

ACUSPHERE INC. ISSUES LETTER TO SHAREHOLDERS

LEXINGTON, MASS., December 19, 2011 -- Acusphere, Inc. (ACUS.PK) today issued the following letter to shareholders:

Dear Fellow Shareholders:

We have been working diligently to support continued development of our lead product candidate, Imagify™ (Perflubutane Polymer Microspheres) for Injectable Suspension. We have now arrived at an important juncture, and we need your support to help effect a reverse stock split to allow the Company to finance the completion of our strategic direction.

Imagify is under development as a cardiovascular drug intended for the detection of coronary artery disease (CAD), the leading cause of death in the U.S. It remains the leading development candidate for myocardial perfusion assessment with ultrasound. It continues to show promise as a radiation-free test for perfusion assessment offering compelling cost and convenience advantages over the current standard of care, nuclear stress testing. It also provides safety advantages over nuclear stress testing: each episode of nuclear stress testing delivers a radiation dose equivalent to between 140 and 800 chest x-rays depending upon the radiopharmaceutical used, whereas Imagify is radiation-free. There is at least a 3 million procedures /\$600 million addressable market for Imagify in Europe, based upon existing procedures. We believe this market could grow significantly since the European population is similar to the U.S. population and the prevalence of heart disease is similar as well (the U.S. addressable market is approximately 10 million procedures/\$2 billion). We continue to believe strongly in Imagify's potential for the indication proposed, and we remain committed to realizing that opportunity for the benefit of Acusphere and its shareholders.

Our strategic approach to securing regulatory approval of Imagify utilizes a two-track focus:

1. Fulfilling the requirements for filing a Marketing Authorisation Application (MAA) to the European Medicines Agency (EMA) for Imagify in the European Union (EU); and
2. Identifying a development partner who will fund the new Phase 3 trial required for U.S. approval of Imagify by the U.S. Food & Drug Administration (FDA), in exchange for commercialization rights to this product in the EU and/or the U.S.

We are delighted that we successfully reached agreement with the FDA under the Special Protocol Assessment (SPA) process on the Phase 3 study design, as we announced in June 2011. We're grateful for the strong support of excellent advisors and financial partners through Burrill Ventures, which provided us with \$10 million in debt financing.

The European Opportunity

Late in 2010, we completed pre-submission meetings with the European Rapporteurs, who are the regulators who lead the review process of the MAA filing. We secured their perspectives and potential questions or challenges that can be effectively addressed in the MAA filing. From these meetings, we gained confidence that the EU review of Imagify may result in a different outcome than the FDA review of our New Drug Application (NDA).

European regulators handle products like Imagify differently than U.S. regulators, thus, any setbacks experienced in the United States will not affect the prospects of success in Europe. For instance, European regulators have a great concern about radiation safety and EU laws preclude doctors from using radioactive medical procedures when non-radioactive alternatives exist. Concern about radiation safety is supported by continuing evidence in prestigious medical journals around the world. Thus, the radiation safety benefit that Imagify can provide may weigh heavily in our favor in the EU's risk-benefit assessment, which is an important part of the final approval decision.

Secondly, European guidelines discourage placebo trials, such as the one that the FDA is now requiring, and encourage instead comparator trials, which was the design we employed in our original clinical trials to support our NDA filing. Since the EMA Rapporteurs indicated that they would ascribe little value to a placebo trial, there is no point in delaying the MAA submission while we await results from a new U.S. Phase 3 placebo-controlled trial. For that reason, we are pushing forward and intend to start the MAA submission, assuming completion of a financing, in the first half of 2012.

To date, we have completed several important requirements for the MAA submission:

- **Clinical efficacy and safety data.** The original Imagify Phase 3 clinical data for the NDA submission has been converted to a format appropriate for the MAA submission. We believe our original Imagify Phase 3 clinical program demonstrates that the efficacy of Imagify with ultrasound is non-inferior, or equivalent, to nuclear stress. Imagify was evaluated in more than 1,000 patients and we believe that it is well tolerated, with a safety profile similar to other drugs used in this patient population.
- **Paediatric Investigational Plan (PIP).** MAA submissions require a PIP agreed to by the EMA's Paediatric Development Committee (PDCO). Earlier this year we reached agreement with the PDCO on a PIP that involves a small clinical trial in 66 children with cardiac disorders that cause myocardial perfusion defects, to be completed by 2017. We plan to commence this small trial after European approval.

We are now focused on accomplishing the next steps involved in readying the MAA filing:

- **Manufacturing data.** Unlike in the U.S., process validation data is required for EU approval. We are working with a contract manufacturing organization (CMO) and are transferring proprietary process equipment to the facility to begin test batches. Upon successful completion of initial test batches, we will be confident that the process validation data will be ready when needed for EMA review. The process validation batches will also supply the clinical trial material required for the U.S. clinical trial.

- **Funding through approval.** Regulatory review of the MAA typically takes 13-16 months from submission. We believe that it is important to begin the MAA review process with adequate financial resources to last through approval. By financing the company properly, we can address questions and concerns raised by the EMA during the review expeditiously, without distraction. We are now seeking additional capital to support the Company's strategic goals and finance our operations through at least the first half of 2012.

