Clinical Drug Development: Challenges and Opportunities

Yale OCR YSIF Workshop
Susan Kelley MD
November 12 2020
Agenda

1. Overview of drug development process, metrics and costs
2. Clinical development and FDA interactions
3. Current mechanisms for expediting drug development/regulatory approval
4. Essentials of trial planning and strategies to increase success rates
Drug Research & Development: High Risk and Expensive

The reality:

• Pharma company expenses to move one drug through R & D to market = $2.6 billion (includes costs of failures). Global BioPharma 2018 spend on drug development = $102 billion

• Investment of $30-40 million per drug from preclinical studies through small phase II trials

• 10-15 years for a new drug candidate to progress from discovery lab through patient testing to regulatory approval and marketing

• Five of 5,000 compounds (0.1%) that enter preclinical testing go onto early stage human trials

• Overall success rate from start of clinical trials to regulatory approval ~ 10-15%; lower for cancer and neurodegenerative diseases

• Global R&D pipeline ~ 16,000 new molecular entities: 4500 in preclinical development (2019)

• ~800 small molecules, antibodies/proteins or vaccines in some phase of development for oncology by Pharma/ Biotech companies


Tufts CSDD, PhRMA 2019, CenterWatch, FDA.gov
Drug Development Time and Cost

Overview of the process of drug discovery and development, costs (time/money) estimated
Overall Clinical Trial Success Rates 2005-2015

Wong et al. Estimation of clinical trial success rates and related parameters. Biostatistics Jan 2018
Clinical Drug Development Success by Therapeutic Area

Trials sponsored by Biopharma companies January 2000-October 2015

<table>
<thead>
<tr>
<th>TA</th>
<th>Ph1 to Ph 2 (%)</th>
<th>Ph 2 to Ph 3 (%)</th>
<th>Ph 3 to Approval (%)</th>
<th>Overall (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>58%</td>
<td>33%</td>
<td>36%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Metabolic/ CV</td>
<td>76</td>
<td>60</td>
<td>52</td>
<td>20</td>
</tr>
<tr>
<td>CNS</td>
<td>73</td>
<td>66</td>
<td>62</td>
<td>26</td>
</tr>
<tr>
<td>Autoimmune/ Inflammation</td>
<td>70</td>
<td>46</td>
<td>64</td>
<td>15</td>
</tr>
<tr>
<td>GU</td>
<td>69</td>
<td>46</td>
<td>66</td>
<td>22</td>
</tr>
<tr>
<td>ID</td>
<td>70</td>
<td>58</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>Overall</td>
<td><strong>66</strong></td>
<td><strong>58</strong></td>
<td><strong>59</strong></td>
<td><strong>14</strong></td>
</tr>
<tr>
<td>Overall w/o Oncology</td>
<td>73</td>
<td>27</td>
<td>64</td>
<td>21</td>
</tr>
</tbody>
</table>

Wong et al. Biostatistics, Jan 2018
### FDA New Molecular Entity (NME) Approvals

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
</tr>
</thead>
<tbody>
<tr>
<td># Novel NME Approved</td>
<td>59</td>
<td>48</td>
<td>~42 as of 10/22/20</td>
</tr>
<tr>
<td># Pts in Trials Supporting Approval</td>
<td>43996</td>
<td>46391</td>
<td></td>
</tr>
<tr>
<td>Female %</td>
<td>56</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>White Non- Hispanic %</td>
<td>69</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Black %</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Asian %</td>
<td>10</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Hispanic %</td>
<td>14</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 65 y %</td>
<td>15</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>US patients %</td>
<td>47</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

- NME = first NDA (small molecule) or BLA (biologics) approval for a drug at US FDA
- Data from FDA through Oct 2020
## FDA New Molecular Entity Approvals by Therapeutic Area

<table>
<thead>
<tr>
<th>Therapeutic Areas</th>
<th>2018 N=59 NME approvals</th>
<th>2019 N=48 NME approvals</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncology</td>
<td>17 NME (5157 pts) 36% US pts</td>
<td>11 NME (3593 pts) 24% US pts</td>
<td>2019: 73% pts in registration trials non-Hispanic white</td>
</tr>
<tr>
<td>Neurology</td>
<td>8 NME (7404 pts)</td>
<td>6 NME (10390 pts)</td>
<td>2019: 70% US pts</td>
</tr>
<tr>
<td>Inf Dz</td>
<td>11 NME (12404)</td>
<td>4 NME</td>
<td>2019: 2-4% US pts</td>
</tr>
<tr>
<td>Psychiatry</td>
<td>5 NME (3645 pts)</td>
<td></td>
<td>2019: 70% US pts</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td>6 NME (1255 pts)</td>
<td></td>
</tr>
</tbody>
</table>

