SubQ Bioavailability Considerations

Manuel Sanchez-Felix

CASSS – CM&C Strategy Forum Europe 17th to 19th October 2022
Introduction

Highlight Trends from IV to SC products driven by patient needs

Subcutaneous Drug Delivery & Development Consortium

Subcutaneous Bioavailability Challenges

Summary
Patient Centered Advantages & Trends of Subcutaneous

Trend in mAB from IV to SC

- Transition is being accelerated by COVID
- New classes of bispecific show higher efficacy SC
Patient Centered Advantages & Trends of Subcutaneous

Trend in Peptide from IV to SC in development pipeline

Ahil Ganesh, Carolyn Heusser, Sudhakar Garad & Manuel Sanchez-Felix, Patient-centric design for peptide delivery: Trends in routes of administration and advancement in drug delivery technologies, Medicine In Drug Discovery, 2021
Subcutaneous Drug Delivery & Development Consortium

**Vision**
Our vision is to **transform patient care and improve patient outcomes** leading **fundamental advancements in subcutaneous drug development and delivery**

**Mission**
The mission of the Subcutaneous Drug Development & Delivery Consortium is to **collaboratively address the most pressing subcutaneous dosage and delivery issues and opportunities** in a precompetitive manner.
Accelerating the development of novel technologies and tools for subcutaneous delivery of biotherapeutics

To Expedite Progress in the Subcutaneous (SC) Field and Facilitate the Development of Novel Biotherapeutics, a Concerted Effort Must be Made to Foster Academic–Industry Collaborations

**Patient-Physician Interactions**
- Gap in understanding how physician interactions influence patients’ expectations and experiences

**Patient Experience**
- Deeper understanding needed of how patient experience impacts patient preferences

**Payer Preference**
- Payers sometimes put IV and SC therapies in the same cost category

**Clinical Trial Considerations**
- Optimal time to SC clinical trial initiation during product lifecycle is unclear

**High Dose/Volume Delivery**
- Misguided perceptions of development of large-volume (>2 mL) and high-dose SC technologies

**Bioavailability**
- Bioavailability of biologics is unpredictable and variable

**Immunogenicity**
- Inconsistent understanding of SC immunogenicity, testing methodologies, and quality attributes

**Patient Preference: IV vs SC**
- Unclear understanding and prioritization of patient preferences regarding optimal tradeoffs between IV and SC

The top 6 problem statements have been prioritized for 2020, with 6 sub-teams created around these statements (the 2 patient statements have been combined into 1 sub-team).

- High Dose/Volume SC Technology Development
- Bioavailability
- Immunogenicity
- Patient Preference: SC Design Attributes
- Patient Experience & Discomfort
- Clinical Trial Strategy
- Payer Preference
- Patient-Clinician Interactions
Formulation & Device Options for SubQ Delivery – especially of higher doses

- Viscosity reducing agents
- Turning solution into solid suspension
- Combination with subQ enhancers
- Smart injections devices and OBI pumps

Predicting bioavailability of monoclonal antibodies after subcutaneous administration: Open innovation challenge

Manuel Sánchez-Félix, Matt Burke, Hunter H. Chen, Claire Patterson, Sachin Mittal
# Subcutaneous Bioavailability Challenges

