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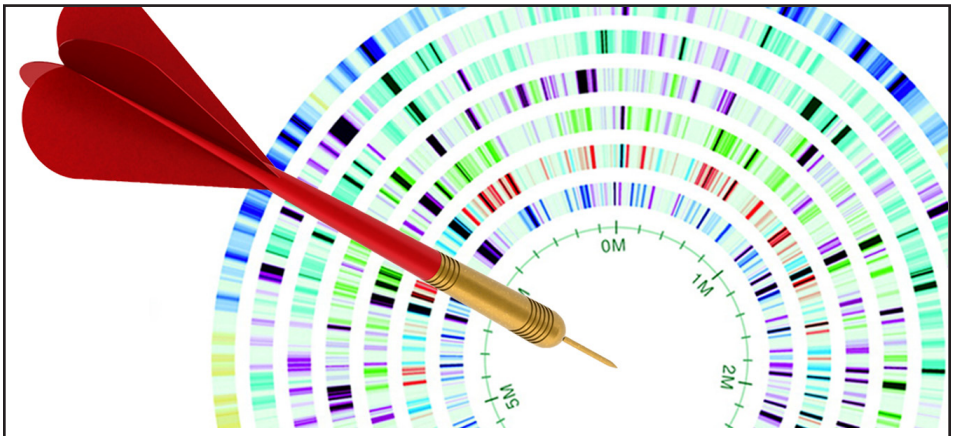

NCI Launches M-PACT Next-Generation Trial As Group System Nears March 1 Transition

By Matthew Bin Han Ong

NCI has launched a pilot study to assess whether assigning cancer patients treatment based on the genetic characteristics of their disease can improve outcomes for patients with advanced metastatic solid tumors.

The Molecular Profiling based Assignment of Cancer Therapeutics, or M-PACT, trial is one of the first to use a randomized trial design to assign treatment based on specific mutations.

Initially launched at NCI, the trial will eventually be opened to researchers in the institute's Early Therapeutics Clinical Trials Network. The plan is to report results by 2017.

(Continued to page 2)

NCI Clinical Trials Enrollment Drops to 17,500

By Paul Goldberg

Enrollment in NCI-sponsored National Clinical Trials Network clinical trials will drop to about 17,500 this fiscal year, the network groups have been told by NCI officials.

This enrollment figure includes 3,600 pediatric patients, so the total adult enrollment will add up to about 14,000, insiders at cooperative groups say.

(Continued to page 5)

Capitol Hill

GAO: FDA Data on Drug Shortages Inadequate

By Conor Hale

FDA needs to improve its access to data if it is to manage drug shortages more effectively, the Government Accountability Office concluded.

The FDA's management of drug shortage data is "inconsistent with federal internal control standards," the GAO report states.

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NCI Launches M-PACT Trial At NIH Clinical Center

(Continued from page 1)

M-PACT is being launched at a time when NCI is completing reconstruction of its network of clinical trials cooperative groups. On March 1, the structure of the cooperative groups will be officially replaced by the National Clinical Trials Network.

The new trials signal redistribution of resources on the part of the institute, observers say. (See story on p. 1) Insiders expect that the number of patients enrolled in all NCI-sponsored trials would drop to 17,500 during the current fiscal year.

The study is the first of the four initiatives the institute is about to launch this year. The other trials are:

• **ALCHEMIST**: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial

• **SWOG1400**: Biomarker-Driven Master Protocol for Second Line Therapy of Squamous Cell Lung Cancer

• **NCI-MATCH**: Molecular Analysis for Therapy Choice

The objective of these trials is to identify subgroups of patients who are likely to benefit from certain treatments and result in new treatments being developed quickly for some cancers.

This could ultimately lead to smaller, more definitive clinical trials, which would be helpful to clinicians in terms of cost and time, NCI officials said.

"We believe that this study will aid patients in the trial that will be conducted initially at the NCI, and subsequently expanded to clinical trials sites participating in the NCI-supported Early Therapeutics Clinical Trials Network," James Doroshow, NCI deputy director for clinical and translational research, said in a statement, unveiling the study. "We also believe that M-PACT can be a model for trials nationwide, particularly those that employ genetically-driven treatment selection approaches in their design."

