The Nebuliser Sub-Team of the European Pharmaceutical Aerosol Group

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on behalf of the sub-team

Session 4: The Remit, Activities and Achievements of The European Pharmaceutical Aerosols Group
INTRODUCTION

• The Nebuliser sub-team was formed about 2 years ago

• Provide technical support to the development of a new Ph. Eur. monograph 2.9.44: ‘Preparations for Nebulisation’
OBJECTIVES

1. Examine need to chill NGI for use in aerodynamic assessment part of monograph

2. Examine need to coat collection cups of NGI to avoid droplet bounce/re-entrainment

3. Provide position statement on appropriate paediatric breathing patterns for drug delivery rate/total drug delivered parts of monograph

4. Provide position statement on use of laser diffractometry as alternative to cascade impaction where appropriate
OBJECTIVE 1: NGI CHILLING

• 6-centre experimental study

• 3-different Nebuliser types

• 1-common formulation (salbutamol sulfate solution)

• Aerosol measured with NGI at room ambient and cooled for >90 minutes in refrigerator (5°C), removed and immediately used to make measurements

Misty-Max* continuous jet nebuliser

PARI LC Plus air entrainment jet nebuliser

AeroNeb Go vibrating mesh
OBJECTIVE 1: OUTCOME

Graphs show mean and 95% CI

- Sizing results consistently demonstrate a smaller aerosol size is obtained using an NGI at ambient conditions

![Graphs showing aerosol size distribution for different devices](image-url)
OBJECTIVE 1 - CONCLUSIONS

1. Cooling the NGI before use for the aerodynamic assessment of nebulised aerosols should be undertaken to avoid bias to finer sizes caused by heat transfer-related evaporation

2. The magnitude of the bias is dependent upon nebuliser type; the largest shift was observed for a constant output jet nebuliser (MistyMax)

3. Variability in the data was not increased when using the NGI cooling procedure

4. Regular cleaning/drying of both interior and external surfaces of the NGI should be undertaken to minimize the risk of corrosion
OBJECTIVE 2: NGI COLLECTION CUP COATING

• 2-centre experimental study
• 2-different Nebuliser types
• 1-common formulation (salbutamol sulfate solution)
• Aerosol measured with NGI at room ambient with uncoated collection cups and with cups coated with high viscosity silicone grease
OBJECTIVE 2: OUTCOME

- There was no indication of biased stage deposition or lower fractions <5 μm and <3 μm or larger MMADs with uncoated surfaces.

- There is no need to coat the NGI cups when nebulised products are investigated.
OBJECTIVE 2 - CONCLUSIONS

NGI collection cups do NOT require coating for Nebuliser aerosol assessments
OBJECTIVE 3: PAEDIATRIC BREATHING PATTERNS

• Some Nebuliser formulations are currently indicated for infants and small children
  • More are likely in the future

• Research has been undertaken to establish if breathing patterns for these patient categories can be standardized

• A multitude of patterns exist with very little effort to standardize global
OBJECTIVE 3: RECOMMENDATION

- A position statement has been developed in discussion with clinical experts.

- Include breathing patterns as per CSA spacer/holding chamber standard CAN/CSA/Z264.1-02:2002 for NEONATE/ INFANT/ SMALL CHILD as options for nebuliser testing where appropriate.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neonate</th>
<th>Infant</th>
<th>Child</th>
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</thead>
<tbody>
<tr>
<td>$V_t$ (ml)</td>
<td>25</td>
<td>50</td>
<td>155</td>
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<tr>
<td>Rate/min</td>
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<td>30</td>
<td>25</td>
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<tr>
<td>Duty cycle</td>
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<td>25%</td>
<td>33%</td>
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<tr>
<td>$V_{min}$ (ml)</td>
<td>1000</td>
<td>1500</td>
<td>3875</td>
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OBJECTIVE 4: LASER DIFFRACTOMETRY (LD)

- LD could be an attractive alternative to cascade impaction in product development:

- Equivalency between the techniques has been established for some solution formulations
  - appropriate precautions should be taken to avoid sources of bias
OBJECTIVE 4: RECOMMENDATIONS

• Position statement published:

• LD is a suitable alternative to cascade impaction *where validated back to the cascade impactor method.*

• The position statement provides guidance that should be incorporated into the Ph.Eur Monograph
NEBULISER SUB-TEAM - SUMMARY

• The sub-team has made several significant contributions to the development of Ph.Eur. Monograph 2.9.44: “Preparations for Nebulisation”

• Its future role is currently under consideration, and will depend on ongoing need to support EPAG in addressing issues that relate to this class of inhalers
ACKNOWLEDGMENTS

SUB-TEAM MEMBERS:

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