The Complexities of Complex Products
(a.k.a. Adrian rants about things that bother him)

Adrian Goodey
PQRI BTC Webinar
28-April-2020
Disclaimer

Not necessarily the opinions of Merck & Co., Inc.
Motivation:

• Delivery of Medicine to the Airways
• Reduced dose
• Rapid Onset
• Accommodates a wide range of modalities
Nasal
Nasal

Motivation:
- Local Delivery to the nose
- Systemic Delivery via the nose
  - Ease of use
  - Rapid onset
Mean Pharmacokinetic Parameters (CV%) for Naloxone Following NARCAN (Naloxone HCl) Nasal Spray and Intramuscular Injection of Naloxone HCl to Healthy Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2 mg – One Nasal Spray in one nostril 20 mg/ml (N=29)</th>
<th>4 mg – Two Nasal Sprays, one in each nostril 20 mg/ml (N=29)</th>
<th>4 mg – One Nasal Spray in one nostril 40 mg/ml (N=29)</th>
<th>8 mg – Two Nasal Sprays, one in each nostril 40 mg/ml (N=29)</th>
<th>0.4 mg Intramuscular Injection (N=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{\text{max}} ) (h) *</td>
<td>0.33 (0.25, 1.00)</td>
<td>0.33 (0.17, 0.57)</td>
<td>0.50 (0.17, 1.00)</td>
<td>0.33 (0.17, 1.00)</td>
<td>0.38 (0.08, 2.05)</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/mL)</td>
<td>2.91 (35)</td>
<td>6.30 (34)</td>
<td>4.83 (43)</td>
<td>9.70 (36)</td>
<td>0.88 (31)</td>
</tr>
<tr>
<td>AUCt (hr·ng/mL)</td>
<td>4.60 (27)</td>
<td>9.64 (24)</td>
<td>7.87 (37)</td>
<td>15.3 (23)</td>
<td>1.75 (23)</td>
</tr>
<tr>
<td>AUCo-inf (h*ng/mL)</td>
<td>4.66 (27)</td>
<td>9.74 (24)</td>
<td>7.95 (37)</td>
<td>15.5 (23)</td>
<td>1.79 (23)</td>
</tr>
<tr>
<td>( t_{\frac{1}{2}} ) (h)</td>
<td>1.85 (33)</td>
<td>2.19 (33)</td>
<td>2.08 (30)</td>
<td>2.10 (32)</td>
<td>1.24 (26)</td>
</tr>
<tr>
<td>Dose normalized Relative BA (%) vs. IM</td>
<td>51.7 (22)</td>
<td>54.0 (23)</td>
<td>44.2 (31)†</td>
<td>43.1 (24)</td>
<td>100</td>
</tr>
</tbody>
</table>

† \( t_{\text{max}} \) reported as median (minimum, maximum)

### Intranasal

**WHEN EVERY SECOND MATTERS**

Using NARCAN® requires no medical training and the device requires no assembly.

Excerpt from Narcan Prescribing Information at [www.narcan.com](http://www.narcan.com) accessed 28-Apr-2020
<table>
<thead>
<tr>
<th>Route</th>
<th>Dose</th>
<th>AUC&lt;sub&gt;0-inf&lt;/sub&gt; (± SD) [pg/mL*h]</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (± SD) [pg/mL]</th>
<th>Median T&lt;sub&gt;max&lt;/sub&gt; (range) [h]</th>
<th>BA [%] relative to IM (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN</td>
<td>10 IU</td>
<td>200 ± 103</td>
<td>374 ± 173</td>
<td>0.08 (0.08 - 0.17)</td>
<td>10 ± 5</td>
</tr>
<tr>
<td></td>
<td>40 IU</td>
<td>913 ± 341</td>
<td>1809 ± 578</td>
<td>0.08 (0.08 - 0.25)</td>
<td>12 ± 4</td>
</tr>
<tr>
<td></td>
<td>80 IU</td>
<td>2170 ± 598</td>
<td>3263 ± 712</td>
<td>0.08 (0.08 - 0.25)</td>
<td>14 ± 3</td>
</tr>
<tr>
<td>IM</td>
<td>40 IU</td>
<td>7922 ± 1679</td>
<td>16186 ± 3921</td>
<td>0.08 (0.08 - 0.17)</td>
<td>reference</td>
</tr>
</tbody>
</table>

- Rapid Onset: T<sub>max</sub> = 5 min, matching IM injection
- Good Bioavailability: 10 – 14% relative to IM injection
- Improved Chemical Stability
Motivation:

• Long-term release profile offers convenience and compliance benefits

QD Dosing: 1 week

PK

Time
Motivation:

• Long-term release profile offers convenience and compliance benefits
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Motivation:

- Long-term release profile offers convenience and compliance benefits
Extended-Duration MK-8591-Eluting Implant as a Candidate for HIV Treatment and Prevention
• Sourcing:
  • Low Volume
  • High Demands