Watch Doroshow's recent presentation on M-PACT on The Cancer Letter website.

NCI isn't alone in focusing on specific targets. Targeting of specific mutations has become more frequent in the pharmaceutical industry, resulting in better registration trials, FDA's top cancer official Richard Pazdur said in an interview with The Cancer Letter last week (The Cancer Letter, Feb. 14).

"We are redefining the traditional diseases by this science," Pazdur said. "Drug development is much more focused, and decisions are being made on the basis of understanding the molecular basis of the disease rather than the number of responses observed in an early phase study."

NCI: Are Targeted Treatments Better?

"Patients will have their tumors genetically screened and if a pre-defined mutation is found, they will receive treatment with targeted agents," Shivaani Kummar, head of NCI's Developmental Therapeutics Clinic and the principal investigator of the trial, said in a statement.

"What we don't know, however, is whether using this approach to assign targeted treatments is really effective at providing clinical benefit to patients, as most tumors have multiple mutations and it's not always clear which mutation to target and which agent is most likely to provide maximal benefit," Kummar said. "This study hopes to address some of these questions in the context of a prospective, randomized trial."

Few types of tumors have just one mutated gene that triggers cancer progression. Once a gene is mutated, it can lead to the activation of multiple pathways, resulting in disease progression and potentially requiring multiple interventions.

The M-PACT trial is designed to determine whether patients with specific mutations that have been demonstrated in laboratory systems to affect drug effectiveness will benefit from a specifically chosen targeted intervention and whether these interventions lead to better outcomes.

"So this is basically a response rate and progression-

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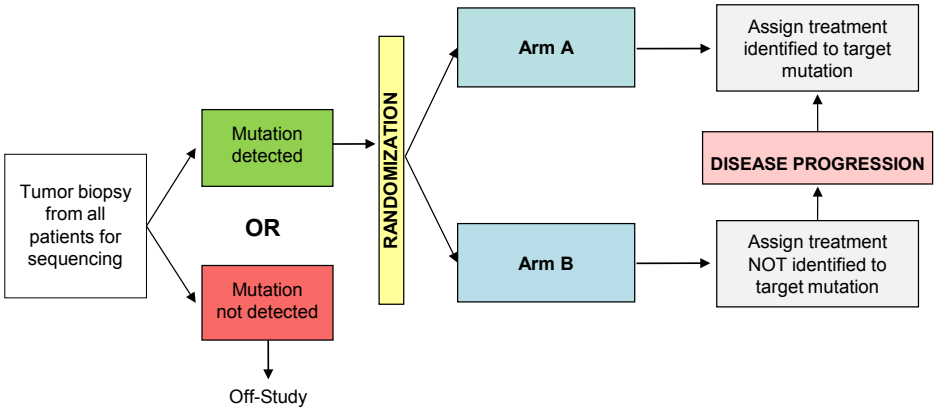
NCI's M-PACT Clinical Trial: Study Design



- Fresh tumor biopsy on-study and at progression
- Primary endpoint response (CR + PR) and 4-month PFS improved for agents chosen on the basis of specific mutations
- Crossover from Arm B (non-mutation–directed) to Arm A (mutation-directed) treatment at progression
- Trial open across NCI's Phase I/II network (>30 NCI-designated Cancer Centers)
- Accrual expected to begin Q1-2014

Source: NCI

free survival study," Doroshow said at the Dec. 10, 2013 meeting of the National Cancer Advisory Board. "This is also an umbrella study. It's a series of nested phase II investigations in which, if any of these look promising, it can be expanded. If not, it will be dropped and different arms can be entered.

"What is important is all the patients get fresh tumor biopsies, and we have the resources to do that," Doroshow said. "If a mutation is detected, they are randomized to initial treatment with mutation-directed therapy, or treatment with a drug that you would expect would not affect that mutation, and they will get biopsied again at progression, and then at treatment with the drug that we would have initially treated them for, had they been on the other arm."

M-PACT Enrollment

After screening hundreds of people, 180 patients with advanced refractory solid tumors will be enrolled in M-PACT based on their genetic profiles.

During the screening process, samples of the tumors will be genetically sequenced to look for a total of 391 different mutations in 20 genes that are known to affect the utility of targeted therapies, according to NCI.

