GW PHARMACEUTICALS

RESPONSE TO PROPOSED AMENDMENTS TO THE POISONS STANDARD (MEDICINES/CHEMICALS)

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1 BACKGROUND ON GW PHARMACEUTICALS AND OUR EXPERTISE

About GW

- GW Pharmaceuticals (GW) is a pioneering global biopharmaceutical company that has established a world-leading position in cannabinoid science and medicines. Founded over two decades ago in response to significant unmet patient need, patients remain our key focus and improving their quality of life, our motivation.

- GW's mission is to unlock the potential of the cannabis plant through rigorous scientific investigations, extensive clinical trials and regulatory approvals to transform the lives of seriously ill patients and their families.

- GW complies with the three fundamental pharmaceutical pillars of safety, quality and efficacy which underpin international pharmaceutical regulatory standards. We passionately believe this tried and tested approach to developing licensed medicines is in the best interests of patients and clinicians.

- GW's work has seen nearly 6,000 patients globally being involved in regulated clinical trials, the collection of upwards of 115,000 years of human safety data, 80 peer reviewed publications, and the generation of high-quality evidence, which has appeared in the New England Journal of Medicine, Lancet and The Journal of the American Medical Association (JAMA). *(Devinsky et al, 2017) (Thiele et al, 2018) (Devinsky et al, 2018) (Miller et al, 2020).*

GW's work in Australia

- In 2017 GW entered a partnership with an Australian organisation, Emerge Health, to make SATIVEX® (nabiximols) available to Australian patients with moderate-to-severe spasticity related to Multiple Sclerosis (MS). This medicine is approved in more than 25 countries globally.

- GW is now working with Emerge Health to seek TGA-approval for the U.S Food and Drug Administration (FDA) and European Medicines Agency (EMA)-approved EPIDYOLEX® (cannabidiol) for Dravet Syndrome (DS) and Lennox-Gastaut Syndrome (LGS), two forms of rare, childhood onset, refractory and severe forms of epilepsy. EPIDYOLEX® (cannabidiol) recently received Orphan Designation and Priority Review determination from the TGA.

- GW is committed to conducting high-quality research and clinical trials in Australia. In 2016 GW signed two memoranda of understanding (MOUs) with the Queensland and New South Wales state governments to facilitate research into the clinical use of cannabis-derived medicines and support compassionate use schemes for patients with refractory epilepsy.

- Since this time, GW has conducted several clinical trials in Australia, including for the treatment of Tuberous Sclerosis Complex (TSC) and DS and LGS with EPIDYOLEX® (cannabidiol). This data comprised a key part of the evidence dossier submitted to the EMA and FDA for GW's cannabidiol licensing for DS and LGS, and now EPIDYOLEX® (cannabidiol) is under review with the TGA.

Our expertise and offer to the TGA

- In our journey to creating world-first medicines, we have assembled a large, talented in-house team of world leading professionals with expertise spanning discovery research, botanical growing, pre-clinical and clinical R&D, product development, manufacturing and testing.

- Working in partnership with prominent physicians, scientists and subject matter-experts around the world, our team has created the equipment, methods, scientific platform and standards that ensure we are a world leader in the cannabinoid field. Through this process we have honed our ability to manufacture and supply our medicines to a large number of patients.

- As a world leader, we understand that we have an important role to play in informing and shaping the external environment to realise the full medical potential of the cannabis plant, while ensuring patient safety and the protection of public health

- This includes the provision of accurate, evidence-based information on cannabinoid sciences, medicines and regulation, and support for policy makers and the healthcare community where it will benefit patients and ensure the protection of public health.

- GW welcomes the opportunity to respond to the Proposed Amendments to the Poisons Standard (Medicines/Chemicals) consultation alongside our partner in Australia, Emerge Health. GW is committed to offering scientific expertise and data to support regulators, such as the TGA, to help the next stage of its work on these issues and we hope our response will serve as the basis for ongoing dialogue as the TGA seeks to review and finalise its proposals.

2 GW RESPONSE TO PROPOSAL TO AMEND THE SCHEDULING OF CANNABIDIOL (ITEMS 2.2 & 2.5)

2.1 Executive Summary

GW are advocates for the tried and tested pharmaceutical prescription medicines approach for CBD and cannabis; however, we recognise the rise in patient demand for CBD-based products and the need to for the TGA to act. We are therefore supportive of the TGA's broad direction of travel – we agree that there must be a safety-first approach taken to this issue. As we set out in our response below, the finer details of the TGA's proposal, such as daily dosing and safety assessments, need to be reviewed based on all the available evidence and GW is happy to support this through sharing our pre-clinical and clinical data.

