PharmaDrug Advances DMT-Analogue Program for Glaucoma with Production of Medical Device Designed to Provide Sustained Control of Elevated Intraocular Pressure

- *Prototype medical device engineered to deliver sustained, sub-psychedelic quantities of candidate DMT-analogues*
- *In vitro, time dependent drug elution profile evaluated for three candidate molecules*
- *Biocompatibility of drug-loaded medical device demonstrates cell-based safety at doses anticipated to be within therapeutic range*
- *Current results provide Company with refined focus for two candidate molecules*

Toronto, Ontario--(Newsfile Corp. - April 7, 2022) - PharmaDrug Inc. (CSE: PHRX) (OTCQB: LMLLF) ("**PharmaDrug**" or the "**Company**"), a specialty pharmaceutical company focused on the research, development and commercialization of controlled-substances and natural medicines such as psychedelics, cannabis and naturally-derived approved drugs, is pleased to announce that in collaboration with the Terasaki Institute for Biomedical Innovation (TIBI), it has successfully completed fabrication of a novel medical device capable of delivering sustained, low (sub-psychedelic) quantities of their undisclosed tryptamine-based pharmaceutical to the front of the eye; the intended purpose of which is to potentially lower intraocular pressure (IOP) in patients suffering from glaucoma. Additionally, a head-to-head drug elution study of the Company's three undisclosed DMT-analogue candidates has now been completed and supportive cell-based biocompatibility has been examined for all three candidate molecules. Future *in vivo* efficacy testing in an accepted model of primary open angle glaucoma (POAG) is currently being planned with the goal of providing all necessary support to file an investigative new drug (IND) application with the United States Food and Drug Administration (the "**FDA**") to conduct clinical studies.

Paul Van Slyke, CSO of PharmaDrug commented, "We are excited to announce that our recently fabricated proprietary medical device, designed to deliver controlled release of tryptamine-based pharmaceutical agents, has now progressed from the concept stage into a functioning prototype. Drug release rates were successfully characterized for each of the candidates under evaluation and as such, the current studies provide the Company with the critical data necessary to fine-tune fabrication efforts while also facilitating informed design for its future IND-enabling efficacy studies which will use a well accepted animal model of glaucoma".

The aim of PharmaDrug's DMT-analogue research program in ocular health is to develop suitable prototype medical devices capable of sustained ocular drug-delivery while also confirming efficacy, biocompatibility and stability of its candidate molecules in models of elevated IOP. Previous press releases (Feb 23, 2022, and Dec 13, Nov 5, Aug 5, 2021) have provided updates on *in vitro* potency, surrogate markers of efficacy and safety/toxicity. With today's announcement the Company is pleased to deliver on several additional key objectives-namely, fabrication of its drug eluting medical device and *in vitro* biocompatibility test results. The research program scope currently underway includes full establishment and demonstration of candidate molecule loading capacity, release rate evaluations for conjugated materials as well as model organism testing to support an IND application with the FDA in the future.

The Company has now completed fabrication and initial testing of its novel medical device designed to deliver therapeutic quantities of its DMT-analogues to the front of the eye. Specifically, drug-loaded medical device prototypes were suspended in a biological solution meant to mimic the somewhat harsh environment of the eye. Samples, maintained at body temperature were removed at defined periods of time over sixteen days and were quantified to determine concentration and rate of drug elution for each

of the Company's three candidate molecules. The stability of one of the candidate molecules did not meet minimal necessary criteria and has now been eliminated from further consideration. The remaining two DMT-analogues displayed suitable 2-week provisional stability and elution characteristics that support further evaluation and optimization. One candidate molecule/medical device in particular, displayed a consistent drug elution profile from days 2-16 (end of study) suggesting that drug delivery of greater than two weeks may be possible. The biocompatibility of drug-loaded medical devices was examined by way of monitoring cell proliferation and live/dead staining on human ciliary muscle cells over time. Concentrations expected to be within the therapeutic range were found to not statistically impact cell viability for any of the drug-loaded medical devices.