If mutations of interest are detected, using a molecular sequencing protocol for tumor biopsy samples evaluated by FDA, those patients will be enrolled in the trial and randomly assigned to one of two treatment arms to receive one of the four treatment regimens that are part of the study.

"This study is, I think, of great significance, not only because it may help us understand particular mutations and particular therapies in a randomized context, but also it has over about a year and a half process that helped us understand how to deal with the FDA, how to put together an IDE for the lockdown algorithm for the mutational analysis, and I hope it will start soon," Doroshow said at the NCAB meeting.

"It will also, and this is not a minor consequence, take roughly a thousand patients entered to get to 250 patients who have the mutations of interest.

"This will bring to NCI about a thousand fresh biopsies that we hope to establish as PDX models, to all be genetically characterized and then a series—at least another 100, or 200, or more matched to biopsies for patients at the time of progression who will also be established as PDX and kinase cell lines," Doroshow said. "So it could be a very important repository of metastatically-biopsied patients with clinical histories that could be useful for the extramural community."

Objective

- Assess whether the response rate (CR+PR) and/or 4-month PFS is improved following treatment with agents chosen based on the presence of specific mutations in patient tumors.
  - Only patients with pre-defined mutations of interest will be eligible
  - Study treatments, regardless of cohort, will be chosen from the list of regimens defined in the protocol
  - Arm A: Receive treatment based on an study agent prospectively identified to work on that mutation/pathway
  - Arm B: Receive treatment with one of the study agents in the complementary set (identified to not work on one of the detected mutations/pathways)

NCI officials said patients with specific tumor types should have received certain therapies prior to being enrolled in NCI's M-PACT to ensure they receive the best treatment already known to provide benefit.

For instance:

• Patients with melanoma whose tumors have mutations in the V600E region of the BRAF gene should have received and progressed on a specific BRAF inhibitor therapy to be eligible for NCI's M-PACT trial.

• Patients with lung cancer should have had their tumors tested for the presence of EGFR and ALK gene mutations, and, if mutations were detected, they should have received and progressed on therapies targeting EGFR or ALK, respectively.

• Patients with all types of solid tumors will be considered for trial eligibility. For the randomization, patients will be assigned to Arm A (they will receive a treatment regimen prospectively identified to target their specific mutation or relevant pathway) or Arm B (they will receive a treatment regimen not prospectively identified to target their specific mutation or relevant pathway). Patients in Arm B will have the option to cross over to Arm A to receive therapy identified to target their specific mutation or relevant pathway if their disease progresses on their initial study treatment. As of January 2014, the study is open for patient accrual. Clinicians hope that they can rapidly enroll patients and report results of their findings by 2017.

Next-Generation NCI Trials in Development

M-PACT is one of several new initiatives that NCI plans to launch in 2014, including the large "Master Protocol" trial announced in November 2013 (The Cancer Letter, Nov. 15, 2013).

The master protocol in advanced squamous cell lung cancer (S1400) is a phase II and III trial that would test five drugs, assigning patients to therapy based on tumor biomarkers.

"To my knowledge, there is nothing like this that has ever been attempted before," said David Gandara, chairman of the SWOG lung cancer committee and director of the thoracic oncology program at the University of California, Davis. "The governance and organizational structure includes the Friends of Cancer Research, Foundation of the NIH, NCI, FDA, and Foundation Medicine, who will provide the genomic screening, and pharma, who will provide the drugs and funding for this.

"Every one of these groups is directly engaged in this master protocol, and each one will lead one of the arms of the study," Gandara said, during a D.C. conference co-sponsored by FOCR and the Brookings Institution Nov. 7, 2013.

The other trials include a study of "exceptional responders" to drugs that seemingly have not worked well for most patients in a given disease but for which a small number—usually less than 10 percent—have a

Patient Population

- Patients with refractory solid tumors that have progressed on at least one line of standard therapy or for which no standard treatment is available that has been shown to improve survival.
- Adequate organ function (AST/ALT<3xULN, Bil < 1.5 xULN, S. Cr < 1.5 x ULN, platelets > 100K, ANC> 1500)
- Study regimens: As long as the same set of protocols are offered to a given set of patients, the number and actual treatments regimens can vary over time

Mutations in DNA repair pathways	Veliparib+ Temozolomide MK1775 + carboplatin
Mutations in the PI3K pathway; loss of PTEN, Akt amplification	mTOR inhibitor -Everolimus
Mutations in the RAS pathway	GSK 1120212 (MEK inhibitor)

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major durable response.

