Session Deliverables

• Defining Unmet Need
  • Brief Drug Development/Regulatory History (US focus)
    • Era of “safety”
    • Drugs must be “safe and effective”
    • Emerging science
      • Observation, opportunity and luck – e.g. penicillin
      • Receptor science
      • Age of the human genome project

• What is An Unmet Need?
Session Deliverables, Continued

• **Stakeholders in “need equation”**
  - Health care providers
  - Patients
  - Regulators
  - Payors – Insurance companies, managed care, governments
  - Pharmaceutical companies – large and small

• **Criteria for Identifying a Marketable Product**
  - The “Target Product Profile”

• **Questions**
  - But feel free to ask along the way
Brief History of the “Game”

- FDA founded to make sure drugs are safe
  - Contamination/death – sulfonamide antibiotic
  - The era of serendipity – penicillin
- Thalidomide Happens
  - The Kefauver Hearings, 1962
  - Focus on efficacy and safety
  - The era of the “receptor” – the benzodiazepines, the serotonin antagonists, the histamine H2 and proton pump antagonists, the SSRIs
- PDUFA (Prescription Drug User Fee Act) – 1992
  - Statutory attempt to accelerate drug approvals
  - The era of the genome
    - “individualized” or segment based medicines
    - Risk vs benefit
    - Gleevec
What is an “Unmet Need”?

- **Cure**
  - Ultimate result – as Dr. Shlevin noted, rarely found
    - Antibiotics
  - Market home run – yes or no?
  - Regulatory, other stakeholder impact – big win

- **“Prevent”**
  - In Pharma industry:
    - Vaccines
    - Drugs, that, e.g.
      - Decrease BP – prevent stroke, MI; decrease cholesterol, prevent CAD; remove beta amyloid from brain, prevent Alzheimer’s
    - If safe, important result – can lead to difficult clinical program
    - Win for regulators and other stakeholders
Unmet Need, continued

- “Treat”
  - Most common paradigm
  - Pure risk vs. benefit
    - Benefit often “in eye of beholder”
    - “Benefit” has therapeutic and financial dimensions
  - Price and therefore revenue driven by, among other things
    - Novelty
    - Acuteness of need (e.g. effective cancer drug)
  - Benefit vs risk (does effectiveness overcome safety concerns, e.g. TNF antagonists in RA)
Unmet Medical Need for Pharma Company

- “Need” for company depends on size, maturity, stage of company
  - Large pharma product need has to generate large revenue, to satisfy shareholders and pay for costs of selling
  - Start up – even an orphan drug (>200,000 patient, usually much less – prevalence) can be valuable
    - Validates company
    - Can command a high price, e.g. Genzyme, new drug recently approved for PNH
  - Mid sized companies frequently target specialties, e.g. UCB – neurology, inflammation (Rheum, GI), requires fewer reps, commands higher price, etc
Stakeholders in “Need Equation”

- Regulators
- Patients
- Pharma Co’s
- Health Care Provider
- Payors
Stakeholder View of Unmet Need
- One Man’s Opinion

• Patients
  • Effective, safe drugs, etc; reasonable price or access; convenience (compliance)

• Health Care Providers
  • Effective, safe – create few or no new problems to treat; minimal drug interactions; novel; solving new problems; easy to use, convenient; widespread access – few hassles when Rx written

• Governments
  • Want to provide benefits (political, chicken in every pot); don’t want to pay for them; rebates, etc

• Third Party Payors – Managed Care, Ins Co’s
  • Solve new problems; safe, effective; novel; reasonable formulary balance; reasonable price; cost effective/value equation (“benefit/risk”); attractive to customers/members

• Pharma/Biotech companies
  • Good profit margin; good risk benefit; drive revenue; solid IP; increasingly specialty driven (lower cost of selling)
Built in Conflicts in Need Equation

- **Regulators**
  - Pushed to approve new drugs faster – PDUFA
  - Patients demand access to even unapproved drugs – supreme court recently rejected this “right”, agreeing FDA had statutory duty to protect consumers from unproven, unsafe remedies
- **Conservative – VIOXX**
  - Not much praise for approvals
  - Don’t like testifying before Congress when problems arise
  - Difficulty coping with innovation, scientific progress
    - Over-worked, low pay, etc
  - Increasingly motivated by economic concerns
Conflicts, cont.