2.2 GW believes passionately in cannabis and its potential medical benefits

GW believes passionately in the potential therapeutic benefits of the cannabis plant and we are united in our belief that cannabis-based medicines have incredible potential to transform the lives of patients and families. Over the past two decades we have established deep experience in researching, developing and delivering novel, breakthrough medicines, undertaking pioneering work to unlock the medical benefit of cannabis through rigorous scientific investigation and extensive clinical trials.

2.3 GW believes the tried and tested pharmaceutical medicines system is the best way to deliver safe and effective treatments for healthcare professionals and their patients

We firmly believe that patients deserve access to medicines of the highest quality – tested for both safety and efficacy in placebo-controlled, randomised clinical trials, and approved by medicines regulators, and manufactured in accordance with current Good Manufacturing Practices (GMP) for pharmaceutical medicines.

GW pursues regulatory approval for its medicines because there is no higher standard. It ensures our medicines are backed by science, proven by data and consistently manufactured. We believe patients and their clinicians deserve access to safe, effective and well-evidenced cannabis-based medicines. This can only be achieved if cannabis (for medical use) is subject to rigorous quality and non-clinical testing, high-quality clinical trials, reviewed and approved by medicines regulators, as is the case with all other areas of medicine. Such research allows us to investigate treatments for some of the most vulnerable patients in society and enables us to work closely and collaboratively with the specialist clinicians that care for them.

We welcome others following our lead – the more substantial, high-quality evidence that can be gathered in support of the medical use of cannabis, before subsequent assessment via the existing medicines regulatory route, the better and safer for those patients who could benefit. We believe it is essential that the TGA and the Australian government, alongside other leading regulators and governments around the world, continue to encourage and incentivise companies to pursue this pathway and develop more licensed medicines.

2.4 GW understands there is an increasing interest and demand for cannabidiol (CBD) products and sympathise with patients seeking treatments that could help them

We have seen a rising interest and patient demand for CBD products all over the world with regulators grappling to keep pace with the explosion of products now available. As a world leader in cannabinoid science and medicines, we respect the need for the TGA to act but are concerned about the safety, quality, effectiveness and legality of some of the CBD products being sold to consumers. Independent testing has highlighted ongoing issues with inaccurate labelling, inconsistent CBD content, unfounded and often misleading medical claims that are illegal and potentially harmful levels of THC.

Safety should be paramount in this area and our extensive research has shown, there is no risk-free dose of CBD-containing products. There is still much that we do not know about CBD and its impact on the human body, but what we do know is that it has side effects, including liver toxicity, somnolence and diarrhoea, and the potential to interact negatively with other medications *(Food Standards Agency, Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment – CBD Update)*. Safety margins especially in respect to maximum daily dosage should account for known and unknown human safety findings, vulnerable populations, inter-subject variability, changes in bioavailability and the likelihood of cumulative exposure. We urge caution when trying to weigh up how to meet demand and ensure safety with appropriate medical professional oversight.

2.5 The TGA/Department of Health safety of low dose cannabidiol literature review is an excellent starting point for decision making on the usage of CBD in Australia – GW believes it can help to expand and progress this review leveraging its pre-clinical and clinical data

GW acknowledges the initial step to identify the current clinical literature with respect to investigating if there is a low dose for cannabidiol with potential therapeutic effect and if so, what that low dose would be. Whilst this approach is to be commended and provides a good baseline for further discussion, GW believes it can contribute to progressing the review whilst also adding our comprehensive understanding of cannabis to inform any final proposals.

As the TGA safety review was primarily focussed on safety, GW believes it is important to raise and discuss two resulting key issues and determinations:

- Cannabidiol formulations in which 98% or greater of the cannabinoid content is CBD and where the upper limit to THC content is 0.2% should be rescheduled
- Maximum recommended total daily dose is 60 mg or less of cannabidiol

Any recommendation on rescheduling with respect to cannabidiol formulations in which 98% or greater of the cannabinoid content is CBD and where the upper limit to THC content is 0.2% needs to be questioned against the rationale put forward to support it. The WHO recommendation based on the review and rationale put forward by the Expert Committee on Drug Dependence (ECDD) on the misuse of cannabidiol was problematic. Most notably, because THC content of an EPIDYOLEX® (cannabidiol) bottle is 0.01% w/v, which is 20 times less than the maximum THC level recommended by ECDD to be allowed in CBD preparations. There is therefore no apparent safety data to support this recommendation.