• Investigations:
  • Multi-layer supply chains
  • Confidentiality agreements limit “skip level” communication
  • Quality systems diverge from Pharma standards
Analysis
Cascade Impaction

- Key performance test for inhaled products
- Aerodynamic Particle Size Distribution (APSD)
Cascade Impaction

- Aerodynamic Diameter – Describes the behavior of airborne particles
- Inertial Impaction – separates particles by aerodynamic diameter
  - Particles with enough momentum escape entrainment in the gas stream and impact on a collection surface
- Environmental Controls Required
  - Temperature, humidity, static
Cascade Impaction

• API mass is fractionated across 8 – 10 components
• Drug is extracted from each for assay by LC
Complexity of APSD Analysis

- Labor intensive
- Error Prone
- Highly sensitive (to everything!)
- Lack of IVIVC for inhaled products
- Metrics are often mis-used
Analysis of APSDs: MMAD Determination
(Mass Median Aerodynamic Diameter)

MMAD by 2-point Interpolation

3.0 microns

MMAD by log-probit

2.1 microns

Cumulative % Mass

API Recovery (mcg)

Throat plate 0 plate 1 plate 2 plate 3 plate 4 plate 5 plate 6 plate 7 filter

Aerodynamic Diameter (mcm)

“linear” regression
Analysis of Long-Acting Parenterals

Polymer API

Dissolution Media

Concentration

C = C_5

(Perfect Sink)

C = 0

PK

Time

Distance

Concentration vs. Distance Graph

Graph shows concentration over time (PK) with a curve indicating a decrease. The concentration is constant at C = C_5 and decreases to C = 0 at a certain distance.
Analysis of Long-Acting Parenterals

Multi-year product means multi-year testing! ...plus the shelf life!

Significant Acceleration of in-vitro release, without changing the mechanism...

Accelerated In-vitro Release → Real Time in-vitro Performance → in-vivo Performance

IVIVC

Concentration

Time

Dissolution Media

Polymer API Void

(Perfect Sink) C = 0

C = C₅
Regulation
Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Quality Considerations
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Division of Dockets Staff (HFA-305), Food and Drug Administration, 5630 Fisher Lane, room 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact (CDER) Richard Lestino at 301-796-1697.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

April 2018
Pharmaceutical Quality/CMC
Revision 1
Control of APSDs: Stage Groupings

- An APSD has two dimensions:
  - Mass (y-axis)
  - Size (x-axis)
- APSD Metrics must account for each
- Impactor Sized Mass tracks changes in total mass
- MMAD tracks changes in aerodynamic size
Control of APSDs

Quality Control of Orally Inhaled Products

Typical QC Metrics:
- Europe: Fine Particle Dose
- US: Stage Groupings
Control of APSDs

In this example, fine particles are chosen as those <4.7 microns

Fine Particles

- Fine Particle Dose
  - The API mass, per dose, with aerodynamic diameter less than 5 microns

- Fine Particle Fraction
  - Fine Particle Mass, expressed as a percentage of the total mass
Control of APSDs: Fine Particle Dose

- PhEur 2.9.18. Preparations for inhalation: *Calculate by interpolation the mass of the active substance less than 5 microns. This is the Fine Particle Dose (FPD).*

Data from IPAC-RS blinded database: HFA Solution MDI w9j801; 201 distributions
Control of APSDs: Fine Particle Dose

➤ FPD is insensitive to *huge* shifts in APSD!

Is this what you intended to manufacture?

Data from IPAC-RS blinded database: HFA Solution MDI w9j801; 201 distributions

FPD thinks so!
Control of APSDs: Fine Particle Dose

Why Does FPD Fail?

The entire APSD is contained within the Fine Particle Dose

...a huge shift in MMAD elicits only a small change in Fine Particle Dose

Data from IPAC-RS blinded database: HFA Solution MDI w9j801; 201 distributions
Control of APSDs: Fine Particle Dose

The liability of fine particle dose (FPD)

Can we rely on the fine particle dose metric alone for quality control?

Adrian P. Goodey, PhD; Jolyon P. Mitchell, PhD, FRSC(UK), CChem, CSci; William H. Doub, PhD and J. David Christopher, MSc

- A: HFA Solution MDI
- B: DPI
- C: CFC Suspension MDI
- D: CFC Suspension MDI
- E: HFA Suspension MDI
- F: CFC Suspension MDI
- G: DPI

Data from blinded IPAC-RS database
Control of APSDs

Quality Control of Orally Inhaled Products

Typical QC Metrics:

• Europe: Fine Particle Dose
• US: Stage Groupings
Control of APSDs

Stage Groupings

- FDA guidance requests a minimum of 3 – 4 groupings
- “Applicants should propose acceptance criteria for groupings of consecutive stages”
- “In most cases three or four groupings should be sufficient to characterize the APSD adequately”
Control of APSDs: Stage Grouping

Data from blinded IPAC-RS database (solution MDI product w9j801)
Control of APSDs: Stage Groupings

Data from blinded IPAC-RS database (solution MDI product w9j801)
Control of APSDs: Stage Groupings

