1) Process Chemistry generally refers to the design and development of synthetic routes for the chemicals, in particular pharmaceutical relevant molecules, which ultimately be applicable to manufacturing on commercial scale. Providing material to enable clinical development and Accumulating process chemistry knowledge set the general framework upon which process chemists balance and prioritize their researches.

2) Strategies for Early and Late Stage Drug Development

<table>
<thead>
<tr>
<th>Early stage</th>
<th>Late stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40-60 kg</td>
<td>&gt;100 kg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Technology development Speed</th>
<th>Cost, throughput</th>
</tr>
</thead>
<tbody>
<tr>
<td>High quality →</td>
<td></td>
</tr>
</tbody>
</table>

3) SELECT Criteria for Process Assessment

<table>
<thead>
<tr>
<th>criteria</th>
<th>subcriteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>process safety (explosions or exotherms)</td>
</tr>
<tr>
<td></td>
<td>exposure to substances harmful to health</td>
</tr>
<tr>
<td>Environmental</td>
<td>volume of wasted natural resources</td>
</tr>
<tr>
<td></td>
<td>substances harmful to the environment</td>
</tr>
<tr>
<td>Legal</td>
<td>infringement of intellectual property rights</td>
</tr>
<tr>
<td></td>
<td>regulations that control use of reagents and intermediates</td>
</tr>
<tr>
<td>Economics</td>
<td>meeting cost of goods target for future market</td>
</tr>
<tr>
<td></td>
<td>investment costs to support development quantities</td>
</tr>
<tr>
<td>Control</td>
<td>control of qualities</td>
</tr>
<tr>
<td>Throughput</td>
<td>time scale of manufacture in available</td>
</tr>
<tr>
<td></td>
<td>availability of raw materials</td>
</tr>
</tbody>
</table>

4) Latest topic

- Establishment of regulation about qualities
  - Most important: quality control
- Acceleration
  - Fast track
  - Breakthrough therapy
  - Priority Review
  - Accelerated Approval
  - Shorten time from clinical trial to market.

5) Agenda of this meeting

- Considerations
- Safety
- Quality management
- Speed up strategy
- Manufacturing of high molecular comp.

6) Topics not covered

- Basic knowledge in detail
- PAT/Kinetics
- DOE (design of exp.), Design space
- Polymorph, GMP
1. Practical Considerations for Process Research

Convergent/linear route

\[ A \rightarrow B \rightarrow C \rightarrow D \rightarrow E \rightarrow F \rightarrow G \rightarrow H \]

Convergent benefit
- Yield (90% each) linear 48%, Conv. 66%
- Save the cost / shorten the lead time

Choose the reagents/solvent
- Consider the following things: toxicity, side reactivity, expense, availability, consistency between lots, stability, robustness, work-up/quench issues, specialized equipment, solubility.

- Solvents avoided: pentane, \(\text{Et}_2\text{O}\) (low fp), \(\text{CHCl}_3, \text{CCl}_4\) (non environmentally friendly), DCE, \(\text{PhH}\), dioxane (carcinogenic), \(\text{MeNO}_2\) (high decomposition energy)

Sanofi solvent selection

![Sanofi solvent selection table](image)

Reaction
- To remove oxygen: sparge with \(\text{N}_2\).
- Acceptable temperature range: \(-40\) to \(120^\circ\text{C}\).

Workup
- Avoid using solid desiccants, azeotrope instead.
- Concentration to dryness is rarely performed, normally solvents are change concentration/add solvent repeatedly.

Purification
- Determine the required number and amounts of washes, extractions, etc.
- Avoid column chromatography.
- Consider using activated carbon plugs to remove polar impurities.

(\text{Richer 2006}, excerpt)

2. Safety

2-1 Scale effect
- Reactions requiring anything "rapid" are difficult to perform.
- Be aware of potential mixing/reaction/quench exotherms.
- May require slower additions, or reflux to absorb the exotherm.

2-2 Highly Exothermic Reaction (Braise Reaction. Merck \textit{OPRD 2013}, 17, 1611.)

\[
\text{R-CN} + \text{Br-} \overset{\text{Zn, TMSCl}}{\text{THF, reflux}} \rightarrow \text{R-} \overset{\text{aq. H}_2\text{SO}_4}{\text{OEt}}
\]

If bromoester is added rapidly, this reaction can be easily reproduced, but Adiabatic \(\Delta T (\Delta T_{ad})\) up to \(200^\circ\text{C}\) (delayed and autocatalytic initiation)

For prevent an overly vigorous delayed initiation:

- 3% of the acetate
- 7% of the acetate
- 30% of the acetate

Do not add more acetate until confirming the desired reaction started.