Test article potency was previously evaluated using an *in vitro* calcium mobilization assay on trabecular meshwork cells; a cell type known to be critically important in the maintenance of healthy IOP. Calcium mobilization is understood to provoke cellular contraction, and specifically in the case of trabecular meshwork cells, is thought to contribute to the maintenance of healthy IOP by channeling aqueous humor away from the front of the eye. Test articles were found to activate calcium mobilization, to levels that were comparable or greater than the experimental positive control, ionomycin. The Company's test articles were also examined for *in vitro* toxicity and were found to be non-toxic to trabecular meshwork cells at concentrations expected to be used in treatment for various eye diseases. Collectively the results of the above studies will be used to select a lead development candidate that will be taken forward into *in vivo* efficacy models for eye diseases, including glaucoma.

The Need for Improved Medications to Treat Primary Open Angle Glaucoma

Glaucoma is a disorder of the optic nerve that results in irreversible vision loss and is the second leading cause of blindness in the world, according to the World Health Organization. Glaucoma impacts more than 2.7 million people aged 40 or older in the United States and current treatments are known to have poor rates of compliance of up to 80% of patients. The global market for glaucoma was estimated by Market Scope at $4.8 billion in 2019 with the U.S. market representing $1.9 billion. Although the exact etiology of primary open angle glaucoma remains poorly understood, and may be variable across patient subsets, it is generally accepted that the observed increase in IOP correlates with progressive vision loss[1]. Current treatments for POAG primarily consist of eye drops that can be grouped into three main categories: prostaglandin analogues, carbonic anhydrous inhibitors, and alpha-2 agonists. While these approaches usually provide partial improvement, they often result in side effects such as redness and stinging and require multiple daily applications; all of which diminish patient compliance. Tryptamines, including DMT-analogues are thought to work in a completely distinct way to lower IOP and as such potentially embody a new class of glaucoma medications that may be used alone, or in combination with already approved medications. The Company's streamlined focus on two highly promising, undisclosed tryptamines as a potential therapeutic solution in treating glaucoma represents a potential paradigm shift.

Modulating the serotonin receptor pathway to improve glaucoma outcomes

Key regions of the eye that regulate fluid dynamics, including maintenance of healthy IOP, are known to be richly decorated with various serotonin receptor family members. Previous research has highlighted the role of serotonin receptor signaling in the regulation of IOP[2-5]. Tryptamines, often hallucinogenic above certain threshold concentrations, constitute a large collection of molecules that selectively act on multiple different serotonin receptors including 5-HT1A and 5-HT2A. Topical application of several different tryptamines have shown early promise in preclinical models of elevated IOP, however formulation, delivery, the potential for undesirable hallucinogenic side effects, and the controlled substances act of 1970 have all contributed to a lack of development of tryptamines to treat this serious threat to vision.

About Terasaki Institute for Biomedical Innovation

The Terasaki Institute for Biomedical Innovation is a biotechnology institute which develops medical

devices and cutting-edge protocols for a variety of diagnostic, monitoring and treatment applications. Their research platforms include work in biomaterials, cellular and tissue engineering, wearable biosensors and organs-on-a-chip, with specific expertise in novel polymer development.

About PharmaDrug Inc.

PharmaDrug is a specialty pharmaceutical company focused on the research, development and commercialization of controlled-substances and natural medicines such as psychedelics, cannabis and naturally-derived approved drugs. PharmaDrug owns 100% of Pharmadrug Production GmbH ("Pharmadrug Production"), a German medical cannabis distributor, with a Schedule I European Union narcotics license and German EuGMP certification allowing for the importation and distribution of medical cannabis to pharmacies in Germany and throughout the European Union. PharmaDrug owns 100% Sairiyo Therapeutics ("Sairiyo"), a biotech company that specializes in researching and reformulating established natural medicines with a goal of bringing them through clinical trials and the associated regulatory approval process in the US and Europe. Sairiyo is currently developing its patented reformulation of cepharanthine, a drug that has shown substantial third party validated potential for the treatment of infectious disease and rare cancers. Sairiyo is also conducting R&D in the psychedelics space for the treatment of non-neuropsychiatric conditions. The Company also owns 100% of Super Smart, a company building a vertically integrated retail business with the goal to elevate the use of functional mushrooms, and psilocybin mushrooms where federally legal, as natural based medicines.