- 201 APSDs expressed in terms of their mass and size
- Limits assigned to each dimension
  - Mass: ± 33%
  - Size: ± 0.5 microns

Data from blinded IPAC-RS database (solution MDI product w9j801)
Control of APSDs: Stage Groupings

• 201 APSDs expressed in terms of their mass and size
• Limits assigned to each dimension
  • Mass: ± 33%
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Control of APSDs: Stage Groupings

Data from blinded IPAC-RS database (solution MDI product w9j801)

**APSDs within Specifications**

**APSDs Out of Specification**

Data from blinded IPAC-RS database (solution MDI product w9j801)
Control of APSDs: Stage Groupings

- Mass and Size limits are translated into Stage Grouping Limits
- Linear regression used to define the dependence of each group on both mass and size
Control of APSDs: Stage Groupings

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Control of APSDs: Stage Groupings

Data from blinded IPAC-RS database (solution MDI product w9j801)

Stage Groupings

- Simultaneous use of acceptance criteria for all three groupings impairs decision making
- High probability of misclassification
Control of APSDs: Stage Groupings

- The Stage Grouping limits correctly classify ~52% of the APSDs.
- Slightly better than a coin toss...

Data from blinded IPAC-RS database (solution MDI product w9j801)
Control of APSDs: Stage Groupings

Correctly Accepted (43%)
✓ Stage Groupings correctly accept 85 APSDs

Incorrectly Accepted (0.5%)
✗ Stage Groupings incorrectly accept 1 OOS APSD

Correctly Rejected (10%)
✓ Stage Groupings correctly reject 20 APSDs

Incorrectly Rejected (47%)
✗ Stage Groupings incorrectly reject 95 acceptable APSDs

Data from blinded IPAC-RS database (solution MDI product w9j801)
Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"

Guidance for Industry and Food and Drug Administration Staff

Document issued on: June 16, 2016
The draft of this document was issued on April 23, 2013.


For questions regarding this document, contact Jennifer Goode, 301-796-6374, jennifer.goode@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Chemical Characterization via Exhaustive Extraction

- The Exhaustive Extraction profile represents the total amount of each constituent that could possibly leach.
- Complex Product + Extreme Conditions + Highly Sensitive Analysis + Rapidly Evolving Standards...
Chemical Characterization via Exhaustive Extraction

- The exhaustive extraction profile represents the total amount of each constituent that could possibly leach.

Threshold of Toxicological Concern (TTC)

- Risk assessments for compounds without tox data rely on TTC.
- TTC used to define Analytical Evaluation Threshold.
- TTC must be specific to the use scenario... Duration of use is hugely important!
### Biocompatibility

![Chemical Analysis](image)

**Semi-Volatile Compounds**  
Compounds | Amount (mcg/device) |
--- | --- |
Compound X | 25 mcg/device |

### Intended Use:
- Single implantable device
- 12 month clinical trial
- Removed after 12 months

### Possible Rates of Exposure:
- **Full exposure in a single day:**  
  25 mcg / 1 day = 25 mcg/day < 120 mcg/day
- **Full exposure over 12 months:**  
  25 mcg / 365 days = 0.07 mcg/day < 20 mcg/day

### Worst Case Assumption:
- Entirety of each extractable leaches into patient

---

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<th>Medical device contact category</th>
<th>Limited (&lt;24 h)</th>
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<td>&gt; 1 month to 12 months</td>
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<tr>
<td>Daily intake (µg/d) of any one constituent</td>
<td>120</td>
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<sup>a</sup> Long-term includes devices commonly described as permanent contacting (see ISO 10993-1).

<sup>b</sup> The 1.5 µg/d value is based on 10⁻⁵ cancer risk and 60 kg (adult) body weight. [8][12]
Semi-Volatile Compounds

| Compound X | 25 mcg/device |

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**Biocompatibility**

**Table 1 — Recommended ICH M7(R1) (2017) TTC values based on ISO 10993-1 medical device contact category**

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- **Long-term** includes devices commonly described as permanent contacting (see ISO 10993-1).
- The 1.5 µg/d value is based on 10⁻⁵ cancer risk and 60 kg (adult) body weight<sup>a,b</sup>.

...Nobel Prize for spontaneous generation of matter?
Summary & Conclusions

• Complex Products offer tremendous benefits to the patient
• Complexity can have a profound impact on the development and availability of products
• Some Complexity is inherent and unavoidable
  • Product Performance tailored to the route of administration
  • Drug-Device interactions of Combination Products
• Some Complexity is avoidable
  • The return on investment for APSD Determination by Cascade Impaction is quite poor
  • Metrics should be well understood, and should be chosen based on the task at hand
  • Acceptance Criteria should be meaningful
Acknowledgements

• IPAC-RS Cascade Impaction Working Group
  • J. David Christopher, William H. Doub, Svetlana Lyapustina
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  • Mic Iwashima, Shunji Haruta, Shuzo Koyama

• Islatravir Implant Team

• Wenlei Jiang & PQRI

• Thank you for your attention!