For deployment at manufacturing scale, investigate use of online instrumentation to monitor the reaction. (PAT)

2-3 Exothermic decomposition

\[
\text{DSC}
\]

This case: >800 J/g

Need to Safety assessment
Safety assessment

For decreasing criticality
- Run the reaction more dilute to decrease MTSR.
- Solvent change (change the MTT)
- Charge the reagents in dosing/several portions (control MTSR)

NBS/DMF OPRD 2014, 18, 354.
Not only NBS, but also DBDMH/DMF: onset 99°C Δ26°C

NaH/DMF (Bretherick’s Handbook of Reactive Chemical Hazards)
Onset 50°C, increased up to 75°C
Plant scale: onset 40°C, increased up to 100°C in 10 min.

2-4 Shock Sensitive

Formation of diazidemethane: After the first step, the CH₂Cl₂ solution was “evaporated away” with DMF at 35°C and 20 torr. After the workup of the next step, a liquid had condensed inside the rotary evaporator, which exploded when a chemist was trying to take it out.

Caution!! HN₃ (hydrogen azide) bp 37°C, explosion occurred at rotovaps/mechanical stirrer.

2-5 Oxygen oxidation

Mixtures of oxygen gas and organic solvents often create flammable atmosphere.

Iron Negishi Coupling with RAEs (JACS 2016, 138, 11132.)
Decomp onset 160°C → Develop alternative chemistry. Merck, OPRD 2013, 17, 1611.
3. Quality of new drug products

3-1 Impurities in new drug products (ICH Q3A)

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Concentration limit (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>2</td>
</tr>
<tr>
<td>Carbon tetrachloride</td>
<td>4</td>
</tr>
<tr>
<td>1,2-Dichloroethane</td>
<td>5</td>
</tr>
<tr>
<td>1,1-Dichloroethene</td>
<td>8</td>
</tr>
<tr>
<td>1,1,1-Trichloroethane</td>
<td>1500</td>
</tr>
</tbody>
</table>

3-2 Residual Solvents (ICH Q3C) ppm/10 g mass

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Concentration limit (ppm)</th>
<th>Concern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetone</td>
<td>410</td>
<td>Hexane</td>
</tr>
<tr>
<td>Chlorobenzene</td>
<td>360</td>
<td>Methanol</td>
</tr>
<tr>
<td>Chloroform</td>
<td>60</td>
<td>2-Methoxyethanol</td>
</tr>
<tr>
<td>Cumene</td>
<td>70</td>
<td>Methylcyclohexane</td>
</tr>
<tr>
<td>Cyclohexane</td>
<td>3880</td>
<td>N-Methylpyrrolidone</td>
</tr>
<tr>
<td>Dichloromethane</td>
<td>600</td>
<td>Nitromethane</td>
</tr>
<tr>
<td>1,2-Dichloroethene</td>
<td>1870</td>
<td>Environmental hazard</td>
</tr>
<tr>
<td>1,1-Dimethoxyethane</td>
<td>100</td>
<td>Pyridine</td>
</tr>
<tr>
<td>N,N-Dimethylethamide</td>
<td>1690</td>
<td>Sulfolane</td>
</tr>
<tr>
<td>N,N-Dimethylformamide</td>
<td>880</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>1,4-Dioxane</td>
<td>350</td>
<td>Tetrathialin</td>
</tr>
<tr>
<td>2-Ethoxyethanol</td>
<td>160</td>
<td>Toluene</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>620</td>
<td>1,1,2-Trichloroethane</td>
</tr>
<tr>
<td>Formamide</td>
<td>220</td>
<td>Xylene</td>
</tr>
</tbody>
</table>

3-3 Elemental Impurities (ICH Q3D)

<table>
<thead>
<tr>
<th>Element</th>
<th>Class</th>
<th>Oral PDE mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cr</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Pb</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>As</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Hg</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td>Co</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>V</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Ni</td>
<td>2</td>
<td>200</td>
</tr>
<tr>
<td>Ti</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Au</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Pd</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Ir</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Os</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Rh</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Ru</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Sc</td>
<td>2</td>
<td>150</td>
</tr>
<tr>
<td>Ag</td>
<td>2</td>
<td>150</td>
</tr>
<tr>
<td>Pt</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Li</td>
<td>3</td>
<td>550</td>
</tr>
<tr>
<td>Sb</td>
<td>3</td>
<td>1200</td>
</tr>
<tr>
<td>Ba</td>
<td>3</td>
<td>1400</td>
</tr>
<tr>
<td>Mo</td>
<td>3</td>
<td>3000</td>
</tr>
<tr>
<td>Cu</td>
<td>3</td>
<td>3000</td>
</tr>
<tr>
<td>Sn</td>
<td>3</td>
<td>6000</td>
</tr>
<tr>
<td>Cr</td>
<td>3</td>
<td>11000</td>
</tr>
</tbody>
</table>

Permitted Daily Exposure: The maximum acceptable intake of elemental impurity in pharmaceutical products per day.