- NME = first NDA (small molecule) or BLA (biologics) approval for a novel drug at US FDA
- Data from FDA Feb 2020
Clinical Trial Phases
Phase 0 Clinical Trials

• “Exploratory IND” studies with specific FDA guidance document
• First in human studies utilizing a very low dose and/or low number of doses of an investigational drug per subject
• Demonstrate that the drug is reaching its target, has a desired metabolic profile or is able to be absorbed using the formulation to be tested
• Generally no chance that the subject will derive any clinical benefit from exposure, but risk of toxicity is very low
• Require biopsies, PK sampling of blood or tissue, and other assessments to demonstrate targeting and preliminary proof of mechanism
• Not suitable for all drugs or disease entities
Phase I Clinical Trials

• First in human study: Slowly escalate the dose in healthy subjects (volunteers) or in target disease patients; starting dose and dosing schedule based on preclinical efficacy and toxicology studies

• Objectives:
  – Determine “Maximum Tolerated Dose”
  – Define “Optimal Biologic Dose” for use in subsequent trials
  – Define “Dose Limiting Toxicities” and adverse event profile
  – Determine pharmacokinetics/metabolism of the drug in humans
  – Optimize schedule of dosing
  – Explore preliminary clinical activity
  – Explore biomarkers for patient subsets most likely to respond to treatment

Design Phase I to support GO/ NO GO decision on further clinical development- aim to demonstrate safety, proof of mechanism, early evidence of biologic and clinical activity and recommended dose for Phase II
Phase II Clinical Trials

• Confirm dose tolerability and dosing schedule from Phase I; generate clinical efficacy data to support predefined GO/ NO GO Criteria to Phase III

• For Oncology Proof of Concept: establish activity in specific tumor type(s)
  – Randomized Phase II in oncology important for signal confirmation

• For other therapeutic indications, Phase II will utilize standard endpoints for disease efficacy, often randomized with several dose levels versus comparator

• In non-oncology indications, randomized phase II trials explore efficacy of different dose levels against a comparator and determine phase III dose

• Confirm biomarker subsets of patients to define optimal population for Phase III

Remarkable results in phase II oncology trials may support accelerated regulatory approval in area of high unmet medical need
Phase III Clinical Trials

- Large multicenter trials designed to gather definitive evidence for effectiveness and safety of a drug in a specific patient population.
- If trial(s) intended for regulatory filing for commercial approval, design and plan must be reviewed in detail with health authorities before study start.
- If the data are accepted by the regulatory authorities for registration, the product labeling reflects only the patient population included in the phase III trial.

Design phase III trials to optimize chances of attaining the goals of the Target Product Profile
Phase IV Clinical Trials

- Post-approval/post-marketing studies
- Post marketing safety surveillance for low frequency toxicities
- Same general indication as approved label; expanded treatment groups, understudied groups
- Generally not randomized
- Part of publication strategy or to obtain additional safety experience required by health authorities
Regulatory Authority Interactions During Drug Development
Regulatory Processes in Major Regions


- **US**= one agency, FDA. Typical review times for NDA 10 months for standard review, 6 months for priority review. Various acceleration paths.

- **EU** = two agencies, EMA (administrative) and CHMP (scientific). Review time for centralized MAA 210 days with several clock stops possible. After approval, negotiation with individual country reimbursement agencies will determine pricing.
US FDA Regulatory Terminology

• IND=Investigational New Drug: Granted by US FDA as an exemption to allow transportation of a non-marketed drug across state lines for investigational use in humans.

• NDA= New Drug Application: filing for registration and commercial sale of a drug for a new treatment indication.

