DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE

SUMMARY OF THE 60th DIRECTOR'S CONSUMER LIAISON GROUP MEETING

NIH Campus, Building 31, C-Wing Room 10

Bethesda, Maryland

June 27 & 28, 2012

Members Present

Ms. Gwen Darien, Chair
Dr. Jeff Allen
Ms. Susan G. Braun
Dr. Adam Clark
Ms. Andrea Ferris
Ms. Joya Delgado Harris
Ms. Linda House
Ms. Cheryl Jernigan
Mr. Jeff Kaufman
Dr. Deborah Morosini
Mr. Jon Retzlaff
Ms. Wendy Selig
Dr. Michelle McMurry-Heath
Ms. Phyllis Pettit Nassi
Mr. Max Wallace

Speakers

CAPT Valerie Jensen, Associate Director, Center for Drug Evaluation and Research Drug Shortage Program, U.S. Food and Drug Administration
Mr. Russell Wesdyk, Scientific Coordinator, Office of Pharmaceutical Science, U.S. Food Drug Administration
Mr. David Gaugh, Vice President of Regulatory Sciences, Generic Pharmaceutical Association
Mr. Curtis Rooney, President, Healthcare Supply Chain Association
Dr. Lloyd Everson, Vice Chairman and Founder, U.S. Oncology Network
Mr. Robert DeChristoforo, Chief, Pharmacy Department, NIH Clinical Center
Dr. Douglas Lowy, Deputy Director, National Cancer Institute
Dr. Abby Sandler, Executive Secretary, President's Cancer Panel
Ms. Kelli Marciel, Acting Director, NCI Office of Advocacy Relations

Facilitator

Mr. Robert Mittman

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Opening Remarks

Ms. Gwen Darien

- Ms. Darien welcomed the DCLG members, speakers, and guests and mentioned that the meeting was an opportunity to continue the dialogue on generic cancer drug shortages, including the perspective of the generic industry. In addition, the DCLG will have the opportunity to hear updates on ongoing activities of the NCI and the President's Cancer Panel.

- Ms. Darien announced that PDUFA (Prescription Drug User Fee Act) had passed, which among other provisions, requires companies to notify the FDA of potential shortages.

Keynote: FDA Perspective on Cancer Drug Shortages and User Fee Programs

CAPT Valerie Jensen

- CAPT Jensen noted that the number of shortages is currently around the same as last year—more than 80 new shortages for 2012, and over 100 in total posted on FDA's website. Many are cancer drugs.

- Many shortages have been resolved. FDA is working with manufacturers to fix problems or mitigate risks, and working internationally to get drugs, resulting in 84 prevented shortages so far in 2012.

Mr. Russell Wesdyk

- Mr. Wesdyk described the organizational structure of the FDA's Center for Drug Evaluation and Research (CDER). CDER's Drug Shortage Program has 11 full time staff and brings together many groups to address the issue. They worked to prevent 195 shortages in 2011.

- Using the catch phrase "every patient, every time, forever," Mr. Wesdyk explained that the safety and efficacy of a drug is researched in a certain number of clinical batches, and its safety and efficacy must link back to what was found in those clinical batches for as long as the drug is sold.

- There are many more oral drug manufacturers than injectable manufacturers. The processes for manufacturing these two types of drugs are very different, carried out in different plants, with very different machinery.

- FDA's approach to prevention/mitigation includes:

    - Prioritizing medically necessary products, considering the risk/benefit of the drug.

- Ramping up manufacturing by other companies.
- Helping to fix the problem (e.g., filtering out glass particulates).
- Expediting review of applications that can make a difference to physicians and patients, both generic and non-generic, and trying to find applications that have few review inspection issues.
- Exploring a program in which manufacturers can determine whether or not expired drugs are still good to use, which could be helpful during a drug shortage.

- Mr. Wesdyk provided some background on FDA's relationship with generic companies and listed a few ways in which GDUFA (Generic Drug User Fee Act) can help reduce drug shortages.
  - GDUFA will bring in roughly $299 million per year, which is less than ½ of 1% of generic drug sales and is expected to reduce costs.
  - GDUFA requires a 10-month review cycle.
  - Applications are reviewed on a first-come, first-served basis.
  - The user fees are low and there is no penalty for redundancy—there is no additional fee to include a backup facility.
  - Until FDA receives an appropriation, the agency cannot use GDUFA.
  - Each individual user fee is specific to that industry's segment. Mr. Wesdyk believes that no one user fee is the best vehicle to solve all problems, which is why multiple user fees are included. Different solutions are needed for different segments.

