TB Drug Shortages
Results from the NTCA survey and ACET next steps

Jennifer Flood, Sundari Mase, Barbara Seaworth, Neha Shah
MDR Expert Network
November 10, 2011

Essential Components of Tuberculosis Prevention Program (1995)

- Recommendations from the Advisory Committee for the Elimination of Tuberculosis (ACET)
- “Ensuring that patients who have TB receive appropriate treatment until they are cured”
- “Treating patients without consideration of their ability to pay”

WHO Stop TB strategy components and implementation approach

- 6 components
- Component 1: Pursuing high-quality DOTS expansion and enhancement
- Component 1, Element 4: An effective drug supply and management system
  - Uninterrupted and sustained supply of anti-TB drugs fundamental to TB control
  - Reliable system of procurement and distribution of anti-TB drugs should be in place
  - Anti-TB drugs should be available free of charge, both because patients are poor and may not afford them, and because treatment has benefits that extend to society
  - Legislation related to drug regulation should be in place

Drug Shortages 2010

- Number shortages tripled between 2005 – 2010
- Majority are sterile injectables
- Most common oncology drugs, antibiotics, electrolyte/nutritional drugs

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of Tuberculosis Elimination

Essential Components of a Tuberculosis Prevention and Control Program
Screening for Tuberculosis and Tuberculous Infection in High-Risk Populations
Recommendations of the Advisory Council for the Elimination of Tuberculosis
Reasons for drug shortages

- Most common: problems with the manufacturing facility
  - Includes finding glass shards, metal filings, fungal or other contamination especially in injectables
- Delays in manufacturing or shipping
- Active pharmaceutical ingredient shortages
- Increased demand outpacing supply

Others Challenges contributing to drug shortages

- Passive reporting
- Manufacturing issues
- Gray market
- Medically necessary medications
- Short dated medications
- Sole source for drugs
- Lengthy procurement processes for certain drugs

Results of Drug Shortages on Care of Patients

- Medication errors or adverse events
- Adverse consequences related to using alternative medication
- Delays in treatment or procedures
- Need to use less effective drug
- Rationing or restricting drugs
- Increase drug costs
- Staff time dedicated to drug procurement and labor costs for these activities

Tuberculosis and Drug Shortages

- Since 2005, shortages of the following TB medications have occurred: isoniazid, rifampin, cycloserine, ethionamide, rifabutin, amikacin, capreomycin, kanamycin and streptomycin
- September 2011: Concerns for shortages or difficulty procuring Isoniazid
Tuberculosis and Drug Shortages

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<tr>
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<tbody>
<tr>
<td>Kanamycin</td>
<td>Unavailable</td>
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<td>Available</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Available</td>
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<tr>
<td>Amikacin</td>
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<td>Capreomycin</td>
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<td>Levofloxacin</td>
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<td>Moxifloxacin</td>
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<td>Cycloserine</td>
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<td>PAS</td>
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<td>Ethionamide</td>
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<td>Linezolid</td>
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<td>Clofazamine</td>
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</tbody>
</table>

- Red = Unavailable, Orange = Allocation on emergency basis only, Yellow = Short dated or not available at wholesalers, Green = Available, Purple = Investigation Drug requires prior authorization.

What are the challenges to an uninterrupted supply of anti-TB medications?

<table>
<thead>
<tr>
<th>Medications</th>
<th>Challenges to an uninterrupted supply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanamycin</td>
<td>No US manufacturer</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Sole US manufacturer; increased demand cause for Aug/Sept 2011 shortage.</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Materials short for production overseas FDA inspection pending</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Sole US manufacturer. Price increase x 10 since change in manufacturer (2007: $11.71/gram vial; 2010: $137/gram vial after the manufacturer changed from Eli Lilly to Akron; 2011: New report of ~$300/gram vial)</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Sole US manufacturer; price doubled when license transferred from Eli Lilly</td>
</tr>
<tr>
<td>PAS</td>
<td>Sole US manufacturer</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Not immediately available via wholesaler</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Very expensive</td>
</tr>
<tr>
<td>Clofazamine</td>
<td>Requires IND and local IRB approval, process takes 8-10 wks</td>
</tr>
</tbody>
</table>

