Issues in PET Drug Manufacturing

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Topics

- ANDA process for FDG
- User fees
- Contract manufacturing

PETNET's perspective
Colleagues

- Michael Nazerias
- Ken Breslow
- Ed Plut
**PETNET's ANDA process for FDG**

*Observations—*

- June 2007: Submitted application
- May 2008: Preapproval inspections
- June 2008: Submitted additional copies due to administrative error in OGD
- April 2009: Microbiology questions received
- April 2010: Labeling questions received
PETNET's ANDA process for FDG

Concerns—
- Yet to receive questions on CMC section
- Lengthy review process
- Lack of prioritization against PDUFA drugs
- Lack of PET experience in OGD

Recommendations—
- Office of New Drugs should drive the review process
- Inspections of PET manufacturing facilities should consider a centralized approach
User Fees

Observations—
- PDUFA reauthorized in 2007
- Reduced 2008 establishment fees for PET facilities from $392,700 to $65,450
- Fee for applications that require clinical data is same as other NDA drugs ($1,178,000 in 2008)
- User fees do not apply to generic drugs

Concerns—
- Reduction in establishment fees is a good start
- Fees remain excessive given size of US market
For example—

- Total annual US market for FDG is approximately $300 million
- Assume 100 manufacturing sites are required for a nationwide supply of FDG
- If FDG was approved in 2008 with clinical trial data, the user fees would be:
  - Application: $1,178,000
  - Establishments: $65,400 x 100 = $6,540,000

- Total is about $7,700,000 or 2.6% of market
User Fees

By comparison—

- Many individual therapeutic products have total annual sales more than 4x $300 million
- Number of manufacturing sites is much lower
- If a $1.2 billion “Product X” was approved in 2008 with clinical trial data, user fees would be:
  - Application fee: $1,178,000
  - Establishment: $392,700 \times 2 = $785,400

- Total is about $2,000,000 or 0.2% of market
## User Fees

<table>
<thead>
<tr>
<th></th>
<th>FDG</th>
<th>Product X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Market Size</td>
<td>300</td>
<td>1,200</td>
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<tr>
<td>Application Fee</td>
<td>1.178</td>
<td>1.178</td>
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<tr>
<td>Establishment Fee</td>
<td>6.54</td>
<td>0.785</td>
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<tr>
<td>Total User Fee</td>
<td>7.7</td>
<td>2.0</td>
</tr>
<tr>
<td>% of Market</td>
<td>2.6%</td>
<td>0.2%</td>
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</tbody>
</table>

**Values in millions of $**
User Fees

Conclusion—

- Existing user fee structure will create a significant barrier to innovation in the development of new PET biomarkers in the US
- User fees will limit public access to safe and effective PET imaging agents

Recommendations—

- Society/industry groups should lead an initiative to spearhead a fair and equitable user fee structure for PET
Contract Manufacturing

Observations—
- Multiple production sites
- Different operators
- Different equipment

How we ensure product uniformity—
- Qualify facilities, operators and equipment to execute validated processes & methods
- System suitability to ensure equipment operability
- Clearly defined specifications and release criteria
- Routine QC on each batch prior to administration
Contract Manufacturing

*Concerns*—
- Tendency to concentrate on chemistry module instead of the formulation and active ingredient
- Manufacturing standards focus on production and testing of a single biomarker at multiple manufacturing sites

*Recommendations*—
- Focus on active ingredient, impurity profile, and formulation
- Chemistry modules are equipment that can be qualified
- Innovators and contractors need to consider standards that enable production and testing of *multiple* biomarkers at *multiple* sites
Summary

- **ANDA process for FDG**
  - Office of New Drugs should drive the review process
  - Inspections of PET manufacturing facilities should consider a centralized approach

- **User fees**
  - Society/industry groups should lead an initiative to spearhead a fair and equitable user fee structure for PET

- **Contract manufacturing**
  - Focus on the active ingredient, impurity profile and formulation instead of chemistry modules
  - Innovators and contractors need to consider standards that enable *multiple* biomarkers at *multiple* sites