Highlights from discussion with DCLG

- Almost every cancer patient receives a generic drug during their treatment. Shortages that impact cancer patients can also include maintenance drugs, anesthesia drugs, and electrolytes, among others.
- Recently, the media reported the release of a large number of FDA warning letters. Many of these were sent to companies about serious concerns. Some cases were field alert reports, reports from inspections, or company self-reports. The number of warning letters reported in the news included reports issued to tobacco companies, which greatly increased the overall number. It is important to remember that the letters do not cause the problem; the problem has been in existence before the letters are issued.

- The number of antibiotics facing shortage is small. Antibiotics are less complicated to make than oncology drugs, which are extremely complicated. Also many companies manufacture antibiotics, whereas only a few companies manufacture oncology drugs.

- FDA released a letter in early 2012 encouraging companies to report potential shortages. After the letter was sent, reports of potential shortages significantly increased.

- FDA is working with companies who are trying to build manufacturing sites in the United States, which should help to ensure redundancy.

- Manufacturers are generally conservative in setting drug expiration dates. FDA has received positive feedback from companies about the possibility of extending the expiration dates of drugs projected to be in shortage, when data support the safety of doing so.

Panel: Generic Cancer Drug Shortages—Continuing the Dialogue

Mr. David Gaugh

- Mr. Gaugh believes that we should expect the crisis to continue for the next several years.

- Currently, there is a 30% shutdown of generic drug production. Mr. Gaugh suggests that if this 30% capacity returns, drug shortages would be reduced.

- This is a multi-faceted problem, involving insufficient supply of raw materials, inadequate and delayed communications about shortages, and problems associated with manufacturing and release.

- Mr. Gaugh believes that the inadequate communication between manufacturing companies and the FDA will improve with GDUFA. He noted that the notification requirement in the new law cannot be enforced at this time. He also believes that the new legislation puts a lot of the onus on the FDA from a tracking, data set, and informing standpoint.

- Mr. Gaugh stated that this is also a highly concentrated problem, because 80% of drugs on the market are generic; of the total generic injectible market, half are on the shortage list.

- Mr. Gaugh identified four increasing trends: more manufacturing sites have been registered, but the FDA has not hired new inspectors; foreign inspections have increased; warning letters to manufacturing sites have increased; and the number of drugs in shortage has worsened.

- The generic industry, under the auspices of the GPhA (Generic Pharmaceutical Association), created the Accelerated Recovery Initiative (ARI) to recover some products as soon as possible. According to Mr. Gaugh, this is an unprecedented multi-stakeholder initiative that will bring together the FDA, GPhA member companies, the Federal Trade Commission (FTC), and IMS Health (a data-aggregating company in the medical space), among others.

- Under ARI, each company gives IMS Health and the FDA their production planning schedules for the coming months. ARI looks at forward production schedules and tries to predict drug shortages and to pinpoint where FDA should focus.

- According to Mr. Gaugh, 35 generic companies that are members of GPhA have endorsed ARI. Four of the "big five" generic companies are participating. GPhA will also involve brand companies in the future. Currently, GPhA is waiting for FTC approval to launch ARI.

Mr. Curtis Rooney

- Mr. Rooney discussed Group Purchasing Organizations (GPOs), which consist of contracts that aggregate the purchasing power of health care providers and hospitals. GPOs are generally considered good. They help health care providers realize savings and efficiencies.

- He stated that 96% to 98% of hospitals use one or more GPOs to purchase anything from bandages to MRI machines. Most hospitals have between two and four GPO contracts for machines and supplies. For pharmaceuticals, hospitals usually use one GPO contract. These contracts typically last three to five years before they can be re-negotiated.

- GPOs do not actually purchase anything—they are used for group contracting. The distributor buys the product and GPOs have a contract to deliver that product. GPOs are only paid if the hospital or other health care provider buys the product.

- There are currently 15 Healthcare Supply Chain Association (HSCA) members, and these 15 control most of the GPO market according to Mr. Rooney. He further explained that 60% of purchasing volume goes through two major GPOs.

- According to Mr. Rooney, HSCA has actively worked with hospitals to make sure certain drugs are available. HSCA also works with supply partners to find products and to strategize with members and clients on access issues, including substitutions. In addition, GPOs spend a lot of time trying to find products through their own distributors. If GPO's cannot provide a product, they receive no fee.

