World Health Organization

DRAFT WHO TARGET PRODUCT PROFILE FOR AEROSOLISED SURFACTANT THERAPY IN NEONATES WITH RESPIRATORY DISTRESS SYNDROME IN LOW AND MIDDLE INCOME COUNTRIES
DRAFT, V0.1, 20JUNE2022

Introduction

Respiratory distress syndrome (RDS) causes approximately 15% of all neonatal deaths globally.[1,2] Antenatal corticosteroids and early initiation of continuous positive airway pressure (CPAP) both have substantial impacts on RDS mortality.[3-5] There is clear evidence that surfactant therapy reduces RDS in preterm infants and improves survival.[6,7] Surfactant is used as both a rescue and preventive treatment for RDS in preterm infants in high income countries. Currently surfactant administration requires endotracheal intubation with liquid surfactant instillation directly into the trachea. The infant then often requires mechanical ventilation until respiratory status improves.

The World Health Organization (WHO) recommends surfactant for preterm intubated and ventilated newborns with RDS, using animal derived or protein containing synthetic formulations.[8,9] However, current WHO guidelines state that surfactant should only be used in health care facilities where blood gas analysis, newborn nursing care and monitoring are available.[8] Costs of current formulations also remain high. Use of surfactant has been a challenge in low and middle income countries (LMICs) . To date surfactant use has been generally confined to level 3 tertiary level neonatal intensive care units (NICUs) and has been 'out of reach' of many level 2 special care baby units at the district level.[8]

Recent improvements in aerosolisation technology have, for the first time, allowed the administration of surfactant without the need for intubation and ventilation.[10,11] Aerosolised surfactant formulations are likely to be lower cost and require less monitoring and nursing care than conventional formulations.[11] This could allow their use in district level 2 special care baby units in all countries around the world. However, aerosolised surfactant is relatively new and the optimal formulation, administration, and feasibility (including storage and administration) in low resource settings has not yet been addressed.

Thus WHO is seeking input into the minimal and optimal characteristics of an aerosolised surfactant that can be used for neonates with RDS in low and middle income countries (LMICs) and has developed a target product profile (TPP) for comment.

Purpose of the TPP

The purpose of the TPP is to guide product developers about key test characteristics and performance specifications that will meet the needs of end users in LMICs. It describes the minimal and optimal characteristics of an aerosolised surfactant for treatment of RDS in newborns in LMICs.

Overarching principles are that the aerosolised surfactant and delivery system for LMICs should be:

- as safe and efficacious as conventional formulations of surfactant
- feasible for administration and monitoring
- affordable
- able to be used in special care baby units (level 2 and above) in all countries around the world

Methods

In 2021 and 2022 WHO reviewed literature and the world wide web to find existing aerosolised surfactant TPPs for use in neonates. Only one TPP was found.[12] WHO used this TPP to draft a TPP focused on needs in LMICs. A consultative meeting of end users (doctors, nurses, supply chain program officers, members of academic organizations) was held on 11th and 12th January 2022. There were 41 attendees from 16 countries including 13 LMICs. The draft TPP was revised based on the consultative meeting and the current zero draft (v0.1, 20June2022) was developed. The zero draft TPP has now been posted for public consultation with the purpose of inviting comments and suggestions on the TPP.

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No.	Characteristic	Minimal characteristics	Optimal characteristics
	Scope, efficacy and safety		
1	Indication for use	Treatment of RDS not responding to use of noninvasive respiratory support devices (NRS) (e.g. CPAP)	Treatment of RDS regardless of use of noninvasive respiratory support devices (NRS) (e.g. CPAP)
2	Target population	Neonates $\geq$ 1000g birth weight or $\geq$ 28 weeks gestational age with RDS	Any neonate with RDS
3	Target facilities in LMIC	Facilities providing level 2 special care[13] able to refer to level 3 facilities	Facilities providing level 2 special care[13] regardless of referral network
4	Target user (in facilities described above)	User must be a medical doctor who has some training in neonatal care, paediatrician, neonatologist or equivalent	User must be nurse, medical assistant, clinical assistant, medical doctor, paediatrician, neonatologist or equivalent
5	Efficacy	$\geq$ 20% reduction in mortality in infants who receive CPAP plus surfactant compared to infants who receive CPAP alone[14]	$\geq$ 30% reduction in mortality in infants who receive CPAP plus surfactant compared to infants who receive CPAP alone[14] The same or better efficacy than currently available surfactant provided through endo tracheal tube
6	Acceptable safety profile	Comparable to adverse events from current surfactant therapy	Lower than adverse events from current surfactant therapy
	Drug- dosing, route, drug administration		

