Pharmadrug Announces Positive Research Results of Cepharanthine to Treat Multiple Cancers

- *Validates Cepharanthine's potential in treating various cancers with unsatisfactory treatment options*
- *Positions Cepharanthine's 'pipeline in a pill' strategy focusing on esophageal, colorectal, liver and skin cancers*
- *Advance to FDA IND-enabling studies to support human clinical studies*

Toronto, Ontario--(Newsfile Corp. - July 28, 2021) - PharmaDrug Inc. (CSE: BUZZ) (OTC Pink: 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 the completion of their preclinical cancer study which evaluated cepharanthine-2HCl, the active pharmaceutical ingredient in PD-001, the Company's patented oral formulation of cepharanthine. The results from the study validate cepharanthine's potential in treating different types of cancer including esophageal, colorectal, liver and skin. The results also provide confidence in the Company's plan to dedicate resources to advance PD-001 through FDA IND-enabling studies to support Phase 1 and 2 clinical studies. The study was conducted by a respected contract research organization with deep expertise in preclinical oncology model development and drug testing and data corresponding to all studied cancer cell lines have now been reported to the Company.

PharmaDrug was pleased to find that twenty of the sixty cancer cells lines screened showed growth inhibition of at least fifty percent when exposed to cepharanthine levels previously determined to be well tolerated in a human clinical population. Additionally, there were several instances in which cepharanthine displayed growth inhibition which was comparable or superior to current gold standard treatments, including colorectal, liver and skin cancers. More notably, results of the current study demonstrated that esophageal cancer was the most highly responsive of all sixty cancers examined; with cepharanthine showing 99.96% growth inhibition at the top concentration tested and displayed approximately 5-times greater potency (at IC50) than cisplatin, a chemotherapy commonly used to treat esophageal cancer despite the fact that development of chemoresistance to this family of agents is common. Previously the Company announced that it had secured FDA Orphan Drug Designation for cepharanthine in the treatment of esophageal cancer. However, prior to committing to a substantial clinical program for that indication, PharmaDrug looked to further expand on the body of existing supportive data for esophageal cancer, while also potentially revealing new, promising cancer indications. Based on these promising findings, PharmaDrug reiterates that it remains committed to the clinical development of PD-001 for the treatment of patients suffering from esophageal cancer.

The Study

The Company's study examined potential anti-cancer properties of cepharanthine (monotherapy) in a panel of sixty solid and liquid cancer cell types and does so by comparing cell growth inhibition following exposure to cepharanthine as well as current standard of care agents. Cepharanthine has been an approved drug in Japan for approximately 70 years. Generic cepharanthine has been safely and effectively delivered to patients via an intravenous route of administration, however oral administration has not received broad adoption owing to its poor bioavailability. Borrowing from what is already known about safe circulating levels in patients for generic cepharanthine, the Company's current 60 cancer screen was designed to investigate the impact of their patented cepharanthine formulation at concentrations that are predicted to be safe to patients[1]. Using these criteria, PharmaDrug was pleased to find that twenty of the sixty cancer cells lines screened showed growth inhibition of at least 50 percent when exposed to cepharanthine levels previously determined to be well tolerated in a human clinical

population. Additionally, there were several instances in which cepharanthine displayed growth inhibition which was comparable or superior to current gold standard treatments examined.

With these highly encouraging results, PharmaDrug is advancing its cancer program with the initiation of IND-enabling studies to support human clinical studies, such as an *in vitro* efficacy study to assess the potential of cepharanthine to provide additive and/or synergistic benefits in combination (combo-therapy) with current standard of care agents and *in vivo* efficacy studies designed to further validate cancer indication selection with a view to de-risking downstream clinical programs. The outcome of these IND-enabling studies is anticipated to strengthen and broaden the foundation of the Company's intellectual property portfolio, as well as validate the proposed clinical development plans to be put forward to the FDA in future IND applications to conduct both Phase 1 and 2 clinical studies. These efforts will provide PharmaDrug with additional intellectual property, downstream licensing opportunities in the oncology space, but most importantly, a clear path for electing a lead cancer indication for their internal development program.

Daniel Cohen, CEO of PharmaDrug commented: "We are extremely excited with the results of this study demonstrating the potential of cepharanthine in treating multiple forms of cancer known to commonly escape response through the development of chemoresistance. Although cepharanthine is described in scientific literature as a potential cancer therapeutic, we did not expect to see the noted significant growth inhibition in difficult to treat cancers. Cepharanthine is on its way to establishing itself as a once per day, oral anti-cancer therapeutic with a well-established safety profile which will pave the way for an expedited clinical development pathway and future partnering opportunities with pharmaceutical companies. We look forward to providing continued updates on our intellectual property, research, clinical, regulatory and manufacturing activities for PD-001; our novel oral formulation of cepharanthine, with the aim of working towards a first-in-human, proof-of-concept clinical trial under an FDA IND approval."

