Pharmadrug Advances PD-001, Its Patented, Improved Version of Cepharanthine for Oncology and Infectious Disease

- *Committed to the 'pipeline-in-a-pill' approach with PD-001 for certain cancers and COVID-19*
- *Advances cGMP manufacturing of clinical drug supply with Southwest Research Institute*
- *Receives final positive data for recently conducted prostate cancer model and evaluates opportunities to broaden claim set for PD-001 in the treatment of cancer*
- *Initiates IND-enabling efficacy study of PD-001 to treat esophageal cancer*
- *Evaluates opportunities to deepen and broaden testing of PD-001 as a broad-spectrum oral antiviral*

Toronto, Ontario--(Newsfile Corp. - April 1, 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 provide an update on multiple activities currently underway which support the Company's 'pipeline-in-a-pill' approach in the development of PD-001, its patented, orally bioavailable version of cepharanthine for the treatment of cancer and infectious disease.

Following submission of its Type B pre-IND meeting request and briefing package to the U.S. Food and Drug Administration (FDA), the Company received a written response regarding its clinical development plan for PD-001, as a potential oral antiviral pill for COVID-19 and variants of concern. PharmaDrug believes the feedback provides a path to agreements on IND-enabling studies, the design of a Phase 1/2 clinical study, and the overall clinical development plan to move PD-001 forward as an oral treatment for COVID-19. By extension, the FDA guidance also provided important insights on advancing PD-001 as a potential treatment for oncology indications as part of the Company's ongoing strategy of targeting prostate and esophageal cancers. The Company remains focused on completing the remaining IND-enabling studies to support its planned clinical studies.

Based on positive feedback from the FDA on the Company's proposed Chemistry and Manufacturing Control (CMC) program, PharmaDrug has initiated cGMP production at Southwest Research Institute (SwRI) of a quantity of PD-001 that is expected to be sufficient to support development activities through to the end of phase II assessment. Since the Company's press release on January 26th, 2022, bulk active pharmaceutical ingredient (API) has been received by SwRI and the drug substance, cepharanthine-2HCL, is being manufactured. Completion date is expected to be Q2, 2022. Following full characterization of the drug substance for critical quality attributes the drug product manufacturing (enteric coating of the drug substance) will commence. The material produced under these tasks will support IND-enabling activities, such as stability, safety, toxicology, pharmacokinetic and non-clinical efficacy studies, required by the FDA prior to proceeding to human clinical studies. Work completed thus far on the parent molecule, cepharanthine by PharmaDrug and others, potentially de-risks and expedites several aspects of these studies.

Daniel Cohen, CEO and Chairman of PharmaDrug commented, "We are excited to be efficiently moving our PD-001 program towards a clinical trial. The critical path from a timeline perspective is driven by the GMP production of our drug product and the associated non-clinical testing that will be performed on the product. In the meantime, we have identified 3 distinct indications that we believe are of merit for a cepharanthine clinical trial; esophageal cancer, prostate cancer and Covid. Our current lead indication continues to be esophageal cancer, based on the ODD status we received from the FDA, the efficacy data and the current unmet need in esophageal cancer. We plan to continue to add to the breadth of all 3 programs as we execute the activities necessary to bring PD-001 to the clinic."

PD-001 For Prostate Cancer

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.

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. The Company previously reported 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 recently completed 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.

Since releasing interim results from this study (March 9th, 2022), the Company has been provided a final study report. Currently, the Company's intellectual property counsel is working on a provisional patent submission that aims to provide new evidence to support and potentially expand its claim set around the use of PD-001 and cabazitaxel to treat prostate cancer. Agents such as PD-001 which show synergistic benefit when combined with taxanes for the treatment of prostate cancer are sorely needed. The Company plans to provide an update on the final in vivo study outcome soon.

PD-001 For Esophageal Cancer

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 for PD-001 for the treatment of esophageal cancer. To that end, PharmaDrug has now initiated an IND-enabling study to evaluate efficacy and tolerability of orally administered PD-001 in an esophageal cancer model. For this study, PD-001 will be administered alone and in combination with a SoC chemotherapy drug and tumor growth will be monitored. Results of this study are expected in Q2, 2022.

Collectively the Company's panning approach of going from very broad to very specific cancer types which are highly responsive to PD-001 has yielded two high impact hits and has laid a strong foundation for continued development in the oncology space. For reference to previous press releases which detail PharmaDrug's ongoing efforts in oncology please see the Company's press releases dated March 9, Feb 1, 2022 and Nov 18, Oct 15, July 28, 2021.

Cepharanthine for Cancer: Mechanism of Action

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[1-4].

PD-001 For Infectious Disease, Including COVID-19

To date, several third party validated library screens of approved and investigational drugs have identified cepharanthine as a forerunner candidate molecule in the treatment SARS-CoV-2, the virus that causes COVID-19[5-7]. In fact, cepharanthine has now been shown to be highly effective at blocking cell death following exposure to multiple different coronaviruses, including COVID-19, lab-attenuated SARS-CoV (original SARS) and the virus that causes Middle East respiratory syndrome (MERS)[5-7].

In November 2021 an independent research group examined the potential of cepharanthine to limit the cytopathic effects of the South African COVID-19 variant, B.1.3514. It was found that cepharanthine was at least 6-times more active against the South African variant strain than original SARS-CoV-2, and that cepharanthine was the most effective of all the drugs used in the in vitro screen that was perfomed[8]. Although the Omicron variant shares several features in common with the previous South African variant, B.1.351, it remains to be determined how well cepharanthine will perform at treating this emerging threat. Intriguingly, the same authors noted that cepharanthine also displayed significant potency with favorable selectivity index for other RNA viruses including Zika and Ebola[8]. Despite the promising findings for cepharanthine noted above, translation into clinical application has thus far been hampered by the need for the generic formulation of the drug to be delivered by intravenous due to its intrinsically poor oral bioavailability.

As such, it is believed that the Company's novel oral formulation of cepharanthine, PD-001 would be an ideal candidate to evaluate as a potential treatment for mild to moderate COVID-19. By leveraging its exclusive rights to U.S. Patent: 10,576,077, titled "Pharmaceutical Salt forms of Cepharanthine and Tetrandrine", PharmaDrug intends to develop and commercialize PD-001 as an oral antiviral treatment for patients with mild to moderate SARS-CoV-2 infection.

How Cepharanthine May Work to Block Coronavirus Entry

In a recent peer reviewed manuscript cepharanthine was shown to display greater antiviral potency against SARS-CoV-2 than existing clinical development candidates remdesivir, lopinavir, favipiravir, nelfinavir and chloroquine[5]. Researchers identified a putative binding site on the surface of SARS-CoV-2 spike protein known to facilitate viral docking with the human ACE2 receptor. Consistent with this mechanism of action, application of cepharanthine to cells exposed to SARS-CoV-2 fully blocked viral internalization and subsequent production of viral particles 24 hours post infection.[5]

The Company is not making any express or implied claims that its product has the ability to eliminate, cure or contain the Covid-19 (or SARS-2 Coronavirus) at this time.

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[9,10]. However, historically cepharanthine's low oral bioavailability has represented a major obstacle to realizing its full clinical potential.

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% of 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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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 including regulatory approval thereof and the associated studies; the ability to produce PD-001 in a quantity sufficient to support development activities and the timing thereof. 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.

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