• BLA= Biologics Licensing Application: filing for registration and commercial sale of a biologic agent for a new treatment indication.
Sponsor- FDA Interactions During Drug Development

- **Pre-IND meeting**: prior to any human testing, present clinical development plan and initial phase I study design
- **End of phase I meeting**: review dosing and safety data and proposed development plan
- **End of phase II meeting**: obtain feedback on registrational, phase III plans and proposed indication/label
- **Pre-NDA meeting**: review top line data from phase III and filing plans for registration
- **Interim meetings** as needed to obtain guidance for specific issues in drug development
- **Most meetings conducted** via teleconference or with request for Written Response Only
## FDA Meetings During Drug Development

<table>
<thead>
<tr>
<th>Meeting Type</th>
<th>FDA Response Time</th>
<th>Meeting Scheduling Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>14 days</td>
<td>30 days</td>
</tr>
<tr>
<td>B</td>
<td>21 days</td>
<td>60 days</td>
</tr>
<tr>
<td>B (EOP)</td>
<td>14 days</td>
<td>70 days</td>
</tr>
<tr>
<td>C</td>
<td>21 days</td>
<td>75 days</td>
</tr>
</tbody>
</table>

**Type A:** dispute resolution for stalled projects  
**Type B:** PreIND, PreEUA, Pre NDA, Risk mitigation plans, Clinical development plans for drugs with Breakthrough Designation  
**Type B (EOP):** End of Phase 1, 2; PrePhase 3  
**Type C:** neither type A nor B. Development plans for biomarkers, alternate study plans, etc.
For marketing approval in the US:

- **Two** well-controlled randomized controlled trials with at least 80% power to demonstrate the advantage offered by the new treatment (p value <0.05 each). Single trial may be acceptable with very robust results and generally 90% power and p value <0.01 (strength of evidence of two trials).
- Acceptable “validated” endpoints for demonstration of clinical benefit: overall survival benefit preferred as “gold standard” or meaningful improvement in patient symptoms in a Quality of Life instrument.
- For Oncology, other endpoints such as Response Rate, PFS, or improvement in a tumor marker are generally considered “surrogate endpoints”. FDA will consider it a “review issue” whether the data are robust enough to support demonstration of “meaningful clinical benefit” for drug approval.
Current Mechanisms for FDA Expedited Drug Development/Approval

• Fast Track

• Accelerated Approval

• Priority Review

• Breakthrough Therapy Designation
Fast Track

- Introduced in FDAMA 1997; modified in FDASIA 2012

- FDA will respond to application for designation within 60 calendar days

- Qualifying Criteria:
  - A drug that is intended to treat a serious condition AND nonclinical or clinical data demonstrate the potential to address an unmet medical need
  - OR
  - A drug that has been designated as a Qualified Infectious Disease Product

- FDA will take actions to expedite development and review including rolling submission of regulatory approval application modules
Accelerated Approval

• Legislation per 21 CFR part 314 subpart H: introduced in 1992 for AIDS therapies; approval based on preliminary clinical data in diseases that have significant morbidity and mortality and lack adequate treatment options (unmet medical need)

• Requirements (apply to all therapeutic areas):
  – Treats a serious condition AND
  – Generally provides a meaningful advantage over available therapies AND
  – Demonstrates effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict a drug’s clinical benefit

• Post-approval Commitments:
  – Confirmatory Phase III trials to verify anticipated effect using validated endpoints
  – Subject to expedited withdrawal if benefit/risk not confirmed

• 198 accelerated approvals granted by FDA as of June 2019

Cox et al. Clin Transl Sci 2020
Priority Review

• Designation request with filing of original NDA
  – FDA responds within 60 days of receipt of request

• Provides shorter clock for review of marketing application
  – 6 months from acceptance of filing for review, compared with standard 10 months review time

• Requirements to request priority review:
  – Serious condition and, if approved, would provide a significant improvement in safety or effectiveness
  – OR
    • Qualified Infectious Disease Product (QIDP)
    • Priority review voucher from previous Breakthrough Designation
Breakthrough Therapy Designation


• Designation process
  – Request with IND or after; ideally no later than pre-NDA/BLA meeting
  – FDA will respond within 60 calendar days

• Qualifying Criteria
  – 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

• Benefits- FDA will provide “intensive guidance” on efficient drug development to include rolling review and other actions to expedite review.
Purpose: To provide incentives for the development of therapeutics for the treatment of rare diseases that would normally be unprofitable or unpatentable. Definition: US prevalence <200,000 cases

Incentives for Sponsors:
- Reduced regulatory fees
- Tax credit of up to 50 percent of clinical development costs
- Seven years of US market exclusivity in the approved indication (10 years exclusivity in EU)
Orphan Drug Designation Impact


- 6,000 of 7,000 human diseases meet rare disease criteria

- 1983-2019: >6800 orphan drug designation requests to FDA, of these about 5000 granted orphan status

- 1983-2019: about 800 orphan products have received FDA marketing approval for use in rare diseases

- In 2019, 21 of the 48 NME approvals at CDER were for orphan drugs

- Advances in research on Rare and Neglected Diseases suggest potential drug targets of therapeutic value

- Collaborative efforts and novel funding/investment structures needed to convince industry to invest in many of these diseases

www.fdalawblog.net
So--- how can we increase success rates in *Clinical Drug Development and Clinical Trials*?

