Office of Generic Drugs (OGD) Director’s Update

“Meeting GDUFA Commitments – Going for GOLD ”

Kathleen Uhl, MD
Director, Office of Generic Drug
CDER/FDA

GPhA Fall Tech Meeting
October 24, 2016
Disclaimer

• This presentation reflects the views of the speaker and do not reflect official FDA, HHS, or other government opinion or policy.

• I have nothing to disclose.

• FY2016 data represent preliminary data that are being further reviewed and validated for official reporting purposes.
Overview

1. Reminder of GDUFA basics
2. Progress toward goals
   – Formal, negotiated GDUFA goals
   – Stakeholder expectations
3. Application Approvability
4. Closing Comments
Overview

1. Reminder of GDUFA basics
2. Progress toward goals
   – Formal, negotiated GDUFA goals
   – Stakeholder expectations
3. Application Approvability
4. Closing Comments
GDUFA – major program goals

(5 year plan)

1. Metrics
   - Applications, “GDUFA backlog”, inspections, controls

2. Efficiency enhancements

3. Regulatory science
GDUFA -- implementation

*Build the Machine*

- Deep foundational restructuring
- Build infrastructure
- Improve business processes
- Hire and train new staff
- New IT platform
- Improve communications

All to prepare for Year 3 Goal Dates

**AND**

to enable us to hit goal dates for the first time that become progressively tighter over time
GDUFA I -- goal dates

Powerful tool to improve the timeliness and predictability of review
Generic Drug Program is a REVIEW Program

<table>
<thead>
<tr>
<th>Goals</th>
<th>Review Time</th>
<th>FY2015</th>
<th>FY2016</th>
<th>FY2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original ANDA submission</td>
<td>15 months~</td>
<td>60%</td>
<td>75%</td>
<td>90%~</td>
</tr>
<tr>
<td>Tier 1 first major amendment</td>
<td>10 months</td>
<td>60%</td>
<td>75%</td>
<td>90%</td>
</tr>
<tr>
<td>Tier 1 minor amendments (1st-3rd)</td>
<td>3 months*</td>
<td>60%</td>
<td>75%</td>
<td>90%</td>
</tr>
<tr>
<td>Tier 1 minor amendments (4th-5th)</td>
<td>6 months*</td>
<td>60%</td>
<td>75%</td>
<td>90%</td>
</tr>
<tr>
<td>Tier 2 amendment</td>
<td>12 months</td>
<td>60%</td>
<td>75%</td>
<td>90%</td>
</tr>
<tr>
<td>Prior Approval Supplements</td>
<td>6 months*</td>
<td>60%</td>
<td>75%</td>
<td>90%</td>
</tr>
<tr>
<td>ANDA teleconference requests</td>
<td>10 business days</td>
<td>200</td>
<td>250</td>
<td>300</td>
</tr>
<tr>
<td>Controlled correspondence*</td>
<td>2 months</td>
<td>70%^</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td>ANDAs, amendments and PASs in backlog</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>on Oct 1, 2012</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Performance goals in the chart means FDA should take a “first action” (as defined above) on a certain percent of applications, etc. within the timeframes listed; it does not mean FDA should approve applications, etc. within such timeframes.
+If no input required from clinical division
*10 months if inspection required
^4 months
~10 months

Act on 90% by end of FY2017
GDUFA PROVIDES PREDICTABILITY for INDUSTRY

Proposed Year 5 timeline:

- Filing Review (OGD) 0 – 60d
- Review Team Assignment Within 70d
- Kick-Off Meeting Within 90d
- Assessment #1 and Cumulative IR #1 Within 120d
- IR #1 Response Received and Reviewed 4mo – 6.5mo
- Complete Inspection Within 7.0mo
- IR #2 Response Received and Reviewed 6.5mo – 8.5mo
- Wrap-up and Final Review Within 9.0mo

Original ANDA
YEAR 5 – Regulatory Action in 10 months
GOAL – 90%
Regulatory Action = RTR, CR, TA, AP
MORE PREDICTABILITY with TADs for Additional Cycles (Pre-Year 3)

*not a GDUFA I commitment*

<table>
<thead>
<tr>
<th>Category</th>
<th>Pre-cohort Year 3 ANDAs</th>
<th>Pre-cohort Year 3 ANDAs (expedited status)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major (CR)</td>
<td>10 months</td>
<td>7 months</td>
</tr>
<tr>
<td>Minor (CR)</td>
<td>5 months</td>
<td>3 months</td>
</tr>
<tr>
<td>ECD</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>IR</td>
<td>3 months</td>
<td></td>
</tr>
</tbody>
</table>
Overview

