The development case
of Combination product in Japan
“Pre-filled Syringe / Auto-Injector for SC Injection”

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Outline

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- Development History in case of Chugai Product
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  - Challenge to Problems
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    - Process
    - Container & Device
    - Regulation
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    - Point to note for Development of “Combination products that correspond to drugs”
Environmental Analysis of Combination Product Development

World Trend of Parenteral Injection

Self-injection CPs such as AI and pen grow consistently. Specifically, the US market shows drastic increase in sales.

Traditionally, Japanese pharmas were reluctant to develop CPs, but these days steadily increases.
Environmental Analysis of Combination Product Development

In case of Japanese Trend of Parenteral Injection

- Some of the major drivers for the growth of combination products in the Japanese market are an increase in syringes and decrease in ampoules.
- Although shares of Pens and AIs slightly increased over the last 10 years, the shares initiated to rise recently. Specifically, AIs boosted its share in 2014.
- A combination-product development race, which has been commonly observed in the competitive market such as Rheumatoid Arthritis in the USA and Eus since 2000, just gets started in Japan,
Development History of Combination Product

**In case of Chugai Product “ACTEMRA®“**

2005, Launch First domestic antibody product
   Indication : Castleman's disease

2008, Additional indication
   Indication : Rheumatoid Arthritis (RA)

2013, Additional dosage form
   Indication : RA

2015, PFS barrel material change (glass⇒COP)
   Indication : RA

<Vial product for IV >
   antibody conc. : 20 mg/mL

<PFS product for SC >
   <AI product for SC >
   antibody conc. : 180 mg/mL

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Development for SC Injection of ACTEMRA®

Target Product Profile (TPP)

- RA is chronic disease.
- RA patient has physically disabled hands.
- IV product with long treatment time (long infusion time) become a big burden to RA outpatient.

PFS/AI are desirable for QOL improvement of RA patient.

< Target Product Profile (TPP) >

<table>
<thead>
<tr>
<th>Indication</th>
<th>Rheumatoid Arthritis (RA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage form</td>
<td>PFS, AI</td>
</tr>
<tr>
<td>Administration route</td>
<td>SC (max. 1mL)</td>
</tr>
<tr>
<td>Antibody conc.</td>
<td>min. 180mg/mL</td>
</tr>
<tr>
<td>Administration frequency</td>
<td>Once in two weeks</td>
</tr>
<tr>
<td>Quality</td>
<td>Same or better quality of IV product which already in market</td>
</tr>
</tbody>
</table>
Development for SC Injection of ACTEMRA®

Key point of Success

Stable formulation was found in high concentration of drug solution (180mg/mL).

Stable process was found in high concentration / high viscosity of drug solution (180mg/mL).

(Before amendment of the Act) License of “device marketing authorization holder” and “device manufacturer” was gotten by ourselves.

PFS & AI design was discussed with container and device suppliers, and quality improvement was achieved.
Development for SC Injection of ACTEMRA®

Challenge to Problems

1. Formulation
   - Aggregation with high conc. antibody (180 mg/mL)
     Large-scale stabilizer screening was performed, and stable formulation (same or better quality of IV product which already in market) was found.

2. Process
   - High viscosity & gelation with high conc. antibody (180 mg/mL)
     Appropriate condition was found in ultrafiltration (UF) process.

3. Container & Device
   - AI design (Quest for safety & certainty)
   - Improvement of AI injection time
   - Change of PFS Barrel Material (glass⇒COP)

4. Regulation
   - AI product (before & after change of the Act)
Challenge to Problems

Formulation Development (Overall Image)

(F1) Buffer optimization
(Species, Conc, pH)

Buffer (species, conc., pH)

(F2) Stabilizer screening
(F2-1): Main stabilizer selection
(F2-1): Subsidiary stabilizer selection

Candidate stabilizer (Arg, His, others)

(F3) Surfactant optimization
(PX188, PS20, PS80)

Surfactant (species, conc.)

(F4) Stabilizer optimization (Arg, His, etc.)
(F4-1) Optimization main stabilizer
(F4-2) Optimization of subsidiary stabilizer

Candidate formulations

(F5) Stability of candidate formulations
Challenge to Problems

Formulation Development (Example of Study Result (1))

- < Stabilizer screening using design of experiments (DoE) >

![Diagram showing stabilizer screening results with coefficients and levels of statistical significance. The main stabilizer is Arg, and the sub stabilizers are Met and Trp.]

Candidate stabilizer is selected.
Main: Arg
Sub: Met, Trp
Challenge to Problems

Formulation Development (Example of Study Result (2))

< Stabilizer optimization >

Target Quality
- Same or better stability of IV product
- Isotonicity (Osmotic pressure ratio: 1)

Challenge to Problems

Formulation Development (Example of Study Result (2))

- Only Arg: more than 300 mM (Osmotic pressure ratio: more than 2)
- Combination: Arg 100mM + Met 30 mM (Osmotic pressure ratio: 1)
**Challenge to Problems**

*Container & Device Development*

*< Composition of PFS/AI product for SC Injection of ACTEMRA®>*

![Diagram of Syringe Components]

- **Accessory**
  - Finger grip
  - Plunger rod

- **AI parts**
  - Front part
  - Rear part

**PFS product**

**AI product**
Challenge to Problems

Container & Device Development (AI design)

For self-administration of RA patient with disabled hands,

- Better grip on body and cap
- Easy cap removal

< Quest for safety and certainty >

- Needle-stick accident-protected feature
  - Injection needle is covered by safety cover when remove the cap.
  - Safety cover is locked when AI is removed from site of administration.

