Regulatory Issues Related to the Development of Drugs to Treat Painful Peripheral Neuropathy

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Innovative Therapies for Peripheral Neuropathies
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Overview

• Indications and claims:
  – Broad vs. narrow
  – Extrapolation of efficacy

• Combination drugs vs. polypharmacy

• Challenges in analgesic drug development and ACTTION
Indications and Claims

- **Indication** – The specific condition or use the product has been approved for
  - May be broad, e.g., “for the treatment of pain”
  - Or narrow, e.g., “for the management of the pain of diabetic peripheral neuropathy”

- **Claim** – Any advantage conveyed by use of the product that is noted in the label
  - May be explicit, e.g., “demonstrated a 50% reduction in Pain Intensity from Week 1 to Week 12”
  - Or implicit, e.g., “formulation withstands grinding with a {specific power} coffee grinder” implies that the product is abuse-deterrent
Indications and Claims

• Either must be supported by good quality data
• Indications must be supported by a reasonable risk-benefit ratio
• Product must be demonstrated safe in a reasonable number of exposed subjects
• Subjects must represent the appropriate patient population
• Safety evaluations must be adequate and complete
Indications and Claims

• Efficacy generally demonstrated in replicated, adequate and well-controlled studies
• In some cases, extrapolation of safety and/or efficacy data may be allowed, resulting in approval based on single trial or smaller number of subjects
  – New patient population, but similar to the patient population for which product already approved
  – Expanded use, e.g., for progression of disease when slowing of disease has already been approved
  – A new drug product, but within the same class as a previously, well-characterized, approved product
Extrapolation of Efficacy in Neuropathic Pain

• Finding a balance for drug product development
• Allow extrapolation
  – Broader patient population with increase in potential risk of toxicities/adverse events
  – But allows reimbursement patients by insurers compared to off-label use in many situations
  – So, must be supported by sound scientific evidence and clinical judgment
• FDA convened a scientific workshop to address extrapolation of efficacy in analgesic clinical studies, December 2009
• Leading academic pain experts/analgesic clinical trial design experts met for one day
Topical review

Considerations for extrapolating evidence of acute and chronic pain analgesic efficacy

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Table 1
Acute pain (≤30 days): suggested basis for considering the extrapolation of efficacy.

<table>
<thead>
<tr>
<th>Basis for Extrapolation</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 positive trials in acute postoperative pain, each in a different type of surgery</td>
</tr>
<tr>
<td>For example, amputation, herniorraphy, mastectomy, orthopedic surgery (e.g., bunionectomy), thoracotomy, or visceral surgery (e.g., hysterectomy)</td>
</tr>
<tr>
<td>1 positive trial in acute pain associated with nonsurgical trauma</td>
</tr>
<tr>
<td>For example, sprains, strains, and/or fractures</td>
</tr>
<tr>
<td>1 positive trial in acute disease-associated visceral pain</td>
</tr>
<tr>
<td>For example, renal colic, acute pancreatitis, or diverticulitis</td>
</tr>
</tbody>
</table>

Note. The phrase “positive trial” refers to a double-blind randomized clinical trial in which the investigational treatment has shown statistically significant superiority to placebo or, in certain circumstances, to an active comparator (e.g., a lower dosage of the same treatment).
### Table 2
Chronic pain (≥90 days): suggested basis for considering the extrapolation of efficacy.

<table>
<thead>
<tr>
<th>Peripheral neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 positive trials in a single painful polyneuropathy (eg, diabetic, human immunodeficiency virus, chemotherapy) and 1 positive trial in postherpetic neuralgia (PHN), or 2 positive trials in PHN and 1 positive trial in a single painful polyneuropathy</td>
</tr>
<tr>
<td>1 positive trial in chronic postoperative, posttraumatic, or entrapment nerve injury pain (eg, postthoracotomy pain, lumbosacral radiculopathy, complex regional pain syndrome, carpal tunnel syndrome)</td>
</tr>
<tr>
<td><strong>Note:</strong> Once replication of efficacy has been shown in a single peripheral neuropathic pain condition, 1 positive trial in a second condition could potentially serve as a basis for extrapolating efficacy to that condition.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Central neuropathic pain</th>
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</thead>
<tbody>
<tr>
<td>1 positive trial in spinal cord injury neuropathic pain</td>
</tr>
<tr>
<td>1 positive trial in central poststroke pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 positive trials in either a single painful polyneuropathy or in PHN</td>
</tr>
<tr>
<td>1 positive trial in chronic postoperative, posttraumatic, or entrapment nerve injury pain</td>
</tr>
<tr>
<td>1 positive trial in either spinal cord injury pain or central poststroke pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonneuropathic pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 positive trials in either osteoarthritis or nonradicular low back pain</td>
</tr>
<tr>
<td>1 positive trial in a second nonneuropathic pain condition</td>
</tr>
<tr>
<td>1 positive trial in a third nonneuropathic pain condition</td>
</tr>
</tbody>
</table>
Extrapolation of Efficacy in Neuropathic Pain