"Another study is called 'Alchemist' and this study will test an ALK inhibitor and an EGFR inhibitor in patients with selected mutations who have early stage, resectable lung cancer," according to sources at the NCI.

"To have ample patients with these uncommon mutations, this trial will screen over 7,000 patients nationwide over the next five years. Those who don't have the select mutations will be followed and their genomes studied

"The final study, NCI 'MATCH,' will sequence tumors in 3,000 patients with advanced cancer whose disease has progressed on standard therapy to determine in they have a select molecular change for which a targeted agent might be beneficial. NCI will work with a large number of company partners to have as many agents available to cover the majority of actionable mutations."

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Clinical Trials

White Paper Claims NCI Rules Constrict GYN Cancer Research

(Continued from page 1)

Additional 2,600 patients will undergo screening to determine whether they have the appropriate molecular markers to be eligible for an NCTN trial.

In recent years, enrollment in the institute's cooperative group trials has been in the range of 20,000 to 23,000. In 2009, enrollment reached a high of 29,200. That year's accrual included a large screening component associated with one of the largest breast cancer studies ever conducted by the group program.

The groups will be reorganized on March 1 and will become a part of the NCI National Clinical Trials Network. NCTN's mission includes launching a new generation of genomically-guided clinical trials (see story on p. 1).

Recently, officials at the Gynecologic Oncology Group—which has merged with the former National Surgical Adjuvant Breast and Bowel Project and the Radiation Therapy Oncology Group into a single network group called NRG Oncology—said that accrual in all of its phase III trials has been reduced to 201 patients per year.

By way of comparison, in 2010 and 2012 phase III trial accrual in GOG trials averaged 2,190.

"This 90 percent reduction in phase III trial accrual will eradicate the existing gynecologic oncology clinical trials network," GOG officials wrote in a recent white paper addressed to NCI.

The text of the document is posted on The Cancer Letter website.

Following the receipt of the GOG white paper, NCI officials met in person with the group leaders to discuss their concerns.

"We explained that in order to increase research reimbursement to NCTN sites that enroll high numbers of patients (about 50 percent of the sites that currently participate) from $2,000 to $4,000 per patient, we had to lower the overall numbers of enrollments," Jeff Abrams, director for clinical research of the NCI Division of Cancer Treatment and Diagnosis, said to The Cancer Letter. "Our advisors and stakeholders had clearly stated that we needed to increase reimbursements, or else high volume sites would begin to drop out. With that mandate, we had no choice but to lower enrollments in view of a flat NCI budget. Fewer enrollments translates to doing fewer studies."

Speaking on condition that his name wouldn't be used, a member of leadership of one of the groups said the GOG report is "on target."

"Because GOG is a small group of investigators concentrating on a small group of diseases, it is easier for them than for the multi-disease larger cooperative groups to make the points that we all are feeling succinctly," the group official said. "We had a meeting of all of the adult cooperative group chairs and GI cancer chairs in Chicago last month to develop strategies to combat the same issues. Few studies are getting approved, even with widespread and unified support from all the groups, and our research cupboards are bare. The notion that NCI-sponsored cancer research is part of our too-big government, as the Tea Party extremists are saying, is really harmful."

GOG officials say they have been unable to get trials through the "disease steering committees" organized by NCI to prioritize clinical research.

"An unintended consequence of the new restructuring of the Cooperative Groups with the creation of Disease-specific Steering Committees (specifically the Gynecologic Cancer Steering Committee—GCSC) and the NCTN has been a rapid and sustained inability to open gynecologic cancer trials," the white paper states. "This dramatic change threatens the continued existence of a viable network to carry out clinical trials in gynecologic malignancies."

This loss of potential enrollment on phase III trials has not been offset by a concomitant increase in phase II trials.

The cooperative group was "at best remaining static" in phase II accrual, the document states.