1. Reminder of GDUFA basics

2. Progress toward goals
   - Formal, negotiated GDUFA goals
   - Stakeholder expectations

3. Application Approvability

4. Closing Comments
To date, FDA has met or exceeded EVERY formal negotiated GDUFA goal
Projected vs Actual ANDA Receipts

GDUFA implements, 10/1/12

750 Projected ANDAs per year

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

FDA received more than 5 years of projected ANDA receipts in the first 4 years of GDUFA
Monthly ANDA Receipts*

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
“GDUFA Backlog” Applications
Action through 9/30/2016

<table>
<thead>
<tr>
<th>Actions</th>
<th>ANDAs</th>
<th>PASs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with First Action*</td>
<td>2,692</td>
<td>1741</td>
</tr>
<tr>
<td>Percentage Complete</td>
<td><strong>94%</strong></td>
<td><strong>93%</strong></td>
</tr>
<tr>
<td>Approval</td>
<td>669</td>
<td>992</td>
</tr>
<tr>
<td>Tentative Approval</td>
<td>163</td>
<td>4</td>
</tr>
<tr>
<td>Complete Response with an Inspection**</td>
<td>1528</td>
<td>480</td>
</tr>
<tr>
<td>Refuse to Receive</td>
<td>68</td>
<td>2</td>
</tr>
<tr>
<td>Withdrawn Application</td>
<td>264</td>
<td>263</td>
</tr>
</tbody>
</table>

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
**Complete Response with an Inspection is a written FDA communication to an applicant usually describing all of the deficiencies that the agency has identified in an application that must be satisfactorily addressed before it can be approved.

“GDUFA BACKLOG” =
2,866 original ANDAs
1,877 PAS supplements

GDUFA GOAL:
90% get first ACTION by end of GDUFA Year 5 (9/30/2017)

FDA hit the 90% “GDUFA Backlog” metric
15 months AHEAD of schedule
Total ANDA Regulatory Actions* per Month
(AP+TA+CR+RTR)

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
Overall Actions

<table>
<thead>
<tr>
<th></th>
<th>Pre-GDUFA</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FY2012</td>
<td>FY2013</td>
<td>FY2014</td>
<td>FY2015</td>
<td>FY2016*</td>
</tr>
<tr>
<td>ANDA approvals</td>
<td>517</td>
<td>440</td>
<td>409</td>
<td>492</td>
<td>651</td>
</tr>
<tr>
<td>PAS approvals</td>
<td>275</td>
<td>535</td>
<td>659</td>
<td>624</td>
<td>496</td>
</tr>
<tr>
<td>Tentative Approval (TA)</td>
<td>102</td>
<td>95</td>
<td>91</td>
<td>120</td>
<td>184</td>
</tr>
<tr>
<td>Complete Response (CR) ¥</td>
<td>84</td>
<td>1251</td>
<td>1254</td>
<td>1180</td>
<td>1725</td>
</tr>
<tr>
<td><strong>TOTAL</strong> **</td>
<td>978</td>
<td>2321</td>
<td>2413</td>
<td>2416</td>
<td>3056</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DMF Completeness Assessment (CA)</th>
<th>FY2012</th>
<th>FY2013</th>
<th>FY2014</th>
<th>FY2015</th>
<th>FY2016*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1699</td>
<td>1706</td>
<td>901</td>
<td>838</td>
</tr>
</tbody>
</table>

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

** FDA will aspire to the extent possible to maintain levels of productivity at least similar to pre-GDUFA levels, while hiring and training incremental staff necessary to achieve the program performance goals, building necessary systems and implementing outlined program changes in years 1 and 2 of the program (GDUFA Commitment Letter, page 3)


¥ Complete Response both with and without inspections.
ANDA Approvals*

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

NOTE: GDUFA I was negotiated in FY2010 and FY2011.
FY2016 -- A Record Year
Approvals and Tentative Approvals

