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Aerosolized surfactant for neonates

Target product profile: aerosolized surfactant for neonatal respiratory distress

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Abstract

Treatment with surfactant has been found to improve the survival rate of neonates with respiratory distress syndrome, particularly preterm infants. However, surfactant is usually administered by endotracheal intubation and generally only in level-3 neonatal intensive care units. Recent improvements in aerosolization technology have raised the possibility that aerosolized surfactant could now be given in wider range of settings, including resource-poor settings. Consequently, the World Health Organization has developed a target product profile for product developers that describes the optimal and minimal characteristics of an aerosolized surfactant for treating neonates with respiratory distress syndrome in low- and middle-income countries. Development of the target product profile involved a scoping review of systematic reviews and target product profiles of aerosolized surfactant, the constitution of an international expert advisory group, consultations with medical professionals from a wide range of countries and a public consultation. The resulting target product profile specifies that the surfactant and its associated aerosolization device should ideally, among other characteristics: (i) be at least as safe and effective as current intratracheal surfactant; (ii) produce a rapid clinical improvement; (iii) be easy to transport and use (e.g. by nurses in level-2, health-care facilities in low- and middle-income countries); (iv) be affordable for low- and middle-income countries; and (v) be stable when stored in hot and humid condition. In addition, the aerosolization device should be capable of daily use for many years. The introduction of an effective aerosolized surfactant globally could substantially reduce neonatal mortality due to respiratory distress syndrome.

Introduction

Respiratory distress syndrome causes approximately 15% of all neonatal deaths globally.\(^1,2\) The administration of antenatal corticosteroids and early initiation of continuous positive airway pressure both have a substantial impact on mortality from respiratory distress.\(^3–5\) In addition, there is clear evidence that treatment with surfactant, which decreases surface tension at the air–liquid interface in the lungs, reduces the severity of respiratory distress syndrome in preterm
infants and improves survival.\textsuperscript{6–8} Accordingly, surfactant is used routinely in high-income countries to treat preterm infants. Currently, however, surfactant administration usually requires endotracheal intubation to enable direct instillation of liquid surfactant into the trachea. Then the infant often requires mechanical ventilation until respiratory status improves.

The World Health Organization (WHO) recommends the use of animal-derived or protein-containing synthetic surfactant for preterm neonates with respiratory distress syndrome who are intubated and undergoing mechanical ventilation.\textsuperscript{9,10} However, current WHO guidelines state that surfactant should be given only in health-care facilities where blood gas analysis and newborn nursing care and monitoring are available.\textsuperscript{9} Additionally, the cost of current formulations remains high and poses a significant barrier to access. As a result, surfactant use in low- and middle-income countries is challenging.

To date, surfactant has generally been used only in level-3 tertiary neonatal intensive care units and has been out of reach for many level-2 special care baby units in district-level facilities.\textsuperscript{11} There is a need for a low-cost surfactant that can be administered without intubation and mechanical ventilation and is as efficacious and safe as standard surfactant. Many different surfactants and administration methods have been trialled, including less-invasive surfactant administration, which involves administering surfactant using a small catheter.\textsuperscript{12,13} Surfactant delivery via laryngeal mask airway or pharyngeal instillation are other commonly used methods but they also involve passing tubes into the oro- or naso-pharynx.\textsuperscript{14}

Nebulized surfactant has been investigated for many years.\textsuperscript{12} Older jet and ultrasonic nebulizers have several limitations, such denaturation of surfactant and surfactant being trapped in tubing and filters.\textsuperscript{15} Recent improvements in aerosolization technology have made it possible to produce small particles that enable a higher aerosolized dose to be deposited in the lungs.\textsuperscript{12,15} Aerosolized surfactant formulations will probably cost less and be easier to administer than conventional formulations. As a result, they could be used in district level-2 special care baby units in every country around the world. However, aerosolized surfactant is relatively new and currently it is unclear what the best formulation or form of administration would be for low-resource settings or whether storage and treatment are feasible.