Other Challenges for anti-TB medications

- Short dating results in medications being difficult for pharmacies or TB programs to obtain
- Increased cost means that key drugs are no longer affordable by programs and patients
  - Drug costs larger than many TB program’s budget
  - Not covered: students, temp workers, undocumented
  - "Gray-market" suppliers
- Restriction of drugs to investigational use only requires a lengthy application process

Effect of TB Drug Shortage

- Impact felt by patient, programs, providers
- TB programs lose credibility; can’t meet core functions
- Patient’s disease may worsen, acquire further drug resistance, or TB may spread
- Failed response to outbreaks: perfect storm – short on drugs, overwhelmed with disease
- TB not controlled
MDR-TB Case Presentation
Dangers of Drug Shortages

Robert Petrossian
Heartland National TB Center

March 6-8, 2011

March 6
• 7 month admitted with possible viral lower respiratory tract infection
• Stiff neck and bulging fontanelle noted
• Basilar meningitis; severe communicating hydrocephalus
  - Ventriculostomy placed, ventricular fluid: glucose 31, protein 85, WBC 5
  - CSF smear negative

March 8
• Started on RIPE (Tuberculosis suspected)
  - Positive QFT-GIT (March 16, 2011)
  - Father identified as source case
• Discharged to home 3/29/2011

April 14
• Source case
  - INH resistance confirmed, rifampin resistance is suspected.

TB expert recommends
• Stop INH; stop rifampin if resistance is confirmed.
• Add: amikacin, ethionamide, levofloxacin
• Molecular susceptibility testing.
**April 8 – 15, 2011**

- Intermittent vomiting, no weight gain
- Readmitted to hospital

**April 18-20**

- *Rifampin resistance (MDR TB)* is confirmed in source case
- Child receiving **only** pyrazinamide and ethambutol
  - EMB has poor meningeal penetration.
  - Most second line drugs not yet available (levofloxacin en route to HD)

**April 20**

- Pediatric TB expert recommends:
  - Add cycloserine
  - Substitute capreomycin if amikacin is not available.
  - Stop ethambutol (resistance identified in source case)

**April 21**

- Capreomycin substituted for amikacin
- Searching for ethionamide and cycloserine

**April 22**

- Entire 4 drug regimen for MDR-TB given.
  - (Father finally also has access to medications 4/25/2011)

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### Consequences of Drug Shortages

- **Delay of adequate treatment**: **8 days**.
- Patient does not gain weight
- Patient has frequent bouts of vomiting
  - Medication absorption possibly impacted
- Patient noted to be behind on developmental milestones when evaluated by pediatric expert

### TB Meningitis Outcomes

**Mortality (higher than any other form of TB)**

- **23-29%** Adult drug susceptible
  - Doubled when INH resistance is present
- **16%** in pediatric (up to 15 y.o.) drug susceptible TBM
- **43%** for infants <1 year with drug susceptible TBM
- **75%** in pediatric MDR-TB
  - (Small study 8 children, 6/8 HIV+)
- **27%** of survivors report neurological sequelae
**Human Resources Involved in Tracking Down Medications**

- 2 Physician Consultants
- 2 Local Physicians
- Heartland National TB Center Nurse Consultant
- State TB Controller
- State Health Department Nurse Consultant
- State Department Pharmacist
- 2 Local nurse case managers

**Drug Shortage Issues In NYC**

Felicia Dworkin, MD
Bureau of TB Control
Deputy Director, Medical Affairs
New York City Department of Health & Mental Hygiene

**TB Cases and Rates New York City, 1980 – 2010**

- 711 cases in 2010
- 6% decrease from 2009 (760 cases)


