

Urgent Appeal from International Society for Aerosols in Medicine (ISAM) During COVID-19: Clinical Decision Makers and Governmental Agencies Should Consider the Inhaled Route of Administration: A Statement from the ISAM Regulatory and Standardization Issues Networking Group

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THE PRESENT COVID-19 PANDEMIC caused by the SARS-CoV-2 has resulted in massive disruption to the normal operation of societies worldwide. There is currently the prospect of a lengthy period of continued disease outbreak, associated with both serious morbidity and mortality, as well as the significant potential for further waves of infection as regulations regarding population mobility are relaxed. So far, the emphasis for pharmacological/biological agent-based therapies has been focused on agents that are administered by traditional routes, in particular injection. Yet, the location of initial infection (i.e., upper respiratory tract and central airways through direct surface contact or deposition of inhaled droplets) and the route of disease progression after initial infection are primarily through the respiratory system. Furthermore, the morbidity and mortality outcomes are manifested primarily in the respiratory tract, unless and until multiple organ failure occurs.

Members of International Society for Aerosols in Medicine (ISAM), therefore, believe that there is an urgent need to accelerate the development of inhaled therapies for COVID-19.

There are many examples of approved inhaled therapies for respiratory diseases, including for both viral and bacterial infections, for example, the use of inhaled ribavirin for respiratory syncytial virus infection^(1,2) and inhaled zanamivir for influenza infection,⁽³⁾ as well as the treatment of chronic conditions, such as asthma, chronic obstructive pulmonary diseases, pulmonary arterial hypertension, and cystic fibrosis.^(4,5) Furthermore, the use of inhaled measles vaccine in Mexico is an example of a preventative non-injectable strategy that is safe and efficacious.⁽⁶⁾ These inhaled therapies have proven to be both efficacious and safe by achieving high local concentrations at the sites of action in the lungs, while minimizing systemic exposure. Thus, the

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severity and frequency of adverse side effects associated with systemic exposure have been minimized. It has been proposed that inhaled remdesivir should be combined with the current IV treatment paradigm to realize greater potential antiviral activity against COVID-19.⁽⁷⁾

Inhaled therapies can be administered by a wide range of well-established devices, including pressurized metered-dose inhalers, soft mist inhalers, dry powder inhalers, and nebulizers.⁽⁴⁾ These devices are easy to use and are well tolerated by patients/caregivers after appropriate instruction for self administration or caregiver administration. Moreover, adaptations of some of these devices have been developed and approved for use in the hospital intensive care environment, where the patient may be receiving either noninvasive oxygen support or invasive mechanical ventilation for the severest disease symptom management.⁽⁸⁾ The risk from infection due to administration of aerosols can be mitigated, and is lower than the infections due to asymptomatic virus-carrying people entering the hospital and breathing, talking, *etc.* without facemasks.⁽⁹⁾ It follows that inhaled medication has the potential to be administered at all stages of an infection by a respiratory pathogen such as SARS-CoV-2, including pre- and postexposure prophylaxis, mild-to-moderate symptom presentation, and in severe disease. It is understood that appropriate personal protective equipment would be worn during inhaled aerosol administration to mitigate the risk of health care givers becoming infected during patient procedures by contact with exhaled virus particles.^(10,11)

In general, the current regulations in jurisdictions in which medicines are developed frequently take the approach of “one-size-fits-all.” However, the goal of new therapies targeted at the SARS-CoV-2 should be to provide each individual patient with a safe and efficacious treatment tailored to their specific needs. This strategy will likely require different categories of approval pathways based on differing risk/benefit ratios dependent on the disease severity. We assert that the wide variety of currently available devices already approved for inhaled therapy administration offers a large platform for this goal to be met.⁽¹²⁾

The regulatory requirements and decisions should be made weighing carefully the therapeutic risk versus benefit for each type of product and patient population, rather than using the “one size fits all” approach. For example, we suggest the following approaches:

- (1) A last resort drug, for example, indicated for use in association with patients on mechanical ventilation, that is proven to be safe, should have a lower efficacy hurdle to be approved. For example, it is estimated that a treatment that could reduce mortality in severe COVID-19 patients by 20% would require a trial with >5000 subjects to meet the traditional regulatory standards for efficacy.⁽¹³⁾ Clearly, given the impact of the lack of treatments for COVID-19 on the spreading of the infections and economic consequences of the lockdowns with all of the accompanying indirect health consequences, we need to explore urgently expedited development and approval paths (e.g., refs.^(14–16)) rather than rely on the existing framework of pharmaceutical product development that would demand a trial size with very

little prospect of rapid implementation, especially with many competing programs.

