PharmaDrug Announces Interim Positive Findings for the Combination of Cepharanthine and Frontline Chemotherapy for IND-Enabling Prostate Cancer Study

- *Interim results showthat oral cepharanthine plus cabazitaxel (combination therapy) significantly reduced tumor volume and increased tumor growth inhibition at day 21, the final day of dosing*
- *Dose range findings demonstrate that oral cepharanthine-alone was well tolerated in the current in vivo study*
- *Results for oral cepharanthine plus cabazitaxel will be used to support PharmaDrug's recently submitted provisional patent application which details a novel treatment combination for primary, metastatic and chemotherapy-resistant prostate cancer*

Toronto, Ontario--(Newsfile Corp. - March 9, 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 interim positive findings from its ongoing prostate efficacy study demonstrate that the Company's enteric coated, oral formulation of cepharanthine (PD-001), when combined with cabazitaxel, significantly reduces tumor volume and provides improved prostate cancer tumor growth inhibition when administered with cabazitaxel. These interim results, provided to the Company on the final day of study dosing will be used to strengthen claims in its recently submitted provisional patent application which sets forth claims related to the use of cepharanthine plus cabazitaxel and/or other taxane family members used in combination to treat primary, metastatic and chemotherapy-resistant prostate cancer.

In 2021 the Company initiated a series of cancer screening studies aimed at uncovering therapeutic opportunities for cepharanthine when used alone or in combination with standard of care (SoC) chemotherapy drugs. Results from these *in vitro* studies revealed that the combination of cepharanthine and cabazitaxel, a SoC used for castration-resistant, metastatic prostate cancers, provided unexpectedly synergistic reduction in prostate tumor cell survival. Here the Company is pleased to report that a once-per-day oral regimen of PD-001, in combination with cabazitaxel provided statistically significant benefit at the scheduled end of dosing (day 21) in its ongoing prostate efficacy study. Specifically, PD-001 delivered at doses of 3, 9, or 27 mg/kg/day combined with cabazitaxel (3mg/kg/Q3D) provided up to a 64% tumor growth inhibition compared to 37% noted for treatment with cabazitaxel alone. Based on these results, the addition of PD-001 to the SoC, cabazitaxel was found to improve tumor growth inhibition by 73% compared to cabazitaxel-alone. These interim results were deemed to be highly statistically significant, with a p-value less than 0.001 (day 21). The Company will provide complete details of the study outcome when final results become available.

Daniel Cohen, CEO and Chairman of PharmaDrug commented, "We are extremely excited to continue to broaden the use case for PD-001 as a treatment for prostate cancer. While esophageal cancer continues to be our main focus with a goal to move towards an FDA clinical trial, we believe that cepharanthine will ultimately show a wider potential use in the treatment of cancers, specifically in combination with the current standard of care. We will continue to explore cepharanthine's potential therapeutic relationship with existing standard of care chemotherapies."

About PD-001 (Enteric-Coated Oral 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[1,2]. 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 and patented enteric-coated oral formulation of cepharanthine (PD-001) to treat responsive cancers and COVID-19. Compared to generic cepharanthine, PD-001 has been shown in rodent and non-rodent models to possess markedly improved oral 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 to maintain therapeutic levels of drug in circulation. Despite enormous research efforts, metastatic prostate cancer has a 5-year survival of only 31%[3]. Through subsequent rounds of refinement to optimize PD-001 dose and dose interval, the Company endeavours to develop an efficacious, oral therapeutic add-on option to potentially improve outcomes for prostate cancer patients using SoC treatment.

PD-001 for 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 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[4-7]. Collectively the two in vitro screening studies already completed by the Company and the interim in vivo efficacy results provided here, continue to reinforce the potential therapeutic opportunities in oncology for PD-001 when used in combination to provide additive or synergistic benefit to existing SoC treatments. For reference to previous press releases related to PharmaDrug's ongoing efforts in the oncology space please see previous press releases dated Feb 1, 2022 and Nov 18, Oct 15, July 28, 2021. In addition to its ongoing investigations of PD-001 for prostate cancer, the Company plans to fully leverage the streamlined path to approval which comes by way of a recently granted FDA Orphan Drug Designation PD-001 for the treatment of esophageal cancer.

Potential of PD-001 to Treat Prostate Cancer

According to the American Cancer Society, in 2021 there were approximately 248,530 new cases of prostate cancer and about 34,130 deaths from prostate cancer in the United States, and it is the second leading cause of cancer death in American men. Metastatic prostate cancer is commonly treated using androgen deprivation therapy (ADT), including surgical or medical castration, but metastatic castration-resistant prostate cancer (mCRPC) commonly emerges[8]. The taxanes docetaxel and cabazitaxel are approved for the treatment of mCRPC, however resistance to taxanes is known to develop over time. Agents such as PD-001 which show synergistic benefit when combined with taxanes for the treatment of prostate cancer are sorely needed. The Company's forthcoming in vivo studies are specifically designed to address the potential of PD-001 to overcome taxane-based chemoresistance in vivo.

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 Covid-19 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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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 development and commercialization of cepharanthine, the use of study results to strengthen claims the Company's provisional patent application and moving towards an FDA clinical trial relating to treatment of esophageal cancer . 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 to successfully prosecute the above referenced provisional patent application, the ability to complete the steps necessary to proceed with the above referenced FDA clinical trial, 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.

References:

1. *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.*
2. *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.*
3. *https://www.cancer.org/cancer/prostate-cancer/detection-diagnosis-staging/survival-rates.html*
4. *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.*
5. *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.*
6. *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.*
7. *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.*
8. *Komura K, Sweeney CJ, Inamoto T, Ibuki N, Azuma H, Kantoff PW. Current treatment strategies for advanced prostate cancer. Int J Urol. 2018;25(3):220-231. doi:10.1111/iju.13512*

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