- Patients
  - Increasingly sophisticated, demand the newest and best
  - Litigious
  - More involved in their own care/advocates for progress
  - Increasingly less able to pay for Rx, in face of pressures to shift more costs to consumers
  - The age of direct to consumer advertising has had impact
    - Increases awareness and sales
    - Increases exposure and risk to companies
Conflicts, cont

- Third Party Payors – managed care, insurance co’s
  - Drugs can help prevent or shorten hospital stays, prevent expensive surgery, prevent disease complications, but
  - Formularies are now driving costs, now that MD payments and hospital reimbursement is under “control”; drugs are increasingly expensive
  - Need to keep customers happy
    - Attractive formulary, but limit “me too’s”
    - Tiered access, patient cost shifting
  - Care about cost effectiveness
    - Need to partner with Pharma co’s, often, to sort this out
Conflicts, cont

• Providers
  • Want new, better, safer, more effective drugs
  • Under attack from critics re: interactions and support from Pharma industry; conflicts of interest, etc
  • Want decreased paper work, i.e. efficient Rx fulfillment
  • Tired of seeing massive numbers of Pharma reps, but often don’t get drug education elsewhere
  • Under pressure from formularies to hold down costs
  • Occasionally profit from drug infusion
  • Don’t mind “me too’s” as much – variety helpful in patient interactions
Conflicts, cont

Pharma/Biotech

- Increasingly costly drug development
- Innovation now a premium/required
- Conservative regulators, speak of change and innovation but don’t walk the talk
- More specific science, but tougher targets
  - Submissions and approvals are down
  - Drugs difficult to develop, formulate and deliver
- Shareholders require steady profit growth, which is hard to deliver
- Generic competition increasing, patent life under attack and hard to live with in any event
- Blockbusters (> $1.0 BB in sales) often not enough to drive revenue at biggest companies
Criteria for Identifying a Marketable Product

Since innovation is increasingly difficult, science evolving and competition intense, how do companies identify a “marketable product’?

• Pragmatism – founded as start up around an innovative target, and will push to develop and approve

• Focus – work within areas of interest or expertise, e.g. oncology and inflammation specialties; drugs, biologics, devices; drug delivery, etc

• Competitive Intelligence
  • What are others doing? Databases available to search; Clintrials.gov; market research firms; attend meetings, seminars, etc
  • Where is science moving – collaborate with universities, med schools, NIH, occasionally with each other
  • Off shoring – What’s happening in India/China
Target Identification

Once target is identified, agreed upon, selected, an analytic approach is adopted

- **Target Product Profile** - Typically a document that
  - Describes the technology
  - Lays out the competitive landscape
  - Describes steps and timelines to develop product, including regulatory pathway and timing
  - Includes NPV calculations, with commercial plan
  - Describes all potential indications for development
- **Presented to R and D committees** – broad company representation
- **If attractive, approved for development**
# Target Product Profile

**Note:** One TPP to be completed per indication.

<table>
<thead>
<tr>
<th>Trade Mark(s):</th>
<th>Generic Name (INN):</th>
<th>Project ID Number:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therapeutic Area:</strong></td>
<td>Rheumatoid Arthritis</td>
<td>Anti-human monoclonal antibody</td>
</tr>
<tr>
<td><strong>Pharmacological/Chemical Class:</strong></td>
<td></td>
<td>1.US</td>
</tr>
<tr>
<td><strong>Order of/estimated dates of Market Entry in targeted regions:</strong></td>
<td></td>
<td>2.EU</td>
</tr>
<tr>
<td><strong>First Launch:</strong></td>
<td>2015</td>
<td>3.Japan</td>
</tr>
<tr>
<td><strong>PLT Leader:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SPB Approval Date:</strong></td>
<td></td>
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</tr>
</tbody>
</table>

## Target Indication(s):

- **Initial target indication:** Indicated for reducing the signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderate to severe active RA who have an adequate response to one or more DMARDs and are currently taking methotrexate.
- **Extensions to target indication:** Juvenile RA, psoriatic arthritis, oncology, Crohn’s disease, and other inflammatory based conditions.

