Pigs are often used as predictive models of nanomedicine-mediated cardiopulmonary distress reactions in humans. Unlike humans, pulmonary intravascular macrophages (PIM) are abundant in pig lungs. Robust phagocytosis of particles by PIM results in immediate release of large quantities of mediators that correlate with periods of peak cardiopulmonary disturbances. This raises questions on relevance of the pig model to human cases. However, there are suggestions of induction of pulmonary macrophages in certain human diseases (e.g., liver and inflammatory lung diseases). It is conceivable that highly responsive patients may have induced PIM, which could increase sensitivity to blood-borne particles, and the potential risk of pulmonary hemodynamic side effects. Accordingly, it would be necessary to search for constitutive or induced PIM in biopsied or autopsied human lungs, map their phenotype in liver and inflammatory lung diseases, and understand the pathologic implication of phagocyte residency in pulmonary capillaries. In this presentation, I will discuss the roles of PIM and the complement system activation on initiation of adverse cardiopulmonary distress on nanomedicine administration as well as simple strategies that could overcome these problems even in the pig model. Alternative animal models will be suggested for investigating the interplay between induced PIM and the complement system that could closely resemble the human cases and applicable for cardiopulmonary risk assessment in relation to biopharmaceuticals/nanomedicine administration.