Recent Trends in the Regulation of Biotherapeutic Products: U.S. FDA Perspective

CMC Strategy Forum LATAM 2015

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Outline

• Trends in mAb Development
• Regulatory Convergence
• Transparency
• Predictability
• Priority Reviews
  – Accelerated Development Programs
  – Breakthrough Designation
History of Monoclonal Antibodies

Orthoclone 1st mAb
ReoPro
Rituxan Zenapax
Enbrel
Mylotarg
Zevalin Humira
Vectibix
Cimzia
Adcetris
Gazyva
Gazyva


Murine
Chimeric fragment
Intact chimeric humanized
Fc-fusion
mAb-drug Conjugate NDA
Human/ mouse
Human/ phage display
Therapeutic radioimmunoconjugate
Pegylated
mAb-drug Conjugate BLA
Animal rule
Glycoengineered QbD/design space

August 2014
44 mAbs
9 Fc-fusion

Adapted from M. Shapiro, 2013
History of Monoclonal Antibodies

Orthoclone 1st mAb 1986
ReoPro 1994
Rituxan Zenapax 1997
Mylotarg 1998
Zevalin Humira 2000
Vectibix 2002
Humira 2006
Cimzia 2008
Adcetris 2011
Gazyva 2012
BlinCYTO 2013
Vectibix 2015
ruxibacumab 2015

1998 Fc-fusion
1994 Intact chimeric humanized
1997 Chimeric fragment
1998 mAb-drug Conjugate NDA
2000 mAb-drug Conjugate BLA
2002 Therapeutic radioimmunoconjugate
2006 Human/mouse
2008 Pegylated
2011 mAb-drug Conjugate BLA
2012 Glycoengineered QbD/design space
2013 Animal rule
2015 Bispecific

August 2015
51 mAbs
10 Fc-fusion

2015- NOT a mAb- Zarxio = biosimilar filgrastim

Adapted from M. Shapiro, 2013
Regulatory Convergence

Importance to FDA

• FDA has acknowledged an “increasing recognition” of the need to engage in **effective** global regulatory cooperation.

• Federal Food, Drug, and Cosmetic Act – the mission of the FDA

  “shall participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements.”
Regulatory Convergence

FDA Participation, Collaboration, and Support

- ICH - an initial step in convergence, recognizing that not every region is currently part of ICH
- International Conference of Drug Regulatory Authorities (ICDRA)- WHO member states
- FDA/EMA “clusters”- regular discussions
- Regional Platform on Access and Innovation for Health Technologies (PRAIS) – PAHO/WHO
  - “designed to improve transparency, information flow, and collaboration”
Regulatory Convergence

FDA Participation, Collaboration, and Support

• Inspection
  – Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/S) – harmonization of GMP requirements, exchange of information, and potential mutual recognition of inspections
  – EMA-EU MSs- FDA initiatives on inspections
  – Global Harmonization Task Force (GHTF) - Medical Devices

• World recognized standards for some specific products (e.g., to support consistency of potency units and dosing)
Transparency

- FDA’s transparency initiative (see AboutFDA site).
  - Presidential Memorandum on Transparency and Open Government
  - “FDA Basics,” public disclosure, and transparency to regulated industry (task force supports redaction of trade secrets)

- Significant clinical information is available (publications, advisory committees, reviews).

- Drugs@fda – source of approval letters/review packages.

- Some inspectional findings are also available.
  - Inspection observations spreadsheets
  - Warning letters
  - See Inspections, Compliance, Enforcement, and Criminal Investigations on FDA website
Transparency

Commercial confidential information/trade secret information

- Staff Manual Guide for sharing non-public information with foreign government officials (everything through OIP).
  - Confidentiality commitment documents and Memoranda of understanding signed with some countries
- Sponsor can give permission for FDA to talk to other agencies about specific topics (through OIP).
- Information in redacted approval letters and review packages.
- Information/thinking shared during talks and discussions at public conferences.
- Manufacturers can create challenges when publically presenting only select aspects of regulatory actions or presenting without being aware of the Agency’s reasons for approval.
Regulatory Convergence and Transparency

FDA International Programs Office

• CDER Forum for International Drug Regulatory Authorities
  – 5 day program
  – Most recent was Sept 2014

• Biannual Educational Forum-Hot Topics at the U.S. FDA
  – 1 day program
  – Most recent was June 2015

• These include very little CMC content
Transparency

U.S. FDA expectations related to Quality Control and last year’s CMC LATAM Mass Spectrometry Talks

• We do not currently expect that MS methods be included as part of release testing.
• Survey of OPB-regulated BLA products through March 2015.
• Mass Spectrometry was identified in the specifications of two products.
  – Identity
  – Oligosaccharide
# Methods used in QC labs

(OPB-regulated BLA products through March 2015)