Next Steps

Based on the de-risked and positive results from the study, the Company has initiated the following activities:

- Broadening intellectual property strategy with planned filing of provisional patents on cepharanthine for specific cancers. These findings will be made public after being filed with the patent office;
- Expanding orphan drug designations in the U.S. and Europe for certain cancers based on the Company's proprietary results;
- Completing a second, drug combination preclinical study in September which may generate additional discoveries and facilitation a broadening of the Company's intellectual property portfolio;
- Pursuing FDA IND-enabling animal studies in the fall to evaluate the benefit of cepharanthine alone (monotherapy) or when combined with relevant first and second-line chemotherapy drugs to support future human clinical studies; and
- Initiating the scale-up processes and Good Manufacturing Practice (GMP) production of PD-001 (novel oral formulation of cepharanthine) in preparation for the first-in-human proof-of-concept clinical trial.

Cepharanthine's Rationale in Cancer

PharmaDrug's cancer program is based on cepharanthine's known anti-cancer activities. Cepharanthine has been shown in preclinical efficacy models to restore cancer cell sensitivity to multiple unrelated classes of chemotherapy. Multidrug resistance continues to represent a considerable clinical challenge. As such, preclinical cancer studies aimed at elucidating the mechanisms that underly chemoresistance; including the critical role drug efflux pumps play in this phenomenon by reducing the intracellular concentration of chemotherapeutic drugs, are of particular interest to PharmaDrug. Cepharanthine has been shown in preclinical studies to potently reverse chemoresistance by downregulating expression of ABCB1, the transcript of which codes for multidrug resistance protein 1, (MDR1, aka P- glycoprotein). Importantly, several prior *in vitro* and *in vivo* studies have shown that cepharanthine-mediated reductions

in ABCB1 expression restores cancer cell sensitivity to a range of chemotherapeutics including taxanes, vinca alkaloids and platinum-based drugs[2-5]. Collectively the studies currently being undertaken by the Company aim to identify and provide focus to novel opportunities in oncology by revealing optimal drug combinations and situations where PD-001 can prevent, lessen, or reverse chemoresistance, and/or provide additive/synergistic benefit to existing treatments.

About PD-001 (Enteric-Coated Cepharanthine)

Cepharanthine is a natural product and an approved drug used for more than 70 years in Japan to successfully treat a variety of acute and chronic diseases. In clinical research, Cepharanthine has been shown to exhibit multiple pharmacological properties including anti-oxidative, anti-inflammatory, immuno-regulatory, anti-cancer, anti-viral and anti-parasitic properties[5]. However, historically Cepharanthine's low oral bioavailability has represented a major obstacle to realizing its full clinical potential.

The Company is focused on advancing the clinical development of an improved oral formulation of Cepharanthine (PD-001) to treat rare cancers and infectious diseases. Compared to generic Cepharanthine, PD-001 has been shown in rodent and non-rodent models to possess markedly superior bioavailability (more easily absorbed). These findings support the development of an orally administered formulation, and in so doing, removes the undesirable requirement for frequent intravenous dosing.

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. The Company owns 80% of Pharmadrug Production GmbH, 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 EU. The Company also owns 100% of Super Smart, a Dutch company building a modern adult use psychedelic retail business with an elevated and educational focus. PharmaDrug recently acquired Sairiyo Therapeutics, a biotech company that specializes in researching and reformulating established natural medicines with a goal of bringing them through regulatory and research driven clinical trials.

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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: the timing of the proposed non-clinical and clinical manufacturing of Cepharanthine for the Company's rare cancer and infectious diseases programs; the ability to expedite development timelines by leveraging SwRI's existing Cepharanthine preclinical data sets and manufacturing know-how; the ability to advance clinical development of an

improved oral formulation of Cepharanthine to treat rare cancers and infectious diseases; the ability to obtain applicable approval for the use of Cepharanthine to treat esophageal cancer; the timing and potential results of the Company's plan to initiate high throughput studies to screen a large panel of additional cancers; the Company's plans to evaluate the benefit of its novel oral formulation of Cepharanthine in an animal model of SARS-CoV-2 infection and its proposed discussions with regulators regarding same. 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 Sairiyo; the ability to complete the studies referenced herein nd the results thereto; 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.

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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

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