We need to control their impurities amounts.

We need to consider solvent in final several steps.
3-5 Control impurities (example)

**Merck OPRD 2015, 19, 1531.**

![Chemical reactions and structures](image1)

**Pfizer OPRD 2014, 18, 45.**

![Chemical reactions and structures](image2)

**TTC 20 µg/300 mg = 67 ppm**

**All of pMIs were controlled less than 20 ppm**

**Treatment of Hepatitis C virus**

300 mg/day (1-12 months)

Filibuvir

Slow (semi-batch) addition of β-keto-lactone 2 over 4 h to a slurry of aldehyde 3 and Hantzsch ester (HEH) 12 provided a dose-controlled reaction (in situ yield >95%).

GSK OPRD 2010, 14, 1254.

![Chemical reactions and structures](image3)

**Safety, cost, and sourcing issue**

**Unexpected impurity**

**Alternative route**

**Thermal decomp**

**GSK923295A**

R = Cl, OCl, CH₃NMe₂

**Unsociated impurity**

Sarcosine
4. Shorten time from clinical trial to market.

Ex)
Breakthrough therapy

Figure 2  Time to market for agents with breakthrough drug designation compared with a recently approved agent (Kryprolis) without breakthrough status designation. Kryprolis is included for comparison as it was approved at approximately the same time through the accelerated approval designation for a cancer indication (multiple myeloma). SLL, small lymphocytic leukemia. (Source: Kanter Health)

Timeline

Early  Process Research  Late

4-1 Strategy: Acceleration of research

➢ High-throughput Experimentation (HTE)

Initial Synthesis 1-8 x 9-20, 25 mg scale

Route Scouting 0.02 mg/reaction

After Screening 1-8 x 9-20, 25 mg scale

Scale*  HPLC conv.  Yield
0.02 mg  >95%  N/A
25 mg  >95%  79%
1.0 g  >95%  76%

➢ Comprehensive study
➢ Optimization using small amount of starting material

Merck Science 2015, 347, 49.

4-2 Strategy: Shortening of facility design/built

➢ Process design that adapted to the facility

➢ Continuous flow

+ no need to scale up

Filter/dryer

crystallizer

Jamison, T with Novartis Science 2016, 352, 61.

Principal Component Analysis (PCA)

+ Chemoinformatics
Statistically approach
+ Comprehensive study

Structure vs Reaction


Murray, P. OBC. 2016, 14, 2373.
### 5. Diversity

<table>
<thead>
<tr>
<th>Molecular size</th>
<th>Route of Administration</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 kDa</td>
<td>Oral</td>
<td>Do not bind to most PPI targets</td>
</tr>
<tr>
<td>1 to 3 kDa</td>
<td>Oral or Injectable</td>
<td>High potency &amp; selectivity against PPI target</td>
</tr>
<tr>
<td>150 kDa</td>
<td>Injectable</td>
<td>Expensive &amp; inconvenient to administer</td>
</tr>
</tbody>
</table>

**Manufacturing difficulties**

1. Preparative chromatography
2. **Oligonucleotide** solid-phase synthesis (excess of the expensive monomers, loading amount, highly mass-intensive)
3. **ADC** heterogeneous ADCs: non-selective DAR (drug/antibody ratio)

### 5-1 Modified Peptide

*Oprd 2014, 18, 725*

1. **extraction** (van der Marel, Oprd 2006, 10, 1238)
2) Precipitation (Eur. JOC 2013, 6687)

3) Membrane separation (GSK, OPRD 2016, 20, 1439)
5-3 ADC (Igenica, OPRD 2016, 20, 852)

A type of antibody
more than 50 lysines
up to 12 cysteine

**Kadcyla**
from 0 to 10 drug/antibody
(average DAR 3.5)

![Lysine Conjugation](image)

**Cysteine Conjugation**
from 0 to 8 drug/antibody
(average DAR 3.6)

- Homogeneous ADCs via Cysteine Cross-Linking
(Igenica, Mol. Pharm. 2015, 12, 3986)
Ames test procedure

**Salmonella** strain (requires histidine)

- Rat liver extract
- Possible mutagen
- Plate
- Incubate
- Media with minimal histidine
- Plate
- Incubate
- Control plate (natural revertants)

A high number of revertants (his- to his+) suggests the mutagen causes mutations.

Chemical structures:

- **DIAION HP20SS**
  
- **SEPABEADS SP207SS**

---

**Wikipedia**