- Malfunction-injection-protected feature
  - Injection button will be stand by when press safety cover to site of administration. Needle is automatically stick and discharge drug solution when injection button is pressed.
<Instruction for use>

1. Ready for using auto-injector
   Remove the cap from auto-injector. Grip the body of injector firmly and lightly turn the body and pull on the side-way while touch the anti-slip area.
   Caution!: Remove the cap just before use. It is important to inject immediately after removing cap. Drug solution will be solidified when the cap is left opened.

2. Ready for Position
   Hold injection site and lift your skin to ready for position auto injector.
   Caution!: Do not hold auto injector opposite side.

3. Position
   Push auto injector firmly against your skin at 90 degree angle and hold the position until the purple safety cover disappear.
   Caution!: Do not touch or press the injection button while push auto injector against your skin. You will no be able to press the button to start your injection until push firmly against your skin at 90 degree angle.
(4) Press button
Your will hear a 1st “click” as you press the button. Automatically beginning to be delivered. Caution!: Keep holding auto injector firmly against your skin and make sure it stick to your skin.

(5) Count 15 second
Remove your finger from the injection button after press. You will hear 2nd “click”. The 2nd “click” means the lock on the safety cover and is not complete injection. Count 15 second until complete injection. Your will see the purple indicator in the view window lower down and the purple indicator will fill the viewing window.

(6) Lifting needle
After lifting auto injector from your skin, release your finger from injection site. Caution!: Used auto injector should be placed into the case and bring to your health care institution.
Challenge to Problems

Container & Device Development (Improvement of AI injection time)

Viscosity in higher due to high concentration of antibody

To improve AI injection time, overbore needle

Improvement of certainty for administration

![Graph showing the relationship between AI injection time and antibody concentration.](chart.jpg)

- **RWN**: Regular wall needle
- **TWN**: Thin wall needle

![Bar charts comparing AI injection time for RWN and TWN needles.](bar_chart.jpg)

<table>
<thead>
<tr>
<th>Needle Type</th>
<th>AI Injection Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RWN</td>
<td>20</td>
</tr>
<tr>
<td>TWN</td>
<td>15</td>
</tr>
</tbody>
</table>

RWN: Regular wall needle, TWN: Thin wall needle
Challenge to Problems

Container & Device Development (Change of PFS Barrel Material)

<Excellent feature of COP>

● Durable (high intensity)
● Lower dimensional tolerance (highly molding accuracy)
● Needle can be fixed on COP resin by itself (without glue)

PFS barrel was changed from glass to COP for safer usage.
Challenge to Problems

Regulation

< Handling of combination product with amendment of the Act>

[Application for approval of combination product] (2014/10/24 drug food review division 1024/2)

- Definition of combination product was clearly stated.
- Malfunction report is required on mechanical part of sub formation by pharmaceutical license holder.

(Quoted from the 49th General Assembly Materials of the Pharmaceutical Association of the Ministry of Health, Labor and Welfare / Pharmaceuticals Evaluation Committee PMS Subcommittee)

Combination products that correspond to drugs:
Pharmaceutical license holder is responsible for design control of mechanical part of medical device.
Challenge to Problems

Regulation (AI product: before amendment of the Act, ~2014)

**< Drug > Chugai**
- License for drug marketing authorization holder
- License for drug manufacturer
- GMP inspection for drug manufacturer

**< Device > Chugai**
- License for device marketing authorization holder
- License for device manufacturer
- QMS inspection for device manufacturer

**PMDA**
- Drug application (Brand name: ACTEMRA auto injector)
- Report of adverse drug reaction
- Report of device malfunction

**Device application** (Brand name: ACTO-Pen)

**(AI Design developer)**
**(AI parts manufacturer)**
**Supplier A**
Challenge to Problems

Regulation (AI product: after amendment of the Act, 2015~)

**< Combination Product > Chugai**
- License for drug marketing authorization holder
- License for drug manufacturer
- GMP inspection for drug manufacturer

**< Device > Chugai**
- License for device marketing authorization holder
- License for device manufacturer
- QMS inspection for device manufacturer

**Appropriate procurement control under GMP**

- **Drug application**
  (Brand name: ACTEMRA auto injector)

- **Report of adverse drug reaction**

- **Report of device malfunction**

**PMDA**

**Device application**
(Brand name: ACTO-Pen)

(AI Design developer)
(AI parts manufacturer)
Supplier A

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Look back to development

Point to note for Development of “Combination products that correspond to drugs”

< Pharmaceutical license holder point of view >
Pharmaceutical license holder is responsible for design control of mechanical part of medical device. This means we need to catch up regulatory requirement of PFS & device in order to get approval.

Very important !!
Relationship with PFS & device supplier

Very important !!
Relationship with PFS & device supplier to achieve patient-oriented design.

Very important !!
Relationship with PFS & device supplier for maintenance and improvement of product quality after launch.
Thank you very much !!

Innovation all for the patients

CHUGAI PHARMACEUTICAL CO., LTD.

A member of the Roche group