Accelerated CMC Development
A Primer

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Drug Development

Pre-Clinical Development

Phase I

Phase II

Phase III

Phase IV

Life-cycle mgmt.

IND

EOP2

BLA/NDA

Development

Optimization

Validation

0.5yr

2-4 yrs

4-6 yrs

~ 1yr

3-5 yrs

Accelerated Drug Development

CASSS REGIONAL FORUMS
Accelerated CMC Development

• Why
  – Unmet medical needs, e.g. rare diseases, many oncology indications
  – Urgent crisis e.g. Ebola outbreak

• Approach
  – Need to develop strategies to accelerate CMC work to support these cases
  – Acceptable if non-clinical and clinical trials are being done concurrently at same pace
  – Regulatory pathways to support accelerated development available in several countries
## Regulatory Pathways - FDA

<table>
<thead>
<tr>
<th>Programs</th>
<th>Qualification Criteria</th>
<th>Year First Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast Track</td>
<td>A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address unmet medical need OR A drug that has been designated as a qualified infectious disease product</td>
<td>1997</td>
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<tr>
<td>Breakthrough Therapy</td>
<td>A drug that is intended to treat a serious condition AND preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies</td>
<td>2012</td>
</tr>
<tr>
<td>Accelerated Approval</td>
<td>A drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint(^2) or an intermediate clinical endpoint(^3)</td>
<td>1992</td>
</tr>
<tr>
<td>Priority Review</td>
<td>An application (original or efficacy supplement) for a drug that treats a serious condition AND, if approved, would provide a significant improvement in safety or effectiveness Take action on an application within 6 months (compared to 10 months under standard review)</td>
<td>1992</td>
</tr>
</tbody>
</table>


\(^2\)A laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit

\(^3\)Measure of a therapeutic effect that is considered reasonably likely to predict the clinical benefit of a drug, such as an effect on irreversible morbidity and mortality (IMM), enacted with FDASIA 2012
## Regulatory Pathways- Europe (EMA)

<table>
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</table>
| PRIME                         | A major public health interest, unmet medical need
Dedicated and reinforced support                                                                                                                                                                                      | 2016                 |
| Accelerated Assessment        | A major public health interest, unmet medical need
Reduce assessment time to 150 days compare to 210 days                                                                                                                                                               | 2016                 |
| Adaptive Pathways             | Scientific concept of development and data generation
Iterative development with real-life data
Engagement with other healthcare-decision makers                                                                                                                                                                      | 2014                 |
| Conditional Marketing Authorization | An unmet medical need, seriously debilitating or life-threatening disease, a rare disease or use in emergency situations
Early approval of a medicine on the basis of less complete clinical data                                                                                                                                              | 2006                 |
| Compassionate Use             | A life-threatening, long-lasting or seriously debilitating illness which can not be treated satisfactorily with any current authorized medicine                                                                            | 2014                 |

Accelerated Regulatory Pathways - UK

EAMS: Early Access to Medicines Scheme (2014)

• PIM: Promising Innovative Medicine designation

• Scientific Opinion

https://www.gov.uk/guidance/apply-for-the-early-access-to-medicines-scheme-eams
Accelerated Regulatory Pathway- Japan

• 先駆け (SAKIGAKE) = Forerunner or Pioneer

• The MHLW drew up the “Strategy of SAKIGAKE” to lead the world in the practical application of innovative medical products in 2014.

• Designation criteria for SAKIGAKE designation system
  – Medical products for diseases in dire need of innovative therapy
  – Development & NDA in Japan being world’s first or simultaneous with other countries
  – Prominent effectiveness expected on non-clinical and early phase clinical trials
Accelerated Regulatory Pathways-Other countries

• Other countries are also developing similar pathways (eg., Kingdom of Saudi Arabia Verification/Abridged Route)

• All of these share similar characteristics
  – Accelerated review(s)
  – Frequent meetings with agencies
  – Potential for rolling review of submission(s)
  – Opportunities to discuss accelerated CMC development strategies
Accelerated CMC Development

• All of these regulatory strategies require an accelerated CMC strategy (see later talks)
• CMC must not be on the critical path, but must be able to deliver consistent, reliable, and safe products from early clinical trials through market launch
• Various ways to improve CMC Development

Timelines are accelerated, but there is no lowering of the bar for identity, quality, strength, purity of drug product
Strategies and Tactics to accelerate CMC Development (1 of 2)

• Use prior knowledge and/or existing platforms or processes already in place for earlier products
• Develop and validate methods and assays (esp. bioassays) early in process
• Develop specifications early based on limited batches
• Scale up to “reasonable” level quickly
  – Some of these products will not require large scale early since they may have limited populations to treat
• Use existing facility and/or CMO with minimal change to facility and/or process
• Engage agencies early in CMC issues arise
• Final drug product and formulation might be less than optimal for typical drug (i.e., shorter shelf-life, less convenient dosing, etc.) in order to meet rapid development timelines
Conclusions

• Accelerated clinical programs require re-thinking of CMC development process
• CMC must not be on critical path for development
• Engage agencies early and often to ensure acceptable CMC development to support both clinical and final NDA/BLA approval