- 1,312 US-Born
- 587 (78% of NYC cases)
- 1,010 Non-US-Born

*Puerto Rico and U.S. Virgin Islands are included as US-born
†There were 4 cases with unknown country of birth in 2009
MDR-TB and XDR-TB in NYC

Characteristics of MDR Cases (N=11)
New York City, 2010
- 82% are non-US born
- 27% are HIV-positive
- 73% had pulmonary TB only
- 100% of those eligible are on DOT

This group of patients does not include those on an injectable agent &/or 2nd line medications because they are Rifampin resistant or not tolerating standard regimens

Capreomycin Shortage
- First experienced shortage 1/2011, unable to obtain by April (Cardinal Health)
- May 2011: 7 patients in DOHMH clinics were evaluated to switch from capreomycin to amikacin or streptomycin
  - 2 required capreomycin to be continued due to susceptibilities
  - 3 switched to alternative medication
  - 2 were taken off injectable as completing induction phase
- NYC hospitals were unable to get any medication, would ask TB Bureau for assistance
- As of July 2011, only supplier is Akron

Amikacin
- DOHMH pharmacy only has limited supply and does not provide enough per week to the clinics
  - Some companies completely stopped manufacturing or making some doses. From the FDA website:
    - Bedford’s other products are on shortage due to manufacturing delays. There are limited quantities of amikacin 250 mg/mL 2 mL (NDC 55390-0226-02) vials available for direct order or drop shipment only. The 250 mg/mL 4 mL vials are available in limited supply. The company estimates the next release date of the 4 mL vials of mid-October, 2011
    - Hospira discontinued amikacin in May, 2010 due to a raw material shortage.
    - Teva’s product was unavailable due to manufacturing delays. They have amikacin 250 mg/mL 4 mL vials (NDC 00703-9040-03) available. The 2 mL vials are on back order and the company cannot estimate a release date.
    - Sandoz discontinued Amikacin injection in 2006. 

Streptomycin

- According to FDA, Streptomycin supply should be back by the end of September 2011
  - It has been unavailable in DOHMH pharmacy
  - 1 gm streptomycin only became available Friday 11/4/11

Kanamycin

- Has not been available for at least 1 year in the US

Issues Because Of Drug Shortage

- Need to re-assess patient every time an injectable agent is not available
  - Check drug susceptibilities of each patient
  - Previous adverse effects to medication may limit what can use
- Switching from capreomycin to amikacin
  - Changing from lower volume injection to larger volume
  - Can be painful if given IM
  - A PICC line is preferred to administer this drug, but a line may need to be inserted and maintained
  - Need to check for kanamycin resistance

Ethionamide Shortage

- Has been in short supply several times over past few years

From: [email address]
Sent: Wednesday, November 24, 2010 12:48 PM
Subject: RE: ethionamide availability

Dear TB Control Colleagues,

We have been informed of a possible ethionamide drug shortage. We have been monitoring this situation with FDA. Please see drug procurement information for ethionamide below:

Ethionamide (sold as Trecator by Wyeth) is available but is currently short dated. The current remaining inventory expires in February 2011. Until new production is available, if a facility can’t get this from their wholesaler, they can have their wholesaler call Wyeth at 1-800-395-9938 to place the order for them. For ordering purposes the 250mg tablets are sold as bottles of 100, NDC: 00008-4117-01. Wyeth does plan to have new production available soon.

Updates on this situation will be posted on the FDA website soon. I will send the link when available and will keep you posted with any updates on this topic. Thank you very much for your patience with this situation, and as you become aware of other shortages, please let us know.