- (2) A therapy wherein the intended dose has been shown to operate at the plateau of the dose–response curve with good safety can accommodate wider quality control margins than those applied to inhaled products with a narrow therapeutic index. This consideration is important because the development of technologies that satisfy the existing very stringent quality control criteria for inhalation products according to the current regulations greatly increases the development time. Furthermore, the need is too urgent for such delays, in connection with treatment of COVID-19 patients.
- (3) Several of the inhaled therapy candidates in development are with new chemical entities and/or “re-purposed” out-of-patent drugs that will be or have already been approved for other indications and administered by other routes of administration.⁽⁵⁾ The systemic safety of such drugs is often already well documented, and the inhaled doses of these drugs required to achieve high lung concentrations are typically much lower than their daily doses by other routes. Nonetheless, the precise dosing strategy will depend on the pulmonary pharmacokinetics. As detailed in the new U.S. Food and Drug Administration guidance,⁽¹⁷⁾ Phase 1a clinical studies will still be required to establish pulmonary safety before evaluation of primary efficacy of the inhaled therapy. However, to shorten the extent and duration of Phase 1a studies and more rapidly enable dosing in a Phase 1b trial to establish dose and efficacy, existing and/or *in silico* physiologically based pharmacokinetic modeling data could be leveraged to support laboratory and clinical studies.⁽¹⁸⁾ We recommend that the relevant stakeholders should make the full benefit of that information and, in particular, review whether regulatory paths such as 505(b2)⁽¹⁹⁾ can be modified to reflect the urgent need for COVID-19 therapies. This is an example where the prior safety data that the regulatory authorities already have in their possession may be used for the benefit of the society to expedite development.
- (4) In the current pandemic situation, the use of placebo controls should be judiciously reviewed, as this component adds greatly to the cost and duration of trials. One example of a mechanism to minimize the need for the extent of such control groups is to rapidly develop a global anonymized registry of all COVID-19 patients including placebo groups to be able to rapidly analyze the active groups in trials against each other, as well as the active groups against the large placebo groups.
- (5) Case–control studies of large population data bases stratified for all known risk factors would be extremely valuable. Such observational evaluations compare patients who have an outcome of interest (cases) with patients who do not have COVID-19 (controls), and look back retrospectively to compare how frequently the exposure to a risk factor is present in each group to determine the relationship between the risk factor and the disease. For example,

the development and approval of prophylaxes require very large trials to obtain reliable information without access to information from all other such trials, as well as the natural progress of the infection and its COVID-19 manifestations.

We believe that it is important from the outset to take a highly collaborative approach⁽²⁰⁾ between stakeholders (regulators and inhalation drug developers initially, supported by studies at the earliest opportunity involving patients and their caregivers) to share our collective knowledge to deliver therapies that have a high probability of having a favorable benefit/risk ratio in the target population.

In summary, we request that decision makers and policy makers, in particular those involved in public health administration and the regulatory agencies, as well as those providers of funding sources who are considering how to mitigate the COVID-19 pandemic in a timely manner, pay attention and act to access the, as yet, largely untapped potential for inhaled medication delivery to resolve the present urgent need.

Furthermore, we hope that the exploration of the new paths to manage the SARS-CoV-2 health care risks and the experience gained will provide an expeditious path for development of new inhaled medications delivery for any future respiratory pathogen challenges as well.

Author Disclosure Statement

J.P.M., S.C., M.B.D., G.H., S.L., H.M.M., C.D., and B.H. register no conflict of interest. D.C. is an employee of Insmad Incorporated. I.G. consults for companies developing potential inhaled prophylaxes and treatments for COVID-19 infections. A.C. is an employee of Aerogen Pharma Corporation, N.K. and M.N. consult for companies developing inhaled pharmaceutical products. A.B. served as principal investigator in studies sponsored by AbbVie, Allergan, Anthera, DCI, Cempra, Cystic Fibrosis Foundation, National Institute of Health, Novartis, Therapeutic Development Network, Trudell Medical International, Vertex, and Vivus and he serves as science advisor to the International Pharmaceutical Aerosol Consortium on Regulation and Science (IPAC-RS). S.E. received unrestricted research grants, travel fee reimbursements, and speaker fees from Fisher and Paykel health care, consulting fees from La Diffusion Technique Française, consulting fees and unrestricted research grants from Aerogen Ltd., research support for Penn Century, and unrestricted research grant from Hamilton Medical. H.B. is a medical consultant including for Pulmoquine, a company investigating an inhaled therapy for prevention and treatment of COVID-19.

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