- The June 2012 House Committee on Oversight and Government Reform report suggested that GPOs had a hand in the drug shortages, but Mr. Rooney noted that GPO contracts are negotiable, so they must deliver to stay in business.

- DCLG members turned the discussion to quality, and asked Mr. Rooney if GPOs were willing to pay a premium for products with higher quality marks to ensure that these higher quality products are delivered to hospitals. DCLG members suggested creating a quality standard that GPOs require from manufacturers. Mr. Rooney noted that traditionally the FDA sets the bar for quality.

Dr. Lloyd Everson

- According to Dr. Everson, the problem of drug shortages comes down to regulatory and economic misalignment of incentives.
- In 2003, the Medicare Modernization Act came into effect to set a cap on pricing. Dr. Everson believes this is the key to cancer drug shortages today. He stated that strategies thus far to solve the problem have been "band-aid approaches." Stakeholders must deal with the incentives behind the market to solve the problem.
- Dr. Everson went on to suggest that we must have Congress and the Administration work together on drug pricing and make it a more market-driven approach that filters down to delivery.

Highlights from dialogue between panelists and the DCLG

The purpose of this discussion was to review the information provided and further investigate unanswered questions and possible strategies to mitigate the crisis.

On providing incentives for quality capacity:

- A "good housekeeping seal of approval" for certain manufacturing facilities can be considered, but it will increase drug prices.
- Currently no quality standard is imposed by GPOs. They rely on the FDA seal of approval, and if a drug has FDA approval, it's assumed the drug is of high quality.
- DCLG members asked if GPOs would be willing to work with companies that adopt a quality standard beyond FDA's approval of safety and efficacy, and demand that standard from manufacturers. In turn, if hospitals would work only with GPOs that follow this quality standard, this might improve drug quality.
- DCLG members suggested a checklist for manufacturers, GPOs, and hospitals to enhance the delivery of quality products.

On FDA's Role:

- The FDA approves drugs and creates compliance records noting any violations/warnings a manufacturing facility receives. Mr. Wesdyk noted that no one is looking at these compliance records, but they are publicly available.
- Companies have chosen to shut down or slow production lines—FDA hasn't asked any of them to shut down. CAPT Jensen insisted that the FDA does not typically order shutdowns. Knowing how critical the drugs are, the agency avoids ordering shutdowns.

- FDA inspectors are obligated to issue "tickets," but it is unclear how serious the violations are. Companies may be deciding to shut down production lines, not FDA inspectors.

- Compliance actions do not lead to shortages. It's important to think about what compliance buys in our health care system.

- CAPT Jensen stressed that criteria are not relaxed for overseas distributors. She went on to say that when the FDA looks at overseas sources to ward off shortages, the facilities are usually pre-inspected and they pay close attention to bioequivalence.

On pricing and reimbursements:

- Some believe that the average selling price deserves attention and suggests that drug pricing should be driven by the market. Although this is not simply about money, it does not make sense to cap the price when demand has increased and supply has decreased. The U.S. reimbursement system for service in hospitals needs reform.

- Pricing will not affect capacity. All five big generic companies are expanding, but they still have capacity problems.

- Pricing of generic product categories is driven by GPO and distributor relationships, and the companies themselves can make the changes. When hospital budgets are cut, reductions are in the generic drug budget, not the brand name budgets. Thus, changing reimbursement schemes may not help.

On the uniqueness of the current drug shortages:

- GDUFA will help to move the approval process to 12 months, but this might not be enough improvement to prevent or remedy shortages. The determining factors are speed and cost.

- This crisis is different from those of the 1980s and '90s in its order of magnitude. Past drug shortages lasted days or weeks, not months or years. Also, patients today are empowered to speak publicly about the issue and they have compelling stories to share.

- Doctors have to make judgment calls about patient care that they haven't had to in the past.

On creating redundancy in the market to avoid shortages:

- To some, stockpiling is not a viable solution in the sterile injectables market because hundreds of millions of dollars of capital machinery and plants would remain idle because of the stockpile. Companies could lose enormous amounts of money.

On the role of advocates:

- DCLG members have the ability to educate a lot of people on drug shortages. Advocates need to learn to push change from the ground up instead of the top down. Advocacy organizations need to educate people to effectively lobby, but patients should not necessarily be advocates.