U.S. Plans

The successful completion of discussions with the FDA under an SPA covers the design of a placebo-controlled Phase 3 trial for Imagify demonstrating that ultrasound with Imagify is more beneficial than ultrasound without Imagify. This SPA trial will supplement the Phase 3 comparator trials already completed, where we compared Imagify's efficacy against the 'standard of care,' nuclear stress testing. The SPA process creates a written agreement between the FDA and a sponsor on the clinical trial design, including clinical endpoints and size of clinical trial. The process is intended to provide more assurance that if the agreed-upon clinical trial protocol is followed, the clinical trial endpoints are achieved and there is a favorable risk benefit profile, the data should then likely support approval of a NDA. Agreement on a trial design under an SPA is a strategy for minimizing regulatory uncertainty and therefore makes Imagify more attractive to potential development and commercialization partners.

Achieving agreement with the FDA under an SPA process enabled us to broaden our partnering discussions from purely European-focused companies to global companies and those with a U.S. focus. Our partnering discussions are proceeding well, with strong interest and significant due diligence underway by a number of potential partners, including global pharmaceutical companies, European-focused companies with expertise in cardiology, leading imaging companies, and smaller, more entrepreneurial specialty pharmaceutical companies. The due diligence process has culminated in expressions of interest from several companies. Raising additional capital now, so that we can negotiate terms of any partnership agreement from a position of strength, is an important objective for the Company.

The \$10 million debt financing from Burrill Ventures, secured in 2010, enabled us to pursue our strategic goals this year. As you'll see in the unaudited financial information contained in the proxy, our forecasted year-end cash balance is inadequate to fund the company through the first half of 2012. We need additional capital now, since some of our costs will increase as we work to complete the MAA submission and approval process, and we need to push forward with the partnering discussions, on the most advantageous terms to the Company and its shareholders. To raise additional capital, we need additional authorized shares to be utilized in any financial transaction. Therefore our Board of Directors has unanimously recommended that you vote for the reverse stock split, which will make additional shares available for capital financing purposes.

Before I close, I want to express my deep appreciation to Martyn Greenacre, who was elected Chairman of the Board this year. Martyn formerly served as Chairman, Europe, of SmithKlineBeecham Pharmaceutical Company, and since then, has served on boards or management teams of several specialty pharmaceutical and biotechnology companies, including Cephalon, Curis, Neostem, Delsys and Zynaxis. He was chairman of BMP Sunstone, which was bought by Sanofi-Aventis for \$521 million last year. He has served as an independent director of Acusphere since 2001, and we greatly value his insights and perspectives.

In summary, we believe Acusphere is poised for continued success in 2012. We are focusing on the critical steps required for the long-term success of our lead product candidate, Imagify. These include:

- 1) Successfully executing a reverse stock split with the approval of our shareholders.
- 2) Raising adequate capital to fund European regulatory process
- 3) Submitting the MAA in Europe,
- 4) Completing the process validation batches which will provide required data in support of MAA approval as well as the clinical trial material for the U.S. trial and
- 5) Closing potential partnerships in Europe and the U.S.

We appreciate your continued support as we strive to move Imagify forward, and help position it and Acusphere to achieve their potential.

Sincerely,
Sherri C. Oberg
President and CEO

About Acusphere, Inc.

Acusphere (ACUS.PK) is a specialty pharmaceutical company focused on the development and regulatory review for approval of our lead product candidate, Imagify™ (Perflubutane Polymer Microspheres) for Injectable Suspension. Imagify is a cardiovascular drug for the detection of coronary artery disease, the leading cause of death in the United States. Imagify and the Company's other product candidates were created using proprietary technology that enables Acusphere to control the porosity and size of nanoparticles and microspheres in a versatile manner that allows them to be customized to address the delivery needs of a variety of drugs. For more information about Acusphere visit the Company's web site (www.acusphere.com).

Forward-looking Statements

The above press release contains forward-looking statements, including statements regarding the MAA submission for Imagify and likelihood of regulatory approval and the commercial opportunity for Imagify. There can be no assurance that Imagify will be approved for the indication the Company is seeking, or at all. The Company's actual results may differ materially from those anticipated in these forward-looking statements based upon a number of factors, including uncertainties associated with research, development, testing and related regulatory approvals, including uncertainties regarding results of the trial agreed to under the Company's proposed Special Protocol Assessment with FDA and proposed Paediatric Investigational Plan with EMA, and uncertainties regarding the potential effects of not achieving clinical endpoints, capital needs and uncertainty of additional financing, uncertainties regarding the cost, timing and ultimate success of the qualification of the Company's commercial manufacturing facility in accordance with applicable regulatory requirements, complex manufacturing, high quality requirements, lack of commercial manufacturing experience, dependence on third-party manufacturers, suppliers and collaborators, uncertainties associated with intellectual property, competition, loss of key personnel, uncertainties associated with market acceptance and adequacy of reimbursement, technological change and government regulation. The Company notes that effective as of March 3, 2009, pursuant to a Form 15 filing made with the SEC, it is not currently required to file periodic reports with the SEC, including annual reports on Form 10-K, quarterly reports on Form 10-Q and current reports on Form 8-K. Readers are cautioned not to place undue reliance on any forward-looking statements, which speak only as of the date of this press release. The Company undertakes no obligation to publicly release the results of any revisions to these forward-looking statements that may be made to reflect events or circumstances that occur after the date of this press release or to reflect the occurrence of unanticipated events.

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