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

GDUFA starts, 10/1/12

AP & TA
Approvals & Tentative Approvals*

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Reference Listed Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendamustine Hydrochloride for Injection, 25 mg/vial and 100 mg/vial (single-use vials)</td>
<td>Treanda for Injection</td>
</tr>
<tr>
<td>Dasatinib Tablets, 20 mg, 50 mg, 70 mg, and 100 mg</td>
<td>Sprycel Tablets</td>
</tr>
<tr>
<td>Dofetilide Capsules, 0.125 mg, 0.25 mg, and 0.5 mg.</td>
<td>Tikosyn Capsules</td>
</tr>
<tr>
<td>Efavirenz Tablets USP, 600 mg</td>
<td>Sustiva Tablets</td>
</tr>
<tr>
<td>Imatinib Mesylate Tablets, 100 and 400 mg</td>
<td>Gleevec Tablets</td>
</tr>
<tr>
<td>Lacosamide Tablets, 50 mg, 100 mg, 150 mg and 200 mg</td>
<td>Vimpat Tablets</td>
</tr>
<tr>
<td>Mometasone Furoate Nasal Spray, 50 mcg</td>
<td>Nasonex Nasal Spray</td>
</tr>
<tr>
<td>Olopatadine Hydrochloride Ophthalmic Solution USP, 0.1%</td>
<td>Patanol Ophthalmic solution</td>
</tr>
<tr>
<td>Oseltamivir Phosphate Capsules USP, 30 mg, 45 mg and 75 mg</td>
<td>Tamiflu</td>
</tr>
<tr>
<td>Rosuvastatin Calcium Tablets, 5 mg (base), 10 mg (base), 20 mg (base) and 40 mg (base)</td>
<td>Crestor Tablets</td>
</tr>
<tr>
<td>Rufinamide Tablets USP, 200 mg and 400 mg</td>
<td>Banzel tablets</td>
</tr>
<tr>
<td>Sildenafil Citrate Tablets, 25 mg, 50 mg and 100 mg*</td>
<td>Viagra Tablets</td>
</tr>
</tbody>
</table>

*ANDA approved but listed in Discontinued section of Orange Book
Noteworthy approval of a first generic nasal spray

- March 2016, OGD approved the first generic local-acting nasal spray containing mometasone furoate, manufactured by Apotex
- Highly complex product; required novel approaches to demonstrate bioequivalence
- Coordination and collaboration among many offices in CDER and with industry
- New technology - opened a new paradigm for a regulatory pathway in the context of complex drug reviews

For the full story, please refer to the CDER SBIA Chronicles article: FDA Embraces Emerging Technology for Bioequivalence Evaluation of Locally Acting Nasal Sprays
More than 5,400 communications to industry in FY16 during ANDA review

Communication with Industry
Easily Correctable Deficiencies (ECDs) & Information Requests (IRs)

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
Productivity
ANDA Complete Response Letters (CR’s)

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
Generic Drug Review Dashboard

Pre-Year 3 ANDAs
(Lists data since 1/1/16)

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**FDA Snapshot**
- 0 Pending Filing Review
- 72 Filed – No Review Comm.
- 1,372 At Least One Review Communication Issued
- 1,444 with FDA

**Monthly Average**
(July - Sept)
- Complete Responses: 134
- Amendments: 85
- Tentative Approvals: 12

**Industry Snapshot**
- 1,271 Pending Industry Response
- 281 Tentative Approval with Industry
- 1,552 with Industry

**Current ANDA Workload of Original Applications**
- 2,996

**Total Pre-Y3 Application Cohort**
(Since 10/1/2012)
- 1,937 Approvals
- Refuse to Receive: 97
- Resubmitted Y3/4: 130
- No Submission: 653
- Withdrawals (from Cohort): 2,996
- 5,813

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**Numbers are based on current data that will be reviewed and validated for official reporting purposes.**
Prior Approval Supplements (PASs)
Prior Approval Supplements

Exceeding GDUFA Review Goals*

GDUFA PAS Goal

* Goal dates provided on submissions received through November 2015, as those are the goal dates that have actually accrued. The cohort data is not mature enough to report on whole year data

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
Prior Approval Supplements

Exceeding GDUFA Review Goals*

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

Controlled Correspondence
“Controls”
Controls received - per discipline
FY2012 – FY2016*

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
Exceeding Controlled Correspondence Goals

* Goal dates provided on submissions received through May 2016, as those are the goal dates that have actually accrued. The cohort data is not mature enough to report on whole year data.

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes. [Source](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm375079.htm)
Exceeding Controlled Correspondence Goals

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes. [Link](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm375079.htm)
Increases in Controls

- Increasing number of submissions
  - >5,400 controls submitted since GDUFA started
- Increasing complexity
- Still some controls do not follow FDA guidance:
  - FY2014 – 18%
  - FY2015 – 20%
  - FY2016 – 13%
Reminders for Controlled Correspondence Submissions

Before submitting emails to GenericDrugs@fda.hhs.gov refer to the Controlled Correspondence Guidance, September 2015 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM411478.pdf)

- Questions not related to generic drug development
  - contact CDER’s Office of Communications, Division of Drug Information by phone (1-855-543-3784) or e-mail (druginfo@fda.hhs.gov)

- Foreign controlled correspondence inquiries must come through a US Agent

Note: All requests/inquires related to controlled correspondence should come through the Generic Drugs mailbox (GenericDrugs@fda.hhs.gov). This includes requests for the status of a controlled correspondence, request for clarification of a response to a controlled correspondence, or for an explanation of why something was deemed not appropriate for a controlled correspondence.
Helpful hints for Controlled Correspondence Submissions

• The title on communications regarding controlled correspondences is the same as the subject of your email. It is very important that the subject of the controlled correspondence email contain a brief description of the control in order to differentiate between controls.