- DCLG members should look into working with the FTC to get the ARI approved.

Keynote: How Drug Shortages Affect Research

Mr. Robert DeChristoforo

- Mr. DeChristoforo shared his views of how drug shortages affect research.
  - A shortage does not necessarily mean that the drug is "out"; it can also mean that the hospital is having trouble getting it. Hospitals cannot plan because they do not know when they will have access to more drugs.
  - Hoarding can be a problem, but GPOs generally know what their customers are buying and let other hospitals know who is buying what.
  - Drug shortages can lead to medication errors because drugs come in certain doses and replacement products may come in different doses. Physicians have to be strategic about what dose to give.
  - Non-cancer patients use cancer drugs and they are equally important for those patients. For example, non-cancer studies need methotrexate without a preservative. Antibiotics do not have the same shortages because alternative antibiotics are usually available.

- NIH research does not use only investigational drugs. "Repurposing" uses an already approved drug with an investigational drug to see the effects of the combination.

Highlights from discussion with DCLG

- Clinical directors and principal investigators decide which patients get drugs that are in shortage, not the pharmacy.

- The NIH Clinical Center's GPO has assured NIH that they only buy directly from manufacturers, not the gray market, and the FDA approval is assurance of quality.

Facilitated Board Discussion

Several cancer advocacy organizations discussed their objectives, activities, and accomplishments around the current drug shortage crisis.

John Dornan, CEO Roundtable on Cancer (formerly C-Change)

- The CEO Roundtable on Cancer consists of 35 CEOs from private industry. Many members are directly involved in health care, but not all.

- Last fall, the Life Sciences Consortium arm of the CEO Roundtable convened a meeting with representatives from FDA and the generic industry. A few issues that arose during this meeting included:

    - Acknowledgement that quality is important, but inability to see how quality assurance from the purchaser's side directly relates to drug shortages or has the potential to resolve drug shortages.

    - Possibility of stockpiling, as is done with vaccines.

    - Legislative approaches falling short of preventing shortages; legislative approaches only manage shortages.

    - Lack of guidance of what FDA has the authority to do.

    - The solution is not as simple as pricing.

- Mr. Dornan's final key point was that all the entities working on the problem of drug shortages can carry a certain bias or perspective (e.g., business, financial). The DCLG, however, puts patients first.

- DCLG members suggested that the CEO Roundtable work with DCLG to develop an emergency action plan or emergency action group.

Loyce Pace, Livestrong

- Livestrong does not have the capacity or expertise to analyze this problem, but it can contribute the perspectives of cancer survivors.

- Livestrong launched a survey to capture these perspectives, but was surprised at the low response rate *(n* = 192).

- About 66% of respondents felt that they knew something about drug shortages. Only half felt affected by drug shortages. Of the subset that felt affected, 75% did not receive advance notice of unavailability of their meds; 7% weren't told when it would be available; 68% were not told why the drugs weren't available. One explanation for this is that patient-physician communication is lacking.

Kim Ryan, Director of Patient Information Services, Fight Colorectal Cancer (formerly C3)

- Ms. Ryan shared her experience at an oncology conference and reported that many nurses did not know about the current cancer drug shortages because their hospitals had sufficient

supplies of the drugs. She noted that nurses who knew about the drug shortages were generally from smaller towns.

- To address cancer drug shortages, Fight Colorectal Cancer:
    - Attended the FDA's workshop in September 2011.
    - Submitted comment to the House of Representatives Energy & Commerce Committee regarding drug shortages.
    - Partnered with other cancer advocacy groups concerned about the issue.
    - Supported two bills: S. 296 and H.R. 2245.
    - Provided patient spokespersons to NBC News for an investigative story.
    - Provided a patient spokesperson to the White House for Executive Order 13588 Signing (Reducing Prescription Drug Shortages). Increased access to accurate information regarding leucovorin.
- Ms. Ryan suggested that DCLG develop a patient webinar to communicate with patients about cancer drug shortages, why they are happening, and what steps are being taken to mitigate them. She urged DCLG to keep advocacy organizations informed about DCLG's activities so they can relay that information to patients.