Clofazimine

- In NYC, is only used as a 3rd line drug
- Since 2005, can only obtain medication thru an IND from the FDA (paperwork!!!)
  - A protocol and consent form are needed to show the FDA with the application[21CFR 312.42(b)(3)]
  - Annual progress report
  - Side effects need to be reported
- 10 patients were placed on clofazimine as part of a MDR/XDR regimen since 2004
MDRTB & Rifampin Resistant Cases as of 11/2011

- Open cases on therapy: 27
- Cases currently on injectable: 13
- NYC Pharmacy Information: 10/26/11
  - Capreomycin: only available from Akron sporadically (manufacturing issues)
  - Amikacin: Teva Pharmaceuticals and Bedford have manufacturing delays
  - Streptomycin: X-Gen Pharmaceuticals has manufacturing delay, not available until end 10/2011

MDRTB & Rifampin Resistant Cases as of 11/2011

- As of 11/2/11, 10 patients receive injectable agents via NYC DOHMH DOT
  - 4 on amikacin (1 was switched to capreomycin on 11/1, due to availability)
  - 2 on streptomycin
  - 7 on capreomycin
    - The 2 on streptomycin were changed to capreomycin mid October due to lack of available streptomycin.
- 3 additional patients are treated by non-DOHMH facilities, but are also having trouble obtaining medications

Clinical Impact

- So far, no problem with obtaining an alternative medication(s)
  - No patient has gone without an appropriate injectable agent
- Have not noted adverse events related to changing of medications
- No new resistance demonstrated as yet

What happens when we don’t have drugs??

NATIONAL TB CONTROLLER’S ASSOCIATION SURVEY OF TB DRUG SHORTAGES
Background for NTCA Survey

- NTCA had been hearing reports of TB programs having difficulty procuring TB medications especially for multi-drug resistant patients.

- In response, to better assess if there was a national problem with acquiring anti-TB medications and the extent of the problem, the NTCA conducted a nationwide survey.

Methods

- Eligibility criteria:
  - Designated TB Controller of any level program: state, local, county
  - Registered members of the NTCA in November 2010
  - Had a registered and functioning email address

- Survey created on SurveyMonkey by members of the NTCA.

- Survey distributed by email and completed via the internet.

- Answers stored and analysis conducted using SurveyMonkey software.

RESULTS

54% response rate (33/61)

Characteristics of TB programs responding to NTCA survey, 2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of TB Program</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>4 (12)</td>
</tr>
<tr>
<td>State</td>
<td>29 (88)</td>
</tr>
<tr>
<td>Number of TB Cases reported per year</td>
<td></td>
</tr>
<tr>
<td>0 – 50</td>
<td>7 (21)</td>
</tr>
<tr>
<td>51 – 100</td>
<td>10 (30)</td>
</tr>
<tr>
<td>&gt; 100</td>
<td>16 (48)</td>
</tr>
<tr>
<td>Number of MDR Cases Reported per year</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (21)</td>
</tr>
<tr>
<td>1 – 10</td>
<td>20 (61)</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Missing</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Pay HRSA 340B Drug Pricing Program prices</td>
<td>25/29 (86)</td>
</tr>
</tbody>
</table>
Anti-TB medication drug shortages experiences by TB Controllers in the US, NTCA Survey 2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n/N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faced any challenges obtaining MDR-TB medications* in the past 5 years</td>
<td>21/33 (64)</td>
</tr>
<tr>
<td>If yes, which ones?</td>
<td></td>
</tr>
<tr>
<td>Nationwide shortage</td>
<td>21/22 (95)</td>
</tr>
<tr>
<td>Shipping delays</td>
<td>15/21 (71)</td>
</tr>
<tr>
<td>Medications too expensive for their program</td>
<td>13/24 (54)</td>
</tr>
<tr>
<td>Medications too expensive for insured patients</td>
<td>8/20 (40)</td>
</tr>
<tr>
<td>Medications too expensive for uninsured patients</td>
<td>10/20 (50)</td>
</tr>
<tr>
<td>Delays caused by the IND/IRB process</td>
<td>10/17 (59)</td>
</tr>
<tr>
<td>Payor bureaucracy</td>
<td>7/19 (37)</td>
</tr>
</tbody>
</table>

Adverse effects due to challenges

| Delay in starting treatment | 11/19 (58) |
| Treatment lapse/interruption | 6/19 (32) |
| Inadequate Regimen | 6/19 (32) |
| Substantial staff time tied up with drug procurement | 13/19 |