In respect to a maximum recommended total daily dose of 60 mg or less of cannabidiol, data from GW's controlled clinical trials demonstrate that there is no risk-free dose of CBD-containing

products. Significant uncertainty and safety factors need to be considered in respect to daily exposure including drug-drug interactions, other central nervous system and gastrointestinal side effects, special populations, bioavailability (dependant on food, alcohol, specific formulations, routes of administration). Therefore, it is imperative that stringent limits are placed on daily dose and exposure. Any re-consideration of the current regulatory status of CBD, must ensure that a product supplied under lower medical oversight is fully researched and understood to ensure safety with appropriate high-quality data on individual products to confirm decision making around dose in respect to efficacy and safety.

The only available, evidence-based CBD safety profile is that from EPIDYOLEX® (cannabidiol), a formulation of highly purified (>98% w/w), botanically derived CBD which is prescribed under physician guidance. The regulatory approved manufacturing process for GW's medicine is well controlled, consistent and robust. The medicine is released only after rigorous testing according to an approved specification, ensuring product quality, identity, purity, and stability. However, the data for GW's medicine can only confirm the need for rigorous data requirements for each individual CBD containing product before any dosing recommendation is made as the inconsistent composition of non-pharmaceutical CBD products introduces additional risk to the public health.

In an assessment of the safety profile of EPIDYOLEX® (cannabidiol) by GW across dosages lower than those approved for use in patients with LGS or DS, at doses of 5mg/kg/day significant liver findings were seen and from limited data at doses of 1 mg/kg/day and 2.5 mg/kg/day safety risks were also present including adverse reactions. Therefore, key uncertainty factors or safety margins need to be considered when determining daily intake limits for CBD and potential impact upon public health.

2.5 GW is committed to working with regulators, including the TGA, to ensure decisions are taken based on the best available evidence-base

GW has been working actively with regulators around the world to support their work on gathering scientific evidence on the use of CBD and we would like to do the same with the TGA. Doing so will ensure decisions taken on the scheduling and availability of CBD are based on the best available evidence-base. Over the past year we have worked closely with the FDA, the European Union's DG Santé and the UK Food Standards Agency (FSA) to address some of their concerns around the safety and availability of CBD products.

Over the past year, GW has provided support to the FSA's Committee on Toxicity (COT) and Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) on the safety of CBD products in the UK. The FSA's COT initial risk assessment of CBD products was similar to that the TGA's safety review. Subsequently, we provided our publicly available pre-clinical and clinical data on cannabidiol, which the COT leveraged to inform its recently published updated risk assessment on use of CBD in consumer products. During the COT meeting to discuss the updated risk assessment, significant concerns were also raised regarding the safety of CBD products and the lack of available data for products sold over the counter.

The culmination of the FSA's initial work came in February 2020, when the FSA published precautionary CBD consumer advice *(Food Standards Agency, Consumer advice on cannabidiol (CBD) extracts)*, based on the best scientific information available, which advised that those who are pregnant, breastfeeding or taking any medication should not take CBD consumer products. Healthy adults were also advised to think carefully before taking CBD and discuss taking any new CBD-based products with their healthcare professional first. The FSA also took the step to ban any

new CBD products being placed on the market unless they are authorised as 'novel foods' under the European Union regulations, as well as mandating that all CBD products currently on sale submit, and have validated, a novel food application by March 31, 2021 or they will be removed from the shelves.

We believe the FSA COT CBD risk assessment may provide the TGA with further information to inform the criteria for consumers accessing CBD products. Our work with the FSA is ongoing and we are involved in expanding their evidence base further. GW would be happy to work with the TGA on a similar basis and answer any questions they have on the data included in the FSA COT risk assessment.

GW has engaged with the FDA throughout 2019 and continues to support FDA's assessment of appropriate parameters for consumer-market CBD products by making our data and scientific expertise available through submission and ongoing dialogue. GW presented at the FDA public hearing in May 2019 on scientific data and information about cannabis containing or cannabis derived products. Subsequently, GW provided an overview of their available data to assist the FDA in their assessment of CBD safety in the mass market setting and discussions on ways to accelerate more FDA-approved therapies to patients. Additional data in respect to safety was submitted with a few follow up discussions. We continue to have dialogue with FDA as they progress their thinking around consumer-market CBD products; in the meantime, you may wish to consider FDA's latest consumer update report on CBD. *(FDA, What You Need to Know (And What We're Working to Find Out) About Products Containing Cannabis or Cannabis-derived Compounds, Including CBD)*

2.6 The importance of a TGA safety, quality and efficacy assessment

While we can have confidence in the key attributes of a medicine, including its composition, its safety profile and the patients where it could help, equally important is where it could potentially harm. We were therefore pleased to read that a robust assessment of safety, quality and efficacy will be in place for any CBD products wishing to be sold to consumers via a pharmacist only model; however, we would be keen to gain a better understanding of the specific requirements of this assessment before any decision is made.