Facilitated Board Discussion: Next Steps

DCLG members discussed the opportunities they see for advocates to be involved, with whom, and how. Ways in which DCLG might further address this issue include the following:

- Develop an understanding of how the global increase in the use of pharmaceutical medicines has affected drug availability and shortages.
- The public needs to know what is being done about cancer drug shortages, what the outlook is for the future, and what is going to happen or needs to happen.
- The media are portraying GDUFA as the answer to the problem. However, there are many other issues and GDUFA only requires advanced notice of potential shortages.
- DCLG should consider both short-term and long-term issues/actions. Consider what has been brought to the last two meetings and synthesize it as a group with the patient perspective in mind. Communicate to constituents.
- DCLG could potentially develop a webinar to share everything learned over the past two meetings with the cancer advocacy community.

- OAR provided clarification of NCI's role in cancer drug shortages.
    - This is not an issue that NCI can solve, but NCI can use its convening power to help DCLG connect the dots.

The session adjourned at 4:06 p.m.

Day 2: June 28, 2012

National Cancer Institute Update

Dr. Doug Lowy

- Dr. Lowy presented some of NCI's recent and ongoing activities. His updates included:
    - An overview of R01 investigative initiative grant applications—NCI funds at the 15th percentile.
    - Announcements of two new programs, including the Center for Cancer Genomics and the Center for Global Health. He mentioned that NCI is searching for a permanent director for the Cancer Informatics Program.
    - A recap of the Team Science meeting held in February 2012.
    - A recap of the Target Validation meeting.
    - An overview of the Provocative Questions initiative: Out of 750 applications, NCI will fund between 50 and 60.
    - A proposal by Dr. Varmus to change the NIH biosketch requirement so that it better represents an applicant's accomplishments.
- Dr. Lowy also provided information about the human papilloma virus (HPV) and the HPV vaccine. Specific highlights include:
    - HPV is the leading cause of cervical cancer, but also causes other cancers in both men and women. Cervical cancer accounts for 10% of cancers seen in women worldwide.
    - Internationally the distribution is different; more non-cervical are cancers caused by HPV.
    - The HPV vaccine does not cause cancer, but there has been negative publicity about adverse effects associated with the vaccine.

        - Controlled trials show that side effects were equivalent to those seen in other effective vaccines and post-licensure surveillance showed a number of side effects that were either equivalent to those of other vaccines or normal behavior characteristics of adolescent females.

        - The target population is adolescents who are not infected.

    - Rigorous clinical tests have shown the vaccine to be effective in both males and females. This has led CDC to make it a routine recommendation.

        - Protection is highest when given to those who have not yet begun sexual activity and those who are in young adolescence.

        - Studies suggest high level protection against HPV for up to 8-9 years.

- The HPV vaccine is expensive. Both the vaccine and screening should be used for successful public health prevention, both domestically and internationally.

- Lack of uptake is an issue and it is suggested that the release and subsequent efforts to mandate its use have exacerbated the problem because the social aspects of the vaccine were not properly addressed.

Keynote: The President's Cancer Panel and HPV Vaccine Update

Dr. Abby Sandler

- The President's Cancer Panel is a federally chartered three-member committee appointed by the President. The Panel monitors the development and execution of the activities of the National Cancer Program, and reports directly to the President of the United States.

- Two new members joined the Panel in November 2011, Dr. Barbara Rimer and Dr. Owen Witte. A third public member will be appointed soon.

- The Panel does not exclusively cover NCI issues. The Panel is only advisory and will not write guidelines.

- The next four workshop meetings will focus on "Accelerating Progress in Cancer Prevention: the HPV Vaccine Example."

- The upcoming workshops will explore the HPV vaccination as a model for cancer prevention; achieving widespread HPV vaccine uptake; clinical practices, standards, and economic implications related to the HPV vaccine; and challenges of global HPV vaccination.

- The goal is to provide recommendations that will help with the global uptake of the HPV vaccine and find lessons learned that can be applied to future cancer-related vaccines.
- In a discussion following Ms. Sandler's presentation, DCLG members thought that appointing someone to attend the public workshops and reporting back would be useful.
- Ms. Sandler noted that the Panel's charter does not include any authority to enforce recommendations, and she urged the DCLG to spread awareness about the Panel reports and recommendations.

OAR Update

Ms. Kelli Marciel

- Incoming Office of Advocacy Relations (OAR) Director Kelli Marciel provided information on her background and gave a status update on OAR, including departing and incoming staff and a new strategic plan for the office.
- Moving forward, Ms. Marciel will be engaging with DCLG members one-on-one and in groups between meetings.