* MDR medications include Capreomycin, Amikacin, Kanamycin, Moxifloxacin, Levofloxacin, PAS, Cycloserine, Ethionamide, Linezolid, Delamanid

Services provided by TB programs in the US, NTCA Survey, 2010

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n/N, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct clinical care for MDR patients</td>
<td>13/32 (41)</td>
</tr>
<tr>
<td>Consultative care to MDR TB patients</td>
<td>27/32 (84)</td>
</tr>
<tr>
<td>Oversight only for MDR TB patients</td>
<td>12/33 (36)</td>
</tr>
<tr>
<td>Directly supply MDR TB medications to patients</td>
<td>25/33 (76)</td>
</tr>
<tr>
<td>Number programs whose MDR patients are insured</td>
<td>7/33 (21)</td>
</tr>
</tbody>
</table>

Limitations

- Poor response rate
- Bias sample
- Not representative of all programs in the US with few respondents from the local level
- Majority MDR patients reported by a few states
- Questions not validated prior to survey dissemination

Conclusions

- Shortages in MDR-TB medications have been experienced by many TB programs nationally
- Shortages in MDR-TB medications have adverse consequences
- Many agencies, staff and resources are needed to resolve drug shortages issues
U.S. Drug Shortages

Overview

• Background on CDER Drug Shortage Program
• U.S. Drug Shortage Trends
• Reasons for Drug Shortages
• Industry’s Role
• CDER’s Approach to Prevention/Mitigation of Drug Shortages (includes, drugs, therapeutic proteins, monoclonal antibodies)

Current Relevant Authorities

• Very limited authorities directly related to drug shortages
• Limited notification requirement
  – Only requirement is notification of sole source discontinuation
  – No consequence for failure to notify
• Manufacturing capacity - FDA cannot dictate the production quantity
• Program operates largely based on voluntary participation of industry

U.S. Shortages

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Involving Sterile Injectables</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>61</td>
<td>60</td>
</tr>
<tr>
<td>2006</td>
<td>56</td>
<td>60</td>
</tr>
<tr>
<td>2007</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>2008</td>
<td>110</td>
<td>110</td>
</tr>
<tr>
<td>2009</td>
<td>157</td>
<td>157</td>
</tr>
<tr>
<td>2010</td>
<td>178</td>
<td>178</td>
</tr>
</tbody>
</table>

Year
Shortage Trends
Injectables-- 2010

• 54% - Due to Product Quality/significant CGMP issues (e.g., particulate, contamination, impurities)
• 21% - Due to Delays/Capacity issues
• 11% - Due to Discontinuations
• 5% - Due to raw material (API) issues
• 4% - Increase in demand due to another shortage
• 3% - Due to loss of manufacturing site
• 2% - Due to component problems/shortage

Reasons for Shortages – Older Sterile Injectables
When a firm has manufacturing/quality problem with older injectables or discontinues a product, a shortage usually occurs

• Not enough manufacturing capacity
• Industry consolidation
  – Fewer firms making these products
  – Seven (?) manufacturers make up large percentage of this market
  – Contract manufacturers – firms contract out manufacturing as well as acting as contract manufacturers
• Lack of redundancy
  – Multiple products made on existing manufacturing lines
• Complex manufacturing process
• Generally not economically attractive
  – e.g., propofol 20ml sells for $0.48/vial

FDA’s Approach to Shortage Prevention/Mitigation - 1

• Consider medical necessity
• Risk/Benefit of the drug always considered
• FDA does everything possible within our authority to continue availability while minimizing risk to patients.
• For manufacturing/quality problems – work with the firm to address the issues.
• Flexibility may be employed to address shortages to mitigate any significant risk to patients (e.g., Cytarabine injection)