<table>
<thead>
<tr>
<th>Method</th>
<th>Number of Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>SEC (GPC, GF)</td>
<td>83 products</td>
</tr>
<tr>
<td>SDS-PAGE</td>
<td>49 products</td>
</tr>
<tr>
<td>CGE (SDS/LDS)</td>
<td>34 products</td>
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<tr>
<td>IEX</td>
<td>38 products</td>
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<tr>
<td>cIEF/icIEF</td>
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<tr>
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<tr>
<td>CZE</td>
<td>6 products</td>
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<tr>
<td>RP-HPLC</td>
<td>43 products</td>
</tr>
<tr>
<td>HIC</td>
<td>5 products</td>
</tr>
</tbody>
</table>
Predictability

U.S. FDA Review Timelines

• IND (clinical study) 30 days from receipt

• BLA (FDA Desk Reference Guide- publically available)
  – Priority 6 mo from filing (8 mo from receipt)
  – Standard 351a 10 mo from filing (12 mo from receipt)
  – Standard 351k (biosimilar) 10 mo from receipt

• BLA Supplements
  – Prior Approval Supplement (PAS) 4 mo from receipt (6 mo for biosim.)
  – Changes Being Effected (CBE-30/CBE-0) 6 mo from receipt
Predictability

U.S. FDA Review Timelines

• Standard Meetings- IND or BLA
  – Type A (stalled program) – within 30 days of request receipt
  – Type B (major milestone) – within 60 days
  – Type C (other) – within 75 days

• Biosimilar Meetings – IND or BLA
  – Type 1 (stalled program) – within 30 days of request receipt
  – Type 2 (specific issues or questions) - within 75 days
  – Type 3 (in-depth data review and advice) – within 120 days
  – Type 4 (discuss format and content) – within 60 days
Predictability

Challenges

• Resources.

• Our review clock does not stop for responses to information requests.

• PAS – a 4 month clock regardless of the need for inspections.

• Priority/expedited reviews of a new product.
  – Frequent need for information requests requiring significant time for response (additional data)
  – Inspections required

• Biosimilars review – analytical similarity data review is extremely time consuming.
Expedited Development
To address unmet medical need in the treatment of serious or life-threatening conditions

• Fast Track Designation
  – Nonclinical or clinical data demonstrate potential to meet unmet need
  – Actions to expedite development and review: frequent interactions
  – Rolling review, may be eligible for priority review

• Priority Review Designation
  – Would provide a significant improvement in safety or effectiveness
  – 6 (from filing)/8 (from receipt) month BLA review clock
    (vs. 10/12 month standard BLA review clock)

• Accelerated Approval
  – Use of a surrogate endpoint/intermediate clinical endpoint that is reasonably likely to predict clinical benefit

• Breakthrough Therapy Designation
  – Clinical evidence indicating substantial improvement for a clinically significant endpoint
BT Designation Actions

- Granting meetings throughout the development of the drug
- Providing timely advice and interactive communication with the sponsor
- Taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment
- Assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review and to serve as a scientific liaison between the cross-discipline members of the review team
- Involving senior managers and experienced review staff
Breakthrough Therapies

CDER Actions (through 7/24/15)
– FY 2012: 2 requests, 1 granted, 1 denied
– FY 2013: 92 requests, 31 granted, 52 denied
– FY 2014: 96 requests, 31 granted, 51 denied
– FY 2015: 80 requests, 18 granted, 32 denied

– CY 2013: 3 new drug approvals (obinutuzumab 11/1; ibrutinib 11/13)
– CY 2014: 9 new drug approvals, 5 supplement approvals
– CY 2015: 4 new drug approvals, 5 supplement approvals

Breakthrough biotechnology product approvals include Gazyva, Keytruda, Opdivo, and Blincyto.
Expedited Development- Challenges

“The sponsor of a product that receives an expedited drug development designation will probably need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program. The sponsor’s product quality team and CMC teams should initiate early communication with FDA to ensure that the manufacturing development programs and timing of submissions meet the Agency’s expectations for licensure or marketing approval.”
Breakthrough Products – Experiences and Challenges

• Expedited product and clinical development is possible, but requires a strong commitment and careful planning.
  – Process development and product characterization needs to keep pace with clinical development.
  – A commercial manufacturing process needs to be ready to consistently deliver the clinical performance stated on the label and to meet market demand.
  – There are no major CMC shortcuts for a breakthrough product; expectations for a BLA submission do not change.

• Sponsors should request CMC-specific meetings as soon as possible upon receiving BT designation and should put an appropriate amount of thought into subsequent meeting requests/questions/packages.

• FDA challenges include resources, expedited review timelines, and some applications for licensure in which product/process knowledge is not as well developed as would be typical for standard development.
Conclusions

• Higher levels of regulatory convergence, transparency, and predictability are actions that could support the advancement of medicine and rapid and continual patient access to high quality effective therapeutics and, therefore, are goals that every regulatory authority should consider.

• Regulatory agency participation in expedited product development and review can also promote enhancement of public health.

• However, these matters present many challenges to the U.S. FDA and are likely to present similar challenges to other health authorities, and we should set manageable goals and enhance these activities over time.
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Thank you for your attention

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