The WHO has now developed a target product profile that describes the optimal and minimal characteristics of an aerosolized surfactant that can be used for neonates (i.e. infants
younger than 28 days) with respiratory distress syndrome in low- and middle-income countries. The profile’s purpose is to inform product developers about the key performance specifications and test characteristics of an aerosolized surfactant that will meet the needs of end-users in these countries. The overarching principles underlying the target product profile are that the aerosolized surfactant and its delivery system should: (i) be as safe and efficacious as conventional surfactant formulations; (ii) be capable of being administered and monitored in low- and middle-income countries; (iii) be affordable for these countries; and (iv) be capable of being used in special care baby units in level-2 or higher facilities in all countries globally.

Methods
A scoping review of systematic reviews and target product profiles of aerosolized surfactant for preterm neonates was performed. Then WHO developed a preliminary outline of a target product profile that focused on the needs of low- and middle-income countries. In this process, the principles outlined by WHO’s Science Division in 2022 for developing target product profiles were followed.16

Subsequently, an expert advisory group of 10 external experts from several WHO regions was identified by WHO’s secretariat by scanning the literature and contacting networks and colleagues. Group members were chosen to ensure technical expertise, interest, wide geographical representation and a gender balance. The result was a diverse group of individuals with expertise in neonatology, clinical practice, health promotion, policy and programmes, administration and service delivery (Table 1).

On 11 and 12 January 2022, a consultative meeting was held for individuals involved in the use of surfactant, such as doctors, nurses, pharmacists, administrators, procurement officers, programme managers, policy-makers and members of academic organizations. There were 37 attendees from 16 countries, including 13 low- and middle-income countries. All members of the expert advisory group and participants in the consultative meeting completed WHO declaration-of-interest and confidentiality forms. No individual had a conflict of interest. In addition, the biographies of expert advisory group members were posted on WHO’s website at the time of the consultative meeting.

The preliminary target product profile was developed further on the basis of the consultative meeting and an initial, or zero, draft was produced. The zero draft was posted on
WHO’s website on 20 June 2022 for public consultation with the purpose of inviting comments and suggestions. Subsequently, 22 sets of comments were received and incorporated into a revised version of the target product profile, which was reviewed and finalized by the expert advisory group and WHO’s secretariat. The final target product profile is now available online.17

Target product profile

Use, efficacy and safety of aerosolized surfactant
According to the target product profile,17 aerosolized surfactant should preferably be suitable for treating respiratory distress syndrome in all neonates, regardless of the use of noninvasive respiratory support devices (e.g. continuous positive airway pressure). The minimum requirement is that it should be suitable for use in neonates: (i) who are not responding to noninvasive respiratory support; or (ii) who have a birth weight of 1000 g or more or a gestational age of 28 weeks or more. The surfactant should preferably be suitable for use in special care units in level-2, health-care facilities in low- and middle-income countries, regardless of their referral network.11 At a minimum, it should be suitable for use in facilities able to refer neonates to level-3 facilities. Preferably, users would include nurses, all medical doctors, paediatricians and their equivalents. The minimum user group would comprise medical doctors with some training in neonatal care, paediatricians and their equivalents.

With regard to efficacy, aerosolized surfactant use should preferably result in a 30% or greater reduction in mortality or in failure to respond to continuous positive airway pressure among infants who receive continuous positive airway pressure plus surfactant compared to infants who receive continuous positive airway pressure alone.18 The minimum efficacy requirement is 20%. Moreover, efficacy should be equal to, or better than, that currently achieved by intratracheal surfactant. Preferably, the aerosolized surfactant should result in fewer adverse events than current surfactant therapy. At a minimum, the adverse event rate should be comparable to that with current surfactant.

Drug dosing and administration
The aerosolized surfactant should preferably need only one dose for maximum effect, which could be administered up to 48 to 72 hours after birth. Moreover, the maximum effect should be at least equivalent to that with current surfactant preparations. The minimum requirement is that three doses or fewer would be needed for maximum effect and that administration could be
started up to 12 hours after birth. Ideally the dose administered should be independent of body weight or dosing should be determined by body weight band (e.g. less than 0.5 kg, 0.6 to 1.0 kg, 1.1 to 1.5 kg and so on). The minimum requirement is that dosing should be determined by body weight in mL/kg.