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THE CANADIAN SECURITIES EXCHANGE HAS NOT REVIEWED NOR DOES IT ACCEPT RESPONSIBILITY FOR THE ADEQUACY OR ACCURACY OF THIS RELEASE.

This press release contains "forward-looking information" within the meaning of applicable securities legislation. All statements, other than statements of historical fact, included herein are forward-looking information. Generally, forward-looking information may be identified by the use of forward-looking terminology such as "plans", "expects" or "does not expect", "proposed", "is expected", "budgets", "scheduled", "estimates", "forecasts", "intends", "anticipates" or "does not anticipate", or "believes", or variations of such words and phrases, or by the use of words or phrases which state that certain actions, events or results may, could, would, or might occur or be achieved. In particular, this press release contains forward-looking information in relation to: future in vivo efficacy testing in an accepted model of primary open angle glaucoma (POAG), the ability to complete the required studies and obtain regulatory approval, and the impact the Company's potential products will have on treating glaucoma. This forward-looking information reflects the Company's current beliefs and is based on information currently available to the Company and on assumptions the Company believes are reasonable. These assumptions include, but are not limited to the ability of the Company to successfully execute on its plans for the Company and its affiliated entities; the ability to obtain required regulatory approvals and the Company's continued response and ability to navigate the COVID-19 pandemic being consistent with, or better than, its ability and response to date.

Forward-looking information is subject to known and unknown risks, uncertainties and other factors that may cause the actual results, level of activity, performance or achievements of the Company to be materially different from those expressed or implied by such forward-looking information. Such risks and other factors may include, but are not limited to: general business, economic, competitive, political and social uncertainties; general capital market conditions and market prices for securities; the actual results of the Company's future operations; competition; changes in legislation affecting the

Company; the ability to obtain and maintain required permits and approvals, the timing and availability of external financing on acceptable terms; lack of qualified, skilled labour or loss of key individuals; risks related to the COVID-19 pandemic including various recommendations, orders and measures of governmental authorities to try to limit the pandemic, including travel restrictions, border closures, non-essential business closures, service disruptions, quarantines, self-isolations, shelters-in-place and social distancing, disruptions to markets, economic activity, financing, supply chains and sales channels, and a deterioration of general economic conditions; and a deterioration of financial markets that could limit the Company's ability to obtain external financing.

A description of additional risk factors that may cause actual results to differ materially from forward-looking information can be found in the Company's disclosure documents on the SEDAR website at www.sedar.com. Although the Company has attempted to identify important factors that could cause actual results to differ materially from those contained in forward-looking information, there may be other factors that cause results not to be as anticipated, estimated or intended. Accordingly, readers should not place undue reliance on forward-looking information. Readers are cautioned that the foregoing list of factors is not exhaustive. Readers are further cautioned not to place undue reliance on forward-looking information as there can be no assurance that the plans, intentions or expectations upon which they are placed will occur. Such information, although considered reasonable by management at the time of preparation, may prove to be incorrect and actual results may differ materially from those anticipated.

The Company's securities have not been registered under the U.S. Securities Act of 1933, as amended (the "U.S. Securities Act"), or applicable state securities laws, and may not be offered or sold to, or for the account or benefit of, persons in the United States or "U.S. Persons", as such term is defined in Regulations under the U.S. Securities Act, absent registration or an applicable exemption from such registration requirements. This press release shall not constitute an offer to sell or the solicitation of an offer to buy nor shall there be any sale of the securities in the United States or any jurisdiction in which such offer, solicitation or sale would be unlawful.

Forward-looking information contained in this press release is expressly qualified by this cautionary statement. The forward-looking information contained in this press release represents the expectations of the Company as of the date of this press release and, accordingly, are subject to change after such date. However, the Company expressly disclaims any intention or obligation to update or revise any forward-looking information, whether as a result of newinformation, future events or otherwise, except as expressly required by applicable securities law.

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