## Commercialized Product Examples

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Tradename</th>
<th>MW (kDa)</th>
<th>SC bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Humira®</td>
<td>148</td>
<td>Human: 52–62% (64%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monkey: 94–100% (96%)</td>
</tr>
<tr>
<td>Alirocumab</td>
<td>Praluent®</td>
<td>146</td>
<td>Human: 85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monkey: 73–77%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Rat: 44–97%</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>Ilaris®</td>
<td>145</td>
<td>Human: 63–67%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Monkey: 60%</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>Cimzia®</td>
<td>91</td>
<td>Human: 76–88%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rat: 24–34%</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel®</td>
<td>150</td>
<td>Human: 76%</td>
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<td></td>
<td></td>
<td></td>
<td>Monkey: 73%</td>
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<tr>
<td></td>
<td></td>
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<td>Mice: 58%</td>
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<tr>
<td>Golimumab</td>
<td>Simponi®</td>
<td>150</td>
<td>Human: 53%</td>
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<td></td>
<td>Monkey: 77%</td>
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<tr>
<td>Omalizumab</td>
<td>Xolair®</td>
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<td>Human: 53–71% (62%)</td>
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<td></td>
<td></td>
<td></td>
<td>Monkey: 64–104% (84%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mice: 90%</td>
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<tr>
<td>Bevacizumab</td>
<td>Avastin®</td>
<td>149</td>
<td>Monkey: 98%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Rat: 69%</td>
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<td></td>
<td></td>
<td></td>
<td>Mice: &gt;100%</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Mabthera®</td>
<td>145</td>
<td>Human: 71%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Minipig: 71%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Monkey: 63%</td>
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<tr>
<td>Sarilumab</td>
<td>Kezara®</td>
<td>150</td>
<td>Human: 80%</td>
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<td>Monkey: 78%</td>
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<tr>
<td>Trastuzumab</td>
<td>Herceptin®</td>
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<td>Human: 82%</td>
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<td>Minipig: 82%</td>
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<tr>
<td></td>
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<td></td>
<td>Mice: 83%</td>
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mAB Subcutaneous Bioavailability Challenge

The subcutaneous bioavailability of monoclonal antibodies is influenced by a combination of molecular/formulation properties and physiological factors.

mAB Subcutaneous Bioavailability Challenge

In silico absorption modelling is successfully used in oral formulation development for compound selection, formulation design, specification setting and sometimes even in lieu of clinical bioequivalence studies.

Compared to oral, SC models are less well established, and are acknowledged as complex due to multiple, interrelated nonlinear pathways.

Empirical and mechanistic models have been developed.

None can predict SC mAb bioavailability bottom-up.

Aim to predict or understand factors affecting rate and extent of absorption and impact on PK profile.

Knowledge gaps/opportunities to improve the models have been proposed.

**Schematic representing SC Bioavailability**

**Example mAb SC PK profile**
mAB Subcutaneous Bioavailability Challenge

**Vision**

- **In-silico & In-vitro**
- **Translation of Bioavailability**
- **Bring Together Communities to Work on Needs**

Subcutaneous Bioavailability Challenges

Open Challenge

Classification system concept for mAbs: molecular transport vs catabolism extent

<table>
<thead>
<tr>
<th>Molecular Transport</th>
<th>Catabolism Extent</th>
</tr>
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<tbody>
<tr>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>High</td>
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<tr>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>High</td>
</tr>
</tbody>
</table>

(consider injection site & lymphatic system as well as irreversible binding or immune cell capture)
mAB Subcutaneous Bioavailability Challenge

Provide three sets of data to validate hypotheses:

- Table capturing SC bioavailability data in human and corresponding preclinical species for a range of marketed mAbs.
- Excel document containing information on 26 marketed mAbs, physicochemical data, etc.
- Excel document containing PK data for the 12 therapeutic proteins described in the publication by Gill et al. (Gill et al. 2016).

Call to Action:

- Seeking to engage industry academia and government agencies to find solutions to advance capabilities in this area.
- On a case-by-case basis, access mAbs from member companies for investigations relevant to the objectives of this publication.
- On a case-by-case basis, provide letters of support for government research grants.
- Connecting researchers to other collaborators with complementary interests and capabilities that may be of mutual benefit.
- Compile any research findings on the challenge set and generate a publication after 2 years to provide an update on advances.
Summary

• Transition from IV to Subcutaneous Products is driven by patient and payer needs
• “Subcutaneous Drug Delivery & Development” Consortium formed to address known risks and gaps
• Multiple high-dose and high-volume formulation options are available to help transition your product to a more convenient patient-centric product
• The consortium has published an “open” SC bioavailability vision and challenge
Thank you
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References

- Ahil Ganesh, Carolyn Heusser, Sudhakar Garad & Manuel Sanchez-Felix, Patient-centric design for peptide delivery: Trends in routes of administration and advancement in drug delivery technologies, Medicine In Drug Discovery, 2021
