PharmaDrug Announces Positive Research Results for Cepharanthine in the Treatment of Multiple Cancers When Used Alone and in Combination with Chemotherapy

- *Cepharanthine reproducibly demonstrates potential as a monotherapy in treating multiple cancers with unsatisfactory treatment options*
- *Identified 4 cancer types where cepharanthine provides additive or synergistic inhibitory effects when combined with standard of care (SoC) chemotherapy*
- *Continued focus on esophageal cancer as most highly responsive cancer examined*
- *FDA IND-enabling animal efficacy studies planned for Q4, 2021 examining cepharanthine efficacy alone, and in combination with, SoC chemotherapy to support Phase 1 and 2 clinical studies*

Toronto, Ontario--(Newsfile Corp. - October 15, 2021) - PharmaDrug Inc. (CSE: PHRX) (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 interim positive results for their preclinical cancer study which evaluated the effectiveness of cepharanthine-2HCl alone, or when used in combination with standard of care (SoC) chemotherapy.

Based on the results of a large *in vitro* cancer screen, the Company had previously identified a short list of 23 cancers that were highly responsive to cepharanthine-2HCl. PharmaDrug was recently provided results for 17 of the 23 cells lines being evaluated by an independent contract research organization and is pleased to announce that greater than 80% of those short-listed cancers once again displayed sensitivity to cepharanthine-2HCl at, or below levels previously determined to be well tolerated in humans. Thus far, esophageal cancer continues to be the most responsive of all cancers tested; with cepharanthine-2HCl displaying at least 2-times greater potency for esophageal cancer than the next most sensitive cancer type. Novel therapeutics in the oncology space are most often assessed as an 'add-on' to SoC agents during clinical development. As such, the current study was designed to evaluate the potential for cepharanthine-2HCl to provide additive or synergistic benefit in such settings. Of the 17 cancer cell lines tested thus far, four instances of drug synergy (cepharanthine+chemotherapy) were revealed.

Daniel Cohen, CEO of PharmaDrug commented, "We are extremely excited about the research results and the potential of cepharanthine to treat various cancers as it allows us to confidently advance our pipeline-in-a-pill strategy for not only infectious diseases, but now also oncology. The current results reinforce the potential of cepharanthine as a monotherapy and now also potentially as a synergistic agent when combined with SoC for the treatment of cancer. As such, the primary focus in our oncology program will continue to be esophageal cancer, for which we have already received FDA orphan drug designation. Encouraged by these recent findings, IND-enabling animal efficacy studies to support future human clinical studies in oncology will commence in November."

That esophageal cancer was shown to be the most highly responsive cancer examined further validates the Company's motivation to expeditiously advance the clinical development of its patented enteric-coated oral formulation of cepharanthine (PD-001) for esophageal cancer and leverage the benefits of its FDA orphan drug designation granted by the FDA earlier this year. Furthermore, the Company intends to use data from the current study, including identification of synergistic drug combinations (cepharanthine+chemo) to file new intellectual property. In anticipation of the positive research results, the Company has recently manufactured a non-GMP lot of PD-001 for planned animal efficacy studies in oncology and will commence production of a cGMP PD-001 lot to support its upcoming IND-enabling

studies and potential FDA Phase 1 and Phase 2 clinical studies in 2022.

Rational Use of Cepharanthine to Treat Cancer

PharmaDrug's cancer program is based on cepharanthine's known anti-cancer activities. Cepharanthine has been shown in multiple preclinical efficacy models to inhibit cancer cell proliferation, induce cancer cell apoptosis (death) and restore cancer cell sensitivity to multiple unrelated classes of chemotherapy. Multidrug resistance in particular, 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[1-4]. 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 or synergistic benefit to existing treatments. PharmaDrug's planned animal efficacy studies, designed around the outcome of the current *in vitro* study, are most ideally suited to experimentally examine the role of cepharanthine in restoring chemosensitivity.

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 effects[5,6]. 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 Issuer 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 recently acquired 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 3rd party validated potential for the treatment of Covid-19 and rare cancers. Sairiyo is also conducting R&D in the psychedelics space for the treatment of non-neuropsychiatric conditions. The Issuer 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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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 and 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.

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.

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References:

1. Saito T, Hikita M, Kohno K, Tanimura H, Miyahara M, Kobayashi M. Enhanced expression of the multidrug resistance gene in vindesine-resistant human esophageal cancer cells. Oncology. 1994 Sep-Oct;51(5):440-5. doi: 10.1159/000227380. PMID: 8052486.

2. Zhou P, Zhang R, Wang Y, Xu D, Zhang L, Qin J, Su G, Feng Y, Chen H, You S, Rui W, Liu H, Chen S, Chen H, Wang Y. Cepharanthine hydrochloride reverses the mdr1 (P-glycoprotein)-mediated esophageal squamous cell carcinoma cell cisplatin resistance through JNK and p53 signals. Oncotarget. 2017 Nov 27;8(67):111144-111160. doi: 10.18632/oncotarget.22676. Erratum in: Oncotarget. 2021 Jan 05;12(1):61-62. PMID: 29340044; PMCID: PMC5762312.

3. Huang CZ, Wang YF, Zhang Y, Peng YM, Liu YX, Ma F, Jiang JH, Wang QD. Cepharanthine hydrochloride reverses P glycoprotein-mediated multidrug resistance in human ovarian carcinoma A2780/Taxol cells by inhibiting the PI3K/Akt signaling pathway. Oncol Rep. 2017 Oct;38(4):2558-2564. doi: 10.3892/or.2017.5879. Epub 2017 Aug 4. PMID: 28791369.

4. Zahedi P, De Souza R, Huynh L, Piquette-Miller M, Allen C. Combination drug delivery strategy for the treatment of multidrug resistant ovarian cancer. Mol Pharm. 2011 Feb 7;8(1):260-9. doi: 10.1021/mp100323z. Epub 2010 Dec 17. PMID: 21166459.

5. Bailly C. Cepharanthine: An update of its mode of action, pharmacological properties and medical applications. Phytomedicine. 2019 Sep;62:152956. doi: 10.1016/j.phymed.2019.152956. Epub 2019 May 10. PMID: 31132753; PMCID: PMC7126782.

6. Rogosnitzky M, Danks R. Therapeutic potential of the biscoclaurine alkaloid, cepharanthine, for a range of clinical conditions. Pharmacol Rep. 2011;63(2):337-47. doi: 10.1016/s1734-1140(11)70500-x. PMID: 21602589.

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