  Example subject line format: Controlled Correspondence: ‘DRUG PRODUCT & RLD Application No.’ – ‘BRIEF DESCRIPTION OF INQUIRY’
  – i.e., Controlled Correspondence: Amoxicillin Capsules 500 mg RLD A061926 – IIG evaluation of Lactose

• Place all questions along with any supporting documentation as an attachment to your email and not in the body of the email.
OGD Filing

• > 900 original ANDAs, resubmissions, and PASs underwent filing review in FY2016
### Filing – Refuse to Receive (RTR)

*(Based on cohort year of submission)*

<table>
<thead>
<tr>
<th>YEAR</th>
<th># RTR’s</th>
<th>% of Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>FY2010</td>
<td>146</td>
<td>18%</td>
</tr>
<tr>
<td>FY2011</td>
<td>142</td>
<td>16%</td>
</tr>
<tr>
<td>FY2012</td>
<td>156</td>
<td>14%</td>
</tr>
<tr>
<td>FY2013</td>
<td>193</td>
<td>19%</td>
</tr>
<tr>
<td>FY2014</td>
<td>191</td>
<td>13%</td>
</tr>
<tr>
<td>FY2015</td>
<td>124</td>
<td>23%</td>
</tr>
<tr>
<td>FY2016</td>
<td>215</td>
<td>23%</td>
</tr>
</tbody>
</table>

Compared with PDUFA Refuse to File (RTF): early on ~10-30%; FY2016 <5%.

• Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.
Guidance Development

- **New Guidance**
- **Revised Guidance**

<table>
<thead>
<tr>
<th>Year</th>
<th>FY 13</th>
<th>FY 14</th>
<th>FY 15</th>
<th>FY 16</th>
<th>FY 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Guidances Posted</td>
<td>102</td>
<td>78</td>
<td>223</td>
<td>135</td>
<td>67</td>
</tr>
<tr>
<td>New Guidance</td>
<td>61</td>
<td>56</td>
<td>69</td>
<td>94</td>
<td>34</td>
</tr>
<tr>
<td>Revised Guidance</td>
<td>41</td>
<td>22</td>
<td>154</td>
<td>41</td>
<td>33</td>
</tr>
</tbody>
</table>
Noteworthy guidances
Translating GDUFA regulatory science into FDA standards

• “Product-specific” guidances
  – ~200 per year
  – October 2016 – 67 guidances – 34 new and 33 revised
  – Developing more for complex products
    • ~15 for inhalation products

• New “general” guidances
  – Abuse-Deterrent Generic Opioids (March 2016)
  – Transdermal Adhesion (May 2016)
  – rDNA peptides (on public guidance agenda, in progress)
  – Drug-device combination (in progress)
GDUFA research portfolio: Focus on Access to Generics

Advancing the science of equivalence in 10 areas:

• Complex active ingredients
• Topical dermatological products
• Inhalation products
• Ophthalmic products
• Nasal products
• Liposomes and nanomaterials
• Microspheres (long-acting injectables)
• Complex drug-device combinations
• Abuse-deterrent formulations
• Transdermal delivery systems

http://www.fda.gov/forindustry/userfees/genericdruguserfees/ucm370952.htm
GDUFA research portfolio: Focus on Access to Generics

• Each area in portfolio is a $billion/year market without generic competition
• Coordinated internal and external research drives progress
  – ~90 active contracts and grants
• Huge public health impact with small regulatory science investments -- large return on investment (ROI)
  – Guidance on complex products
  – Internal alignment on complex issues
  – Confidence in generic substitution
  – Tool development
  – Faster and smarter generic drug development and review
For more information:

OGD Office of Research Standards presents
Scientific Agenda Update and
Complex Product Discussion

Wednesday, October 26, 9:30-10:00 AM
Additional important OGD updates
First-cycle approvability in OGD Office of Bioequivalence

• 141 ANDAs, submitted between 10/1/14 and 1/15/15
• OB determined the conclusions of the bioequivalence review of original ANDAs were \(~70\%\) approvable on the first cycle
  • High rate of adequate bioequivalence reviews due to availability of product-specific guidances
• Continued Improvement
  • Identify correctable problems with the BE submission and review
  • Self-examination of processes and communication with industry, to hopefully increase the rate of first-cycle approvable bioequivalence reviews even further
OGD Office of Bioequivalence: Publications and Presentations

