPAR/epidyolex

[3] Food and Drug Administration (FDA). Drug Approval Package: Epidiolex (Cannabidiol). (Access to all FDA reviews of Epidiolex submission dossier).
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000TOC.cfm

[4] Guidance on the preparation and presentation of an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283 Revision 1.
https://www.efsa.europa.eu/en/efsajournal/pub/6555

[5] Committee on Toxicity (COT). Scoping paper on the potential adverse effects of CBD products. TOX/2019/32. https://cot.food.gov.uk/sites/default/files/tox2019-32.pdf

[6] Government Chemist CBD Food and Cosmetic Ring Trial Final Report Cannabidiol and controlled cannabinoids. T. Hambidge. 2021.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/995466/Ring_Trial_Final_Report_with_appendix_1_and_2.pdf

[7] World Health Organisation (WHO). Cannabidiol (CBD). Critical Review Report.
https://www.who.int/medicines/access/controlled-substances/CannabidiolCriticalReview.pdf

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