GW cares deeply about patients and thus adheres with the three fundamental pharmaceutical pillars of safety, quality and efficacy:

- **Safety** entails an extensive pre-clinical study package examining toxicity, drug-drug interactions, pharmacology, dosing and abuse potential; clinical trial data exploring potential harm, side effects and safe dosage; and ongoing, post-approval surveillance and pharmacovigilance.

- **Quality** ensures the medicine is manufactured to in full compliance with current good manufacturing practices for prescription drugs. cGMPs ensure adherence to safe limits on impurities, such as heavy metals and pesticides, batch-to-batch consistency with a stable shelf life, uninterrupted supply to patients, and ongoing oversight by regulators through inspections and affirmative reporting requirements.

- **Efficacy** involves evaluating the effectiveness and dosing of the potential medicine by comparing to a placebo or standard of care in thousands of patients and providing an unbiased assessment of where a medicine may work and may not.

These are the universally accepted safety, quality and efficacy standards for medicines. We welcome further clarity on the proposed safety, quality and efficacy assessment the TGA would undertake. At present, we cannot provide support to the proposal without clarity on how this assessment would compare to the existing TGA system of assessing medicines.

2.7 High standards must be met by individual products – a dedicated assessment for each one sold

Evidence from one medicine, does not mean a particular cannabinoid, or products with a purportedly similar cannabinoid composition from other manufacturers, will have the same safety and efficacy profile. Data, especially safety data, should not be extrapolated from one product to another, primarily because the composition is variable, with variance in the composition of the active components. Even minor differences in composition may lead to very different clinical safety, efficacy and dosing profiles.

For this reason, GW strongly suggests that only data specific to the individual product is considered when the TGA is assessing products to add to Schedule 3.

GW is committed to working alongside the TGA to help the next stage of its work on these issues. We believe safety should be at the forefront of thinking behind the proposed scheduling of cannabidiol and the development of licensed cannabis-based medicines still encouraged to support patients, their families and healthcare professionals.

3 REFERENCES

- Devinsky et al, 2017. Orrin Devinsky, J., Helen Cross, Linda Laux, Eric Marsh, Ian Miller, Rima Nabbout, Ingrid E. Scheffer, Elizabeth A. Thiele, and Stephen Wright. *Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome.* New England Journal of Medicine, 2017; 376:2011-2020DOI: 10.1056/NEJMoa1611618.
- Devinsky et al, 2018.Devinsky, O., Patel, A., Cross, J., Villanueva, V., Wirrell, E., Privitera, M., Greenwood, S., Roberts, C., Checketts, D., VanLandingham, K. and Zuberi, S. (2018). *Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome.* New England Journal of Medicine, 378(20), pp.1888-1897.
- Food and Drug Administration, 2020. *What You Need to Know (And What We're Working to Find Out) About Products Containing Cannabis or Cannabis-derived Compounds, Including CBD*
- Food Standards Agency, February 2020. *Cannabidiol (CBD) - Consumer advice on cannabidiol (CBD) extracts.*
- Food Standards Agency, February 2020. *Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment – CBD Update.*
- Miller et al, 2020. Ian Miller, Ingrid E. Scheffer, Boudewijn Gunning, et al. *Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome.* The Journal of the American Medical Association (JAMA), 2020;77(5):613-621. doi:10.1001/jamaneurol.2020.0073.
- Thiele et al, 2018 Thiele, E., Marsh, E., French, J., Mazurkiewicz-Beldzinska, M., Benbadis, S., Joshi, C., Lyons, P., Taylor, A., Roberts, C., Sommerville, K., Gunning, B., Gawlowicz, J., Lisewski, P., Mazurkiewicz Beldzinska, M., Mitosek Szewczyk, K., Steinborn, B., Zolnowska, M., Hughes, E., McLellan, A., Benbadis, S., Ciliberto, M., Clark, G., Dlugos, D., Filloux, F., Flamini, R., French, J., Frost, M., Haut, S., Joshi, C., Kapoor, S., Kessler, S., Laux, L., Lyons, P., Marsh, E., Moore, D., Morse, R., Nagaraddi, V., Rosenfeld, W., Seltzer, L., Shellhaas, R., Sullivan, J., Thiele, E., Thio, L., Wang, D. and Wilfong, A. (2018). *Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, doubleblind, placebo-controlled phase 3 trial.* The Lancet, 391(10125), pp.1085-1096.