• On the topic of potential prevention and improvement of BE deficiencies in future original ANDAs:
Office of Generic Drug Policy

• Primary role in GDUFA II negotiations
• Significant Policy Deliverables
  – MMA Final Rule
  – Issuance of scientific guidances (in collaboration with ORS)
    – Assessing Adhesion for Generic TDS and Topical Patches
    – Evaluating Abuse Deterrence of Generic Opioid Products
  – Anticipated issuance of regulatory guidances
    – 180-Day Exclusivity
    – Referencing Products in ANDAs
    – Determining 505(b)(2) or 505(j) Pathway
• Orange Book Mobile App
• Orange Book 2.0 Upgrade
For more information:

ODG’s Office of Generic Drug Policy
Patent & Exclusivity
Wednesday, October 26, 8:00-9:30 AM
OGD
COMMUNICATIONS
Communication Enhancements

• Monthly Activities Report of the Generic Drug Program
• Quarterly Generic Drug Review Dashboard
• Generic Drugs listserv
  – OGD RPMs using in signature block
  – >800 signed up in first month
• Office of Generic Drugs Annual Report
• GDUFA Regulatory Science Report
• CDER Drug Safety Report
Communication Enhancements

• Monthly **Activities Report** of the Generic Drug Program

• Quarterly **Generic Drug Review Dashboard**
  – http://go.usa.gov/cunHT

• Office of Generic Drugs **Annual Report**

• GDUFA **Regulatory Science Report**
  – http://www.fda.gov/forindustry/userfees/genericdruguserfees/ucm370952.htm

• CDER **Drug Safety Report**
Generic Drug Review Dashboard

Review productivity and current workload with FDA and with industry

Updated Quarterly

Four reports available:

- Total Original ANDA Workload Activity for Pre-GDUFA Year 3 Application Cohorts
- Total Original ANDA Workload Activity for All Unapproved Applications
- Original ANDAs - Total Agency Actions for the Most Recent 12 Months
- ANDA Prior Approval Supplements - Total Agency Actions for the Most Recent 12 Months

http://go.usa.gov/cunHT
Orange Book Express Mobile App

• Search the public Orange Book Database for Approved Drugs and Patent and Exclusivity Information

• Search all marketing statuses (Rx, OTC, Discontinued) with one search

• Identify Reference Listed Drugs and determine if a drug product is considered to be a therapeutic equivalent

• Browse patent delistings and newly added patents

• Launched 11/9/2015
Continuing Enhancements

http://go.usa.gov/xDPEh
CDER Drug Safety Report


• Safety across the drug product lifecycle
• Tracked Safety Issues (TSIs)
• Safety Labeling Changes (SLCs) & Drug Safety Communications (DSCs)
  – Jan. 2015 to July 2016 - >1,600 SLCs
• FAERS and Sentinel
  – Signal identification & tracking
• Abuse Deterrent Opioids
• OGD Clinical Safety and Surveillance Staff (CSSS)

How do we measure success?

• **Formal negotiated GDUFA Goals**

• **Stakeholder Expectations**
  1. Number of approvals (and tentative approvals)
  2. Progress on Approving ANDAs vs. first action on “backlog”
World of ANDAs

- Currently **APPROVED** ANDAs = 10,000*
- Unapproved ANDAs = 4,000*

Many approved ANDAS are not marketed

*Approximate Values, September 2016
ANDAs at FDA

*Approximate Values, September 2016
FDA’s Generic Review Pipeline
By submission cohort as of September 30, 2016

ANDAs & ANDA Re-submissions

PRE GDUFA SUBMISSIONS
FY2013  Year 1
FY2014  Year 2
FY2015  Year 3
FY2016  Year 4

First FDA review pending  Under FDA Review (includes many re-submissions)

2,273 Approvals & Tentative Approvals Post-GDUFA

Approx. 2,200 Total ANDAs
ANDAs at FDA
(n = ~2,200)

• Year 3 & 4 ANDAs (GDUFA goals are in the future)
  – Most are “on the FDA clock” and “within goal”
• Many are resubmissions or amendments
  – Especially for Pre-GDUFA submissions, Year 1 & 2
  – Most are ANDAs with multiple review cycles
• Small percentage pending 1\textsuperscript{st} review
  – Most of these are Year 4 -- some of these were submitted 3-4 weeks ago
• Small percentage have missed GDUFA goals

\textbf{SUMMARY:}
1. FY2015 & 2016 – meeting & exceeding GDUFA goals
2. Pre-Year 3 - < 100 ANDAs not touched by FDA and no communications to industry
Complete Response Letters (CRs) & TA’s - not yet responded to and with industry