## Target Population(s) and Use in Special Populations:

<table>
<thead>
<tr>
<th>Infants □</th>
<th>Pediatrics ✓</th>
<th>Adolescents ✓</th>
<th>Adults ✓</th>
<th>Elderly ✓</th>
<th>Other (specify) □</th>
<th>Both sexes ✓</th>
<th>Men only □</th>
<th>Women only □</th>
</tr>
</thead>
</table>

## Target Profile:

- **Indication:** Reducing the signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderate to severe active RA who have an inadequate response to one or more DMARDs, and are currently taking methotrexate.

## Minimum Acceptable Profile:

- **Indication:** Reducing the signs and symptoms, inhibiting the progression of structural damage and improving physical function in patients with moderate to severe active RA who have an inadequate response to one or more DMARDs, and are currently taking methotrexate.

## Value Proposition and Positioning

- **Monoclonal antibody will be used as a first biological choice in replacement of any other anti-TNF therapy**

## Dosage and Administration

- **To be administered every 2-4 weeks.**
- **Self-administration with an auto injector of liquid formulation**

- **To be administered every 2 weeks.**
- **IV infusion in clinic setting.**
<table>
<thead>
<tr>
<th><strong>Dosage and Administration</strong></th>
<th>To be administered every 2 weeks. Self-administration with an auto injector of liquid formulation</th>
<th>To be administered every 2 weeks. IV infusion in clinic setting.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>ACR20≥70% ACR50≥50% ACR70≥30%</td>
<td>ACR20≥60% ACR50≥40% ACR70≥20%</td>
</tr>
<tr>
<td><strong>Tolerability / Safety</strong></td>
<td>Superior tolerability compared to current anti-TNFs</td>
<td>Equivalent tolerability compared to current anti-TNFs</td>
</tr>
<tr>
<td><strong>PK, ease of use…</strong></td>
<td>To be administered every 2-4 weeks. Self-administration with an auto injector of liquid formulation</td>
<td>To be administered every 2 weeks. IV infusion in clinic setting.</td>
</tr>
<tr>
<td><strong>Price / Reimbursement</strong></td>
<td>Enbrel level</td>
<td>Enbrel level</td>
</tr>
<tr>
<td><strong>Time Window</strong></td>
<td>2015</td>
<td></td>
</tr>
</tbody>
</table>

**Target Value Proposition:**

Due to the combination of attributes of increased efficacy, better tolerance, ease of administration, antibody will be used as the first-line biological of choice after failure of DMARDs by Rheumatologists.

**Target Product Positioning:**

Due to the combination of attributes of increased efficacy, better tolerance, ease of administration, antibody will be used as the first-line biological therapy for signs, symptoms, prevention of structural damage and improved physical function in patients with active moderate to severe RA who have an inadequate response to traditional DMARDs, and are currently taking methotrexate.

**Target Geographical Scope:**

USA file 2015, launch 2016. EU, Japan and ROW timelines to be determined.

**Target Price:**

Price will be finally defined after confirmation of efficacy/safety profile. It is expected to be in line with current subcutaneous competitors. (Pricing benchmark will be Enbrel twice monthly dosing).
**IP Situation:**

**Patentability:** Please specify patent filings with subject matter claimed (e.g., molecule, process, therapeutic uses, dosage form, etc.), expected patentability, expiry dates, and possible extensions.

**Freedom to Operate:** Please specify the freedom to operate situation with respect to third party patents including any agreements in place or under negotiation.

**Patent Expiry Date:** Please specify the patent expiry date and/or potential for renewal.

**Data Exclusivity/Protection:** Please specify the anticipated or actual duration of data exclusivity for the targeted regions.