During administration of the aerosolized surfactant, there should preferably be no interruption to the operation of any noninvasive respiratory support device. The minimum requirement is that the device should be interrupted for less than 5 min. A measurable clinical improvement (e.g. improved oxygenation, reduced oxygen requirement or less breathing effort) should preferably be apparent within 15 min of treatment completion. The minimum requirement is an improvement within 60 min. In addition, the maximum benefit of treatment should preferably be achieved within 2 hours of treatment completion. The minimum requirement is within 6 hours. Preferably, at least 30% of the surfactant should be deposited in the alveoli (i.e. in the distal lung region and parenchyma). The minimum requirement is 15%.

**Drug formulation and packaging**

The shelf-life stability of the aerosolized surfactant should preferably be at least 36 months in hot and humid conditions (defined as a temperature of 30 °C or more and a relative humidity of 75%) and the in-use stability should be at least 120 min under these conditions. The minimum requirements are a shelf-life stability of at least 24 months at 2 to 8 °C and an in-use stability of at least 60 min in hot and humid conditions.

The aerosolized surfactant should preferably be synthetic. The minimum requirement is an animal-derived surfactant or protein-containing synthetic surfactant. The drug and its associated aerosolization device must be packaged separately and the final packaging should preferably be capable of being shipped by road, rail, air or sea without the need for a cold chain. At a minimum, the aerosolization device should be capable of being shipped by road, rail, air or sea without the need for a cold chain and the drug should be capable of being shipped through a cold chain. The drug and device must be capable of being disposed of via established pharmaceutical waste streams.

**Aerosolization device**

The aerosolization device must be developed in accordance with appropriate regulatory guidance and standards. Preferably, it should work on both battery and external electricity power sources.
At a minimum, it could be plugged into an external power source. The device must be capable of being used by both right- and left-handed people and must be compact and easy to use and transport.

Ideally it should be possible to learn the skills required to operate the aerosolization device within 2 to 3 hours of training. The minimum requirement is that skills should be learned within 2 to 3 days. It should be possible to set up the device in fewer than five steps and within 5 min or less. The minimum requirement is that it should take 10 steps and 10 min to set up.

The aerosolization device must be designed to ensure that only one unit dose can be administered at a time and it must be capable of being used for several patients with the aid of an appropriate cleaning and disinfecting regimen. In addition, it must meet the standards for noninvasive respiratory support devices and nebulization devices and should preferably function for at least 5 years of daily use. At a minimum, it should function for 2 years of daily use.

**Cost**

The cost of the aerosolized surfactant should preferably be less than 5 United States dollars (US$) per dose delivered, the aerosolization device should cost less than US$ 100 and the total cost per infant should be less than US$ 25. The minimum requirements are that the aerosolized surfactant should cost less than US$ 50 per dose, the device should cost less than US$ 1000 and the total cost per infant should be less than US$ 220.

**Conclusion**

Working with an international expert advisory group and after consultations with medical professionals from a wide range of countries and a public consultation, WHO developed a target product profile for an aerosolized surfactant for use in neonates with respiratory distress syndrome in low- and middle-income countries. According to the product profile, the surfactant and its associated aerosolization device should ideally: (i) be affordable; (ii) be stable when stored in hot and humid condition; (iii) be easy to transport and use (e.g. by nurses in level-2, health-care facilities in low- and middle-income countries); (iv) produce a rapid clinical improvement; and (v) be as, or more, effective than current intratracheal surfactant. In addition, the aerosolization device should last for many years of daily use. The introduction of an effective aerosolized surfactant globally would substantially reduce neonatal mortality due to respiratory distress syndrome.
Acknowledgments

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Competing interests:

None declared.

References


Table 1. **Expert advisory group, development of a target product profile for aerosolized surfactant therapy for neonates in low- and middle-income countries, 2022**

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