*Approximate Values, September 2016
CRs & TA’s not yet responded to and with industry (n = ~1,800)

- Not on the Agency’s clock
- TA - ~300 ANDAs
- Complete Response Letter has been issued
- These ANDAs have not yet met the Agency’s standards for approval
  - Deficiencies must be addressed before FDA can approve
- FDA does not know when -- or if -- any of these submissions will come back to FDA for a subsequent review cycle
The data used in this figure are from FDA’s Orange Book (downloaded 1/7/2016). The unit of observation is the drug ingredient. Different useable forms (e.g., salts or esters) of the same core molecule are counted as separate drug ingredients; this does not differentiate between multiple dosage forms (e.g., capsules versus tablets) for the same drug ingredient. Each drug ingredient is identified as having either multiple approved sponsors (dark blue group) or a single approved sponsor.
Overview

1. Reminder of GDUFA basics
2. Progress toward goals
   - Formal, negotiated GDUFA goals
   - Stakeholder expectations
3. Application Approvability
4. Closing Comments
Application “approvability”

FDA will Approve or TA an ANDA WHEN it meets the Agency’s standards for approval
In the past...

CMC Review Cycles for ANDAs to Approval

2009 through July 2014

Number of Approvals

Cycle Number

Moving Average Trendline
Cohort Year 3 Original ANDA Data*

Commitment Goal: Act on 60% within 15 months

Current Performance (through 9/30/2016): 98%

<table>
<thead>
<tr>
<th>Category</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Originals Received</td>
<td>522</td>
</tr>
<tr>
<td>Met Goal</td>
<td>423</td>
</tr>
<tr>
<td>Pending within Goal</td>
<td>90**</td>
</tr>
<tr>
<td>Completed Not within Goal</td>
<td>5</td>
</tr>
<tr>
<td>Pending Overdue</td>
<td>4</td>
</tr>
</tbody>
</table>

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

**3 more months for Cohort Year 3 with pending Goal dates
First Action for Original ANDA (%)

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.*
**Cohort Year 3 Approvals** *(n=22)*

<table>
<thead>
<tr>
<th>ANDA</th>
<th>Applicant</th>
<th>Drug</th>
<th>Date Received</th>
<th>Date AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>207955</td>
<td>SPEAR</td>
<td>Tretinoin</td>
<td>10/1/2014</td>
<td>8/13/2015</td>
</tr>
<tr>
<td>206548</td>
<td>AUROBINDO</td>
<td>Loperamide Hydrochloride*</td>
<td>10/7/2014</td>
<td>12/15/2015</td>
</tr>
<tr>
<td>206402</td>
<td>ALKEM</td>
<td>Gabapentin</td>
<td>10/17/2014</td>
<td>12/23/2015</td>
</tr>
<tr>
<td>206815</td>
<td>INVATECH</td>
<td>Sodium Polystyrene Sulfonate</td>
<td>11/18/2014</td>
<td>2/18/2016</td>
</tr>
<tr>
<td>208101</td>
<td>IGI LABORATORIES</td>
<td>Desoximetasone Ointment</td>
<td>11/26/2014</td>
<td>2/25/2016</td>
</tr>
<tr>
<td>208150</td>
<td>APOTEX</td>
<td>Fluticasone Propionate</td>
<td>12/1/2014</td>
<td>2/29/2016</td>
</tr>
<tr>
<td>208077</td>
<td>AMNEAL</td>
<td>Diclofenac Sodium</td>
<td>12/19/2014</td>
<td>3/18/2016</td>
</tr>
<tr>
<td>208206</td>
<td>AMNEAL</td>
<td>Raloxifene Hydrochloride</td>
<td>2/10/2015</td>
<td>4/8/2016</td>
</tr>
<tr>
<td>208127</td>
<td>CROSSMEDIKA</td>
<td>Trimipramine Maleate</td>
<td>2/18/2015</td>
<td>4/15/2016</td>
</tr>
<tr>
<td>207433</td>
<td>INDICUS</td>
<td>Desipramine Hydrochloride</td>
<td>2/9/2015</td>
<td>5/5/2016</td>
</tr>
<tr>
<td>208191</td>
<td>DR REDDYS</td>
<td>Nitroglycerin*</td>
<td>2/27/2015</td>
<td>8/26/2016</td>
</tr>
<tr>
<td>207049</td>
<td>VERSAPHARM</td>
<td>Voriconazole*</td>
<td>3/6/2015</td>
<td>9/7/2016</td>
</tr>
<tr>
<td>207938</td>
<td>FLAMINGO</td>
<td>Piroxicam*</td>
<td>10/30/2014</td>
<td>9/9/2016</td>
</tr>
<tr>
<td>208301</td>
<td>GLENMARK</td>
<td>Diclofenac Sodium*</td>
<td>3/30/2015</td>
<td>9/13/2016</td>
</tr>
<tr>
<td>208451</td>
<td>AUROBINDO</td>
<td>Eszopiclone</td>
<td>5/29/2015</td>
<td>9/15/2016</td>
</tr>
</tbody>
</table>