**Trademark:** Please specify the status of trademark selection and registration when available.

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**TARGET Dosage & Administration:**

<table>
<thead>
<tr>
<th>Pharmaceutical Form(s)/Size(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Liquid in a prefilled syringe for subcutaneous injection. Preferably at a concentration of approx 200 mg/ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose(s):</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Route(s) of Administration:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted route: subcutaneous self-administration</td>
</tr>
<tr>
<td>• Minimum acceptable route: intravenous administration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dosing Schedule(s)/duration(s):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted dosing schedule: Every 2-4 weeks</td>
</tr>
<tr>
<td>• Minimum acceptable dosing schedule: Every day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Administration with Food:</th>
</tr>
</thead>
<tbody>
<tr>
<td>No restrictions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Packaging/Storage:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted packaging and storage time: Room temperature</td>
</tr>
<tr>
<td>• Minimum acceptable packaging and storage time: 2-8°C protected from light</td>
</tr>
<tr>
<td>Efficacy Message</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1. Efficacious in the treatment of signs and symptoms of RA</td>
</tr>
<tr>
<td>1. Efficacy in stopping/slowing joint destruction compared to anti-TNFs as shown by no progression in approx 70% of patients at 1 year and normalization of significant improvement in HAQ in 50% of patients at 1 year.</td>
</tr>
</tbody>
</table>
### Improvements in various physical function activities ranging from 1 week to 1 year assessments

Assessed via the Health Assessment Questionnaire (HAQ)
Approximately a 50% reduction in HAQ score at 12 months.
Plus other outcome measure to be used.

Enbrel®: At 1 year, 44% of patients had a normal HAQ Score
Humira®: Significant improvement in disability index of HAQ at 6 and 12 months.
SF-36 also showed positive improvement + decrease fatigue

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### Safety and Tolerability Messages:

<table>
<thead>
<tr>
<th>Safety Message</th>
<th>Target Label Claim</th>
<th>Target Outcome Measures (study number that addresses message)</th>
<th>Comparative Competitor Data / Information</th>
<th>Differential Competitive Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Equivalent efficacy in improving physical function compared to anti-TNFs</td>
<td>Improvements in various physical function activities ranging from 1 week to 1 year assessments</td>
<td>Assessed via the Health Assessment Questionnaire (HAQ) Approximately a 50% reduction in HAQ score at 12 months. Plus other outcome measure to be used.</td>
<td>Enbrel®: At 1 year, 44% of patients had a normal HAQ Score Humira®: Significant improvement in disability index of HAQ at 6 and 12 months. SF-36 also showed positive improvement + decrease fatigue</td>
<td>Favorable AE profile as new entrant to market</td>
</tr>
<tr>
<td>1. Equivalent AE profile to anti-TNFs</td>
<td>Lower AE profile</td>
<td>Relatively low incidence of AE and AEs specific to anti-TNFs</td>
<td>Competitors labels</td>
<td>Favorable AE profile as new entrant to market</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Message</th>
<th>Label Claim or Publication</th>
<th>Other Profiling Information (study number that addresses message)</th>
<th>Comparative Competitor Measures</th>
<th>Differential Competitive Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Further pharmacoeconomic data</td>
<td>Only Publication</td>
<td></td>
<td></td>
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</table>

**Unfavorable Profile Elements:**
Approx 7th to 8th biological agent to enter the market

**Special Technical Requirements:**
Any special formulation requirements, etc

**Special Marketing Requirements:**

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1. Superior tolerability  
   Better compliance  
   Lower dropout rates  
   Competitors labels  
   Favorable tolerability versus Remicade

**Other Profiling Messages:** Please specify all other intended messages with reference to competition (e.g., convenience including components such as taste and ease of administration, compliance, pharmacoeconomic benefit, disease management, PK/PD, specific drug/food interactions, etc.). If these are to be label claims then they MUST be supported in the relevant clinical studies.
Summary

- Concept of unmet need depends on perspective of stakeholder
- There remain many unsolved medical problems and needs for new therapies appear to be large
- Development and marketing decisions in pharma companies are driven by
  - Revenue needs, science, stage of company’s development, competition, IP
  - Development decisions are based on risk assessment, including preclinical, clinical and market risks, and precise financial analysis
  - Economic assessments are increasingly important, as development equation changes from efficacy and safety to risk and benefit
Sources of Information

- Wikipedia for FDA information
- “Pink Sheet” and Scrip for Pharma information, including FDA information
- Newspapers, magazines; Forbes is especially useful, particularly the free online edition; Wall Street Journal
- Biospace.com – free online Pharma news service
- BioWorld – subscription weekly
- Medical Advertising News
Thank you for your attention

Questions?