FDA’s Approach to Shortage Prevention/Mitigation - 2

• Encourage remaining firms to ramp up if others manufacturing.
• FDA can and does expedite issues related to addressing shortages (e.g. new manufacturers, increased expiry, increased capacity, new raw material source, changes in specifications).
• In rare cases, temporary importation from unapproved sources
  – 2010 temporary importation of propofol
  – 2011 temporary importation of foscarnet, ethiodol, thiotepa, niorepinephrine, Xeloda, levoleucovorin, leucovorin
Prevented Shortages - 2010

- In 2010, 38 shortages were prevented due to early notification from firms
  - 16 prevented through regulatory discretion (risk of quality/manufacturing issue able to be mitigated and was outweighed by benefit of the drug)
  - 13 prevented through expedited review (new manufacturing sites, suppliers, changes in specification or other changes)
  - 8 prevented through encouraging other firms to ramp up
  - 1 prevented through communication with DEA regarding firm's report to FDA regarding need for quota increase

Prevented Shortages – 2011 (to date)

- In 2011, have seen increased reporting by manufacturers of potential shortages.
  - 99 shortages have been prevented so far due to early notification from firms
    - 84 prevented through expedited review (new manufacturing sites, suppliers, changes in specification or other changes)
    - 12 prevented through regulatory discretion (risk of quality/manufacturing issue outweighed by benefit of the drug)
    - 1 prevented through encouraging others to ramp up
    - 1 prevented through communication with DEA regarding firm's report to FDA regarding need for quota increase
    - 1 prevented through assisting a firm with an import delay

Important to Note:

- FDA plays a key role working with manufacturers to facilitate responses to prevent or mitigate a drug shortage
  - This is a secondary response to mitigate a problem that has already happened
- Manufacturers play a key role in responding to shortages as they make the products that doctors and patients use
- It is important to consider the root cause of a shortage
- If the root cause that leads to a shortage can be prevented, one can get to primary prevention
- Some shortages can be prevented – others cannot be prevented
  - Some shortages involve unforeseen (unanticipated) problems such as a manufacturing line breakdown or other event that causes an unavoidable shortage
  - Manufacturer(s) may not be able to make up production shortfall
  - In some cases risks are significant and would cause patient harm (e.g. sterility problems)

Examples of Recent Quality and Manufacturing Issues Involving Sterile Injectables - 1

- Significant quality issues that have occurred
  - Sterility problems – including bacterial and mold contamination
  - Particles of foreign matter (glass, metal and fibers) in vials
  - Crystallization of the active ingredient
  - Precipitate formation (due to reaction with raw materials or container/stopper with the drug)
  - Newly identified impurities or degradants
Examples of Recent Quality and Manufacturing Issues Involving Sterile Injectables - 2

- Issues that are more easily able to be addressed
  - Errors in labeling or packaging
  - Slightly out of specification results that do not unfavorably alter benefit / risk
- Unforeseen/ Unanticipated issues
  - Manufacturing equipment breakdown
  - Natural disasters or other events causing loss of manufacturing time and in some cases loss of inventory
    - Fire at raw material or finished product manufacturing site
    - Japan earthquake caused several potential shortages
    - Icelandic volcano caused transportation delays

Flexibility - examples

- Allow release of medically necessary products with extra testing and third party oversight
- Build in exemptions for medically necessary products into enforcement actions (e.g., consent decrees)
- Allow distribution of product with filters and alerts to health care providers

Industry’s Role - Potential solutions

- Plan ahead by adding redundancy to manufacturing & raw material supply to prevent shortages of medically necessary drugs (flexible regulatory approaches possible)
- Commitment to quality: proactively identify & promptly correct issues
- Prevent sudden lack of lifesaving medications for consumer
- Notify FDA as soon as aware of an issue that could impact supply. Contact Drug Shortage Program at drugshortages@fda.hhs.gov
  - 38 shortages prevented in 2010 due to early notification by firms
  - 99 shortages prevented in 2011 so far due to early notification

Continuing Role for CDER’s DSP

- Continue working with firms
- Encourage voluntary reporting
- Continue tracking number of shortages and reasons for shortages
- Outreach
  - Health care professionals
  - Consumers
  - Manufacturers

Public Meeting held September 26, 2011 to work with all stakeholders on identifying solutions
Second Line TB Drug Shortages

• Shortages have occurred for same reasons as other older drugs:
  – Many sole source drugs
  – Lack of redundancy and capacity constraints
  – When a quality problem occurs or a firm loses their manufacturing site or supplier, a shortage occurs.