7	Initiation time	If treatment of infant with RDS is started 12 hours after birth it will still have maximum effect	If treatment of infant with RDS is started 48-72 hours after birth it will still have maximum effect
8	Frequency	Needs no more than 4 doses for maximum effect	Needs only one dose for maximum effect
9	Dose	Dosing is mg/kg body weight	Dose is independent of body weight or calculated in 'bands' of body weight (e.g. <0.5kg, 0.6-1.0kg, 1.1-1.5kg etc.)
10	Interruptions to NRS device	Interruptions of NRS device (e.g. CPAP) must be < 5 minutes	NRS device (e.g. CPAP) use must not be interrupted
11	Time of onset of effect	Must have measurable clinical improvement within 60 min of treatment completion	Must have measurable clinical improvement within 15 min of treatment completion
12	Time of onset of maximum benefit	Must achieve maximum benefit within 6 hours of treatment completion	Must achieve maximum benefit within 2 hours of treatment completion
13	Deposition / delivery of dose	Must achieve at least 15% deposition in alveoli (distal lung region/parenchyma)	Must achieve at least 30% deposition in alveoli (distal lung region/ parenchyma)
	Formulation		
14	Shelf life	Shelf-life stability at least 24 months at 2-8 deg C In-use stability at least 60 minutes in hot and humid conditions (defined as ≥ 30 deg C, 75% relative humidity)	Shelf-life stability at least 36 months in hot and humid conditions (defined as ≥30 deg C, 75% relative humidity) In-use stability at least 120 minutes in hot and humid conditions (defined as ≥30 deg C, 75% relative humidity)
15	Composition	Animal derived or synthetic	Synthetic
16	Packaging	Drug product and device must be packaged separately	Same as minimal
17	Shipping	Drug must be capable of being shipped by road, rail, air or sea maintaining cold chain Aerosolisation device and packaging must be capable of being shipped by road, rail, air or sea with no cold chain requirement	Drug plus aerosolisation device and its final packaging must be capable of being shipped by road, rail, air or sea with no cold chain requirement
18	Disposal	Must be disposable using established pharmaceutical waste streams	Same as minimal
	Device		
19	Development standards	The aerosolisation device must be developed in accordance with appropriate regulatory guidance and standards	Same as minimal
20	Power & IT requirements	The aerosolisation device must work using an external power source i.e. plugged into source of electricity	The aerosolisation device must not require an external power source (i.e. source of electricity) e.g. can work with batteries
21	Handedness	The aerosolisation device must be capable of being used by both right & left-handed users	Same as minimal

22	Size / weight	Device must be compact, easy to use and comfortably transported	Same as minimal
23	Ease of operation	The skills and training required to operate the aerosolisation device must be equivalent to a medical doctor with training in neonatal care, paediatrician, or neonatologist	The skills and training required to operate the aerosolisation device must be equivalent to nurse, medical assistant, clinical assistant, medical doctor, paediatrician or neonatologist
24	Device steps required for use	Aerosolisation device must be easy to operate with minimal training and take $\underline{<}$ 10 min of person time to set up	Aerosolisation device must be easy to operate with minimal training and take ≤5 min of person time to set up
25	Unit dosing	Aerosolisation device must ensure only one unit dose can be administered at a time	Same as minimal
26	Functioning	Must meet standards for NRS and nebulization devices. It must function for at least 2 years with daily use	Must meet standards for NRS and nebulization devices. It must function for at least 5 years with daily use.
27	Reusability	The aerosolisation device must be able to be used for multiple patients using an appropriate cleaning and disinfecting regimen	Same as minimal
	Purchasing considerations		
28	Cost of drug only	<$50 per dose delivered	<$5 per dose delivered
29	Total patient costs	<$220 per baby	<$25 per baby

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