*Not first cycle

Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes. Data through September 2016.
## Cohort Year 3 TAs¥ (n=25)

<table>
<thead>
<tr>
<th>ANDA</th>
<th>Applicant</th>
<th>Drug</th>
<th>Date Received</th>
<th>Date TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>208068</td>
<td>Paddock</td>
<td>Diclofenac Sodium</td>
<td>10/30/2014</td>
<td>10/14/2015</td>
</tr>
<tr>
<td>208098</td>
<td>Taro</td>
<td>Diclofenac Sodium</td>
<td>12/12/2014</td>
<td>1/14/2016</td>
</tr>
<tr>
<td>206401</td>
<td>Ajanta</td>
<td>Sildenafil Citrate*</td>
<td>10/16/2014</td>
<td>1/21/2016</td>
</tr>
<tr>
<td>208037</td>
<td>MSN Labs</td>
<td>Lurasidone Hydrochloride</td>
<td>10/28/2014</td>
<td>1/25/2016</td>
</tr>
<tr>
<td>208066</td>
<td>Sun Pharma</td>
<td>Lurasidone Hydrochloride</td>
<td>10/28/2014</td>
<td>1/25/2016</td>
</tr>
<tr>
<td>207944</td>
<td>Par</td>
<td>Aspirin; Dipyridamole</td>
<td>11/28/2014</td>
<td>3/1/2016</td>
</tr>
<tr>
<td>206894</td>
<td>Cipla LTD</td>
<td>Efavirenz; Emtricitabine; Tenofovir Disoproxil Fumarate</td>
<td>11/26/2014</td>
<td>3/22/2016</td>
</tr>
<tr>
<td>208130</td>
<td>Sciegen Pharmaceuticals, Inc</td>
<td>Olmesartan Medoxomil</td>
<td>1/21/2015</td>
<td>4/7/2016</td>
</tr>
<tr>
<td>208097</td>
<td>Glenmark Generics LTD</td>
<td>Norethindrone Acetate; Ethinyl Estradiol; Ferrous Fumarate*</td>
<td>11/28/2014</td>
<td>4/22/2016</td>
</tr>
<tr>
<td>208174</td>
<td>Teva</td>
<td>Ranolazine ER Tablets</td>
<td>12/30/2014</td>
<td>5/12/2016</td>
</tr>
<tr>
<td>208247</td>
<td>Strides Pharma</td>
<td>Roflumilast</td>
<td>3/2/2015</td>
<td>5/31/2016</td>
</tr>
<tr>
<td>208198</td>
<td>Amneal Pharmaceuticals</td>
<td>Diclofenac Sodium</td>
<td>2/18/2015</td>
<td>6/9/2016</td>
</tr>
<tr>
<td>208212</td>
<td>Teva Pharmaceuticals USA</td>
<td>Vilazodone Hydrochloride*</td>
<td>1/21/2015</td>
<td>7/11/2016</td>
</tr>
<tr>
<td>208355</td>
<td>Aurobindo Pharma LTD</td>
<td>Dolutegravir</td>
<td>3/31/2015</td>
<td>9/19/2016</td>
</tr>
</tbody>
</table>

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*Not first cycle
## Cohort Year 3 Cycle Rates* (9/30/2016)

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Cycle</td>
<td></td>
</tr>
<tr>
<td>RTR Rate</td>
<td>20%</td>
</tr>
<tr>
<td>AP/TA Rate</td>
<td>8%</td>
</tr>
<tr>
<td>CR Rate</td>
<td>72%</td>
</tr>
<tr>
<td>Second Cycle</td>
<td></td>
</tr>
<tr>
<td>AP/TA Rate</td>
<td>43%</td>
</tr>
<tr>
<td>CR Rate</td>
<td>53%</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>4%</td>
</tr>
</tbody>
</table>

*All Minor Amendment responses to date

---

*Numbers are based on preliminary data that will be reviewed and validated for official reporting purposes.