• Generally agree with the recommendations
• But we need to take into consideration:
  – Need to get new analgesics to the market
  – Need to have analgesics with broader indications for reimbursement
• So, each product is considered on a case-by-case basis
• Guidelines and Guidances
• It would be helpful if the available clinical practice guidelines for polypharmacy were updated – by the academic community
Polypharmacy vs. Combination Drug Products

• Polypharmacy
  – Generally a “practice of medicine” issue
    • Occasional labels refer to “required” use of the product with other products
  – Adjunctive therapy can be an early or late indication with appropriate development plan
  – New draft guidance document:
    • “Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination”
Polypharmacy vs. Combination Drug Products

In general, decisions about the type or types of marketing application submitted for a combination (e.g., combination application, individual component applications) will depend on how the applicant intends to market the combination and its components.

- (1) If the components of a combination will be marketed as a combination product, (e.g. co-packaged product, fixed-dose combination), a single marketing application for the combination should be submitted.

- (2) If the components of the combination will be marketed as distinct products (separate packaging) intended for use in combination, a separate marketing application for each component of the combination should be submitted.

- (3) In scenario (1) above, if the applicant also intends to market one or more of the components of the combination for use as monotherapy, a separate marketing application should be submitted for the individual component for the monotherapy use.

- (4) In scenario (2) above, if the applicant also intends to market one or more of the components of the combination for use as monotherapy, the same marketing application can be used for the combination and monotherapy uses.
Polypharmacy vs. Combination Drug Products

- Fixed-Combination Prescription Drugs
  - Specific regulation CFR 21 300.50:
    - Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug. Special cases of this general rule are where a component is added:
      - (1) To enhance the safety or effectiveness of the principal active component; and
      - (2) To minimize the potential for abuse of the principal active component
Challenges in Analgesic Drug Development

1. Clinical trial design
2. Clinical trial design
3. Clinical trial design
4. Others
Challenges in Analgesic Drug Development

• Others
  – Limited funding for clinical research
  – Pain research not centralized/coordinated
• The times they are a changing:
  • FDA
    – Consolidation
    – Scientific Workshops
  • NIH Pain Consortium
  • NIDA Drug Development
  • IOM Report: “Relieving Pain in America”
  • IMMPACT
  • ACTTION
Analgesic Clinical Trial Translations, Innovations, Opportunities, and Networks
Background

• Clinical studies, particularly efficacy trials, notoriously flawed for analgesic drug development
  – Frequent failed studies with drugs known to be effective
  – Extremely small treatment effects even when successful
  – Multiple causes, e.g.:
    • Large placebo effect
    • Missing data
    • Study design flaws
    • Study analysis flaws
    • Investigator quality
    • Frequent use of foreign sites
Background

- Although somewhere between 30 and 60 million people suffer from chronic pain in US
- And the dangers of treating acute pain with opioids, NSAIDS or acetaminophen are considerable
- Industry reluctant to put money into novel analgesic development with a low success rate of clinical trials
Rationale

• IMMPACT has performed an enormous service in advancing the field of analgesic clinical trials
• But there’s a wealth of data from failed analgesic trials in FDA files
• Initial FDA efforts under Critical Path Initiative:
  – Small contracts with academic investigators
  – Small contract to evaluate data standardization
  – Confidentiality agreements
  – Data access successful but limited
• Meanwhile – numerous investigators with similar goals working in silos
• Not to mention industry and other government agencies remaining untapped
Rationale

• Previous experience working with Critical Path on a Public-Private Partnership (PPP)
• Why not bring all stakeholders under a single umbrella?
• PPP would allow for:
  – Bringing together the scientific experts
  – Data sharing
  – Closing the research gaps
  – And, leveraging resources
• Dr. Woodcock, Director, Center for Drug Evaluation and Research, completely supportive of proposal
Other FDA Public-Private Partnerships