Clinical Development Success Factors

- Target Product Profile
- Clinical Trial **Design** Success Factors
- Clinical Trial **Conduct** Success Factors
# Target Product Profile - Template

<table>
<thead>
<tr>
<th>Product Properties</th>
<th>Minimum Acceptable Result: Base Case</th>
<th>Ideal Result: Upside Case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Indication</td>
<td>Specific patient subset</td>
<td>Broad patient group</td>
</tr>
<tr>
<td>Patient Population</td>
<td>Labeled indication</td>
<td>Expanded label indication</td>
</tr>
<tr>
<td>Dose Route</td>
<td>SQ, IV, PO, transdermal depends on chemical properties of molecule</td>
<td></td>
</tr>
<tr>
<td>Dose Schedule/regimen</td>
<td>Multiple daily doses</td>
<td>Once daily dosing</td>
</tr>
<tr>
<td>Efficacy</td>
<td>% improvement over SOC to attain significance, meets GO/NO criteria</td>
<td>% improvement exceeds SOC to a more clinically meaningful result</td>
</tr>
<tr>
<td>Safety Profile</td>
<td>Equivalent or somewhat better than SOC</td>
<td>Superior to SOC, best in class safety profile</td>
</tr>
<tr>
<td>Potential for regulatory approval and commercial success</td>
<td>Major Region</td>
<td>Global</td>
</tr>
</tbody>
</table>

Carefully vet the product profile with all stakeholders; Identify Unique Selling Potential; Use TPP as a guide to all clinical plan decisions
Critical Clinical Trial Design Success Factors

- Select patient population to match Target Product Profile
- Clinical trial endpoints must be meaningful to clinical advisors and acceptable to FDA
- Incorporate pharmacokinetic, pharmacodynamic and/or biomarker analyses to strengthen activity signals emerging from early trials
- Use molecular markers as inclusion criteria to enrich for patients most likely to show benefit
- Be realistic about the size and design of study that is practical to complete in a patient group in a reasonable time period: write the simplest protocol possible
- Define statistical power and hypotheses in advance-create a Statistical Analysis Plan for each protocol
Success Strategies in Clinical Trial Conduct (I)

To increase success, save time and manage resources in clinical drug development:

• Select Clinical Advisors and KOLs carefully; engage them actively in study design process

• Select Investigators carefully

• Careful CRO selection and contract negotiation

• Conduct trial feasibility and competitive trial analysis at proposed clinical sites

• Write the simplest protocol possible; Simplify CRF design to capture only critical and required data

• Follow FDA guidance on risk based monitoring--use remote data monitoring to save time and cost

• Use a Clinical Trials Management System vendor; use social media to recruit subjects
To increase success, save time and manage resources in clinical drug development:

• Explore collaborations as risk sharing strategies: NIH cooperative groups, trial consortia, patient advocacy groups, FDA Rare Diseases Grants

• Utilize Data Safety Monitoring Committees as independent reviewers during study conduct

• Global vs regional trial: cost benefit analysis needed

• Standard contracting and budget whenever possible

• Central IRB whenever possible

Set realistic timelines for trial activation, accrual and completion-- and manage expectations carefully!
Involve Collaborators in Clinical Development to Increase Success Rates and Decrease Trial Costs and Duration
Advantages of Patient Advocacy Participation in R&D

• Ensure that goals of patients are kept in forefront

• Ensure patient-friendly trial designs

• Increase patient awareness and accrual to trials: many advocacy groups have Clinical Nurse Navigators to aid patients in trial identification

• Increased credibility and transparency from partnership

• Important presence and influence in discussions with FDA

• Venture philanthropy and financial support by non-profit advocacy groups becoming more common
Thank you for your attention and dedication to bringing new therapies forward!