*3 more months for Cohort Year 3 data still have pending Goal Dates.
ANDA “Approvability”

• Majority of ANDAs received Complete Response (CR) letter
• Frequent deficiencies include:
  – Inadequate CMC
    • Stability, dissolution, inactive ingredients
  – Inadequate facilities
• CR leads to multiple review cycles and long time to AP/TA
Likely to see a decrease in 1\textsuperscript{st} cycle approvals in Year 5 with 10 month goal dates, because less time for multiple information requests (IRs) from FDA to industry to fix application deficiencies.

**Proposed Year 5 timeline:**

<table>
<thead>
<tr>
<th>Step</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filing Review (OGD)</td>
<td>0 – 60d</td>
</tr>
<tr>
<td>Review Team Assignment</td>
<td>Within 70d</td>
</tr>
<tr>
<td>Kick-Off Meeting</td>
<td>Within 90d</td>
</tr>
<tr>
<td>Assessment #1 and Cumulative IR #1</td>
<td>Within 120d</td>
</tr>
<tr>
<td>IR #1 Response Received and Reviewed</td>
<td>4mo – 6.5mo</td>
</tr>
<tr>
<td>Complete Inspection</td>
<td>Within 7.0mo</td>
</tr>
<tr>
<td>IR #2 Response Received and Reviewed</td>
<td>6.5mo – 8.5mo</td>
</tr>
<tr>
<td>Wrap up and Final Review</td>
<td>Within 9.0mo</td>
</tr>
</tbody>
</table>
First Cycle Approval Rate Under PDUFA

CDER NME NDAs/BLAs†
First Action Approval Rate

RIGHT
THE FIRST
TIME

Fiscal Year of Receipt

First Cycle Approvals

- 1993: 36%
- 1994: 23%
- 1995: 30%
- 1996: 50%
- 1997: 35%
- 1998: 25%
- 1999: 54%
- 2000: 31%
- 2001: 25%
- 2002: 50%
- 2003: 48%
- 2004: 42%
- 2005: 45%
- 2006: 52%
- 2007: 52%
- 2008: 46%
- 2009: 43%
- 2010: 56%
- 2011: 70%
- 2012: 72%
- 2013: 78%
- 2014: 89%
- 2015*: 95%
Lessons learned from PDUFA

• Complete Application is critical

• High quality NDA applications result in:
  – Low Refuse To File (RTF) rates
  – High first cycle approval rates
  – Short time to approval
Overview

1. Reminder of GDUFA basics
2. Progress toward goals
   – Formal, negotiated GDUFA goals
   – Stakeholder expectations
3. Application Approvability
4. Closing Comments
What are the reasons for the increase in Approvals/TAs?

1. GDUFA

2. GDUFA

3. GDUFA
What are the reasons for the increase in Complete Response letters?

1. GDUFA
2. ANDAs have deficiencies that need to be corrected before the Agency can approve/TA
3. Multiple review cycles to get to AP/TA
Years 3 & 4 metric goals
How are we doing?

• FDA met or exceeded all Year 3 & 4 metric goals
• Year 4 report to Congress due January 2017
• **GDUFA performance reports**
  http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/UserFeeReports/PerformanceReports/ucm384247.htm
GDUFA I
Year 5 – FY2017

• Review metrics tighten – “Double Whammy”
  – original ANDAs 90% in 10 months
• Not a lot of wiggle room to miss goal dates

Strong Focus on:
• Meeting Target Action Dates (TADs), “due date” for non-goal date pre-year 3 ANDAs
• *First generics*: Avoiding First to File (“FTF”) PIV forfeitures, pursue timely first generic approvals
GDUFA I
Year 5 – FY2017

• Continue to follow the Year 3 & 4 ANDAs (and other applications) through to their GDUFA goal dates
  – There will be overlap during Year 5 of ANDAs with 15 month goals (Years 3 & 4) and those with 10-month goals (Year 5)

• Continue to work on non-goal date applications
What’s next - GDUFA II

• Behind the scenes work - NOW (Year 5 of GDUFA I)
• Hit the ground running in GDUFA II
  – GDUFA Reauthorization
    http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm476940.htm
  – Commitment letter:

• Sessions related to GDUFA II:
  Tuesday October 25, 9-10AM
  Tuesday October 25, 2:45-3:45PM
What else is next?

• Implementation of the eCTD standards.
• Goes into effect Spring 2017
• Applications that do not meet these standards do not get received by FDA, i.e., RTR

• Session related to eCTD:
  Wednesday October 26, 10:30AM-12:00PM
FDA Delivering on GDUFA

• FDA is fulfilling its GDUFA commitments
• In many cases, going above and beyond our negotiated commitments
• We are building a robust, modern generic drug regulatory program
  – Sustainable and predictable
  – Clear and consistent communication
  – Fairness across applications and applicants
Personal reflections
THANK YOU!

U.S. FOOD & DRUG ADMINISTRATION