- Numerous PPPs have been established over the past few years
- Examples:
  - ECG Warehouse (housing over 4M digital ECG)
  - Cardiac Safety Research Consortium (CSRC)
  - Nanotechnology
  - Biomarker Consortium (administered by FNIH)
  - SmartTots (formerly SAFEKIDS)
- Some of these projects have already raised many millions of dollars
Objectives

• Primary objective: develop novel analgesic drugs products
  – “broad spectrum”
  – Targeted
  – Additive and/or synergistic
  – And with less toxicity

• By exploring the flaws in current analgesic clinical trial designs

• Testing novel designs and analyses

• Standardizing data presentation to allow for more efficient exploration and analysis
Objectives

• Raising the funds to support the research
  – Must come from the private partner
  – Sources include:
    • Private foundations
    • Government
    • Stakeholder organizations, e.g., patient advocacy groups, pain societies
    • Industry

• FDA provided seed funding
• And we hope to provide additional funds, if available
ACTTION in Motion

• Decision to select the University of Rochester as contractor, with Dr. Robert Dworkin as PI
  – will establish strong leadership team to manage all elements (scientific and administrative) of this massive undertaking
  – will leverage existing activities and expertise in the field

• One million dollar contract awarded in September 2010
ACTTION mission statement

To identify, prioritize, sponsor, coordinate, and promote innovative activities — with a special interest in optimizing clinical trials — that will expedite the discovery and development of improved analgesic treatments for the benefit of the public health.
Evidence-based clinical trial design for chronic pain pharmacotherapy: A blueprint for ACTION

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Current ACTTION activities, I

- IMMPACT consensus meeting on “The Role of Biomarkers and Related Measures in the Development of Improved Analgesic Treatments” (June 2012).
- ACTTION meeting on “Preclinical and Clinical Models and Methods for Accelerating Analgesic Drug Development” (October 2012).
- Meta-regression analyses of study-level data from published and otherwise publicly-available analgesic clinical trials: (1) neuropathic pain; (2) osteoarthritis; and (3) acute post-operative pain.
- Analyses of patient-level pooled data from neuropathic pain trials (John Farrar); also osteoarthritis, rheumatoid arthritis, and fibromyalgia trials (Farrar in collaboration with Europain).
Current ACTTION activities, II

- Development of pain-specific CDISC database standard for retrospective pooling and for prospective database creation and submission of analgesic trials.
- Development of comprehensive registry of analgesic trials available from government and industry websites and other sources (Mike Rowbotham).
- Systematic review and meta-analyses of safety reporting in analgesic trials, focusing on adherence to CONSORT recommendations; assessment methods; and approaches to data analysis and presentation.
- Development of definitions, classification system, and rating scales for evaluating misuse/abuse in trials of analgesic drugs (modeled after FDA-sponsored C-CASA and C-SSRS for evaluating suicidality in clinical trials).
Current ACTTION activities, III

• Development of novel composite outcome measures for use in analgesic clinical trials, including: (1) pain and physical functioning; (2) pain and use of rescue analgesia; and (3) pain and adverse events (risk-benefit).

• Statistical modeling to examine: (1) treatment of missing data; (2) parametric vs. non-parametric methods of analysis; and (3) power and appropriateness of different analysis techniques, for example, landmark, time-weighted, and area under the curve.

• Development of patient and staff training programs to increase assay sensitivity of pain ratings and other patient-reported outcomes, followed by proof-of-concept trial to test hypothesis that the training increases assay sensitivity.
Opportunities for ACTTION

• Research
  • Facilitate collaborations among stakeholders
  • Sponsor analyses of pooled legacy data
  • Develop more efficient clinical trial designs
  • Reduce patient burden and study costs
  • Explore biomarkers and patient phenotyping
Opportunities for ACTTION

• Education
  • Provide research fellowships and grants
  • Conduct workshops and consensus meetings
  • Develop training materials for study subjects and study staff

• Treatment
  • Expand therapeutic armamentarium
  • Accelerate the development of mechanism-based treatments
New ACTTION RFP

- FDA issued an RFP for additional grant-type funding to be spread over five years
- The amount noted was up to $1 million and last fiscal year we were able to provide $500,000
- Hopefully, some additional FDA funding will be available each year, but
- The bulk of the funding for ACTION will need to come from fund raising efforts by the private partner
Other Stakeholders in Government, Industry, Patient Advocacy and Academia