Updates on Supply

• Capastat (capreomycin) injection – sole source from Akorn – the firm reports supplies available – they are working to meet global demand and increase supplies. FDA has offered assistance (will expedite review of anything needed).
• Seromycin (cycloserine) oral tablets – sole source from Chao Center – available and Chao reports no issues. (Chao was supposed to close per press due to lack of funding but they report this is no longer the case).
• INH tablets – good supply, several firms (Had recent delay at one firm Teva)
• INH injection – sole source Sandoz – short expiry due to stability issue but available.
• Amikacin injection – now available in 4 ml vials from Teva – plans continued good supply. Bedford delayed.
• Trecator (ethionamide) or ETA – oral tablets – had manufacturing issue but now OK from Pfizer.
• Clofazamine (Lamprene) oral – now under IND held by National Hansen’s Disease Program for leprosy and then they distribute under Single Patient INDs for other uses including MDR-TB – information on NHDP website. No manufacturer currently wants to commercially market this.

Recent Drug Shortage Developments

• Executive Order signed by President Obama 10/31/11
  – Requests that manufacturers notify FDA of any discontinuation, or supply issue
  – Increases staff for FDA drug shortage program
  – FDA expedites any changes related to preventing or addressing a shortage
  – FDA will work Dept of Justice on investigation into Gray Market
• Report done by HHS/Assistant Sec for Planning and Evaluation – points to economic, capacity factors
• Report done by FDA – posted on FDA website – looks into all FDA is doing to prevent and address shortages
  • FDA sent notification letter to firms
  • Increased notifications being received from manufacturers after Executive Order and letter from FDA Firms needing expedited reviews, need help with quality problems in order to address and prevent shortages.

Thank You

• FDA drug shortage website is:
• To report shortages our e-mail account is
  Drugshortages@fda.hhs.gov
• FDA Webinar on Prescription Drug Shortages
  Sept. 30, 2011, 11:00 a.m.
  http://www.fda.gov/AboutFDA/Transparency/Basics/ucm272223.htm
DISCUSSION

ACET Advisory Group for MDR-TB
- Working group established June 2011 to address concern about MDR-TB drug shortages
- Problem statement currently in draft
- Potential solution table in draft
- Work to increase awareness of the problem through multiple

Problem Statement
- TB control programs in the U.S lack an uninterrupted supply of drugs needed to treat drug resistant TB.
- Inadequate or interrupted treatment of drug resistant TB can lead to the acquisition of further drug resistance, ongoing transmission of drug resistant TB, and death.
  - These substantially add to financial and public health costs
- The current system for managing drug shortages is not sufficient to ensure an uninterrupted supply of TB drugs.
- The interrupted supply of drugs for drug resistant TB poses a threat to the control of drug resistant TB, to the public health mandate that assures the appropriate treatment of TB, and to the overall public health in the United States

Potential Solutions
- Establish regulatory requirements for early notification to FDA of potential shortages and plans to discontinue
- Add TB drugs to the FDA medically necessary list
- National or regional MDR TB drug repository
- Streamline process for investigational drug use
Potential Solutions

- Register 2nd line drugs with federal Orphan Program
  - provides incentives for manufacturers willing to produce them.
- Offer financial incentives to produce specific drugs
- Additional insurance coverage for 2nd line drugs to address cost issue

Progress is being made

- President’s Executive Order
- Future Legislation
- FDA documents
  - A Review of FDA’s Approach to Medical Product Shortages
  - Economic Analysis of the Causes of Drug Shortages
- FDA already works with manufacturers and prevented 38 drug shortages in 2010

Questions?

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-4646
E-mail: cdcinfo@cdc.gov Web: http://www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.