"The take home message from this analysis is that industry does not have enough interest in running a significantly diversified portfolio of gynecologic cancer trials to keep the GOG viable," the documents states. "Even when maximally engaged, industry is becoming increasingly wary of conducting ovarian trials in the U.S., is conducting more of these ovarian trials abroad and is not interested in any meaningful trials in other gynecologic disease sites.

"The virtual complete shutdown of the gynecologic oncology clinical trials portfolio is disturbing as the GOG has embraced working with clinical trials planning meetings, task forces, and working groups and has emphasized biology-driven trials and advanced surgical trials that incorporate biomarker tests and strong correlative science into study designs."

Last November, GOG held a leadership retreat to analyze the obstacles to launching trials.

According to the white paper, the following themes emerged:

1. The IOM Report stated a key goal of reorganization of the adult cooperative groups was to increase availability and access to clinical trials. The 90 percent reduction in accrual experienced by the GOG over the past few years clearly is in conflict with this goal.

2. The GOG is much more similar to the COG than other adult cooperative groups as comprehensive meaningful research in gynecologic malignancies within the U.S. does not exist in the other cooperative groups.

3. There is a documented disconnect between the GCSC and the GOG/task force components of the NCTN. In addition, there is no clear consistent strategic guidance from CTEP or the GCSC leading to dissolution of the entire gynecologic oncology clinical trials system.

4. The actions of the GCSC are difficult to interpret but are potentially being overly influenced by individuals from other countries who have a direct conflict of interest with a viable well-functioning clinical trials network for gynecologic malignancies in the U.S.

5. The inability of the GOG to participate in a meaningful way in the final deliberations of the GCSC has led to miscommunication and a high rate of trial disapproval. Of note, the exclusion of knowledgeable individuals from deliberations began around 2010 when CTEP became concerned with the high rate of approval of trials by the GCSC. This change has certainly had the intended effect of limiting trial approval as documented above.

NCI: Few Breakthroughs in Ovarian Cancer

NCI's Abrams said that in discussions with GOG, that institute officials noted that having a trial always available for physicians and patients, a feature of the former cooperative group program, was no longer feasible.

To help select the best trials submitted by NCTN members, NCI established committees of disease experts to evaluate the trial ideas, Abrams said. NCI staff also serve on these committees to assure that conflicts of interest are avoided, and the committee's deliberations are fair and balanced, he said. Non-government staff who serve as heads of these committees are recognized internationally as leaders in their respective cancers, he said.

"GOG depends heavily on trials in ovarian cancer to drive their accruals as the other GYN cancers are either well treated with standard approaches or are uncommon and hence trials in these cancers can only enroll smaller numbers of patients," Abrams said to The Cancer Letter. "Unfortunately, there has not been a new breakthrough drug in ovarian cancer treatment in some time now, and thus GOG finds itself with fewer trial ideas of merit in its most common cancer.

"Hopefully, GOG's new partnership with NRG in the NCTN will allow the expanded group to focus on a broader range of cancers," Abrams said. "NCI did indicate to GOG leadership that they will continue to work in partnership with GOG to bring new agents to the clinic in early, phase I-II trials in gynecologic tumors, and it is expected that some of these new drugs will make their way to phase III trials in the NCTN."

Capitol Hill

GAO Suggests New Database For FDA Drug Shortage Data

(Continued from page 1)

"For example, FDA has not created policies or procedures governing the management of the data and has not conducted routine analyses using these data. Such shortcomings could ultimately hinder FDA's efforts to understand the causes of specific shortages as well as undermine its efforts to prevent them from occurring."

The GAO report, titled "Drug Shortages: Threat to Public Health Persists Despite Actions to Help Maintain Product Availability," suggests that FDA build a new system to better wield the information they receive from private manufacturers.

The report was completed as part of a requirement of the Food and Drug Administration Safety and Innovation Act passed in 2012, the law which increased FDA's authority to respond to drug shortages.

Overall, GAO found that while the number of new cases has slowed, the total remains high—and the watchdog agency delivered a few recommendations.

Appearing at a hearing of the House Committee on Energy and Commerce Committee Feb. 10, Marcia Crosse, director of the GAO's health care team, noted a downward trend in the number of new shortages beginning in 2012—a trend which continued through 2013, based on partial data from that year.

"However, while the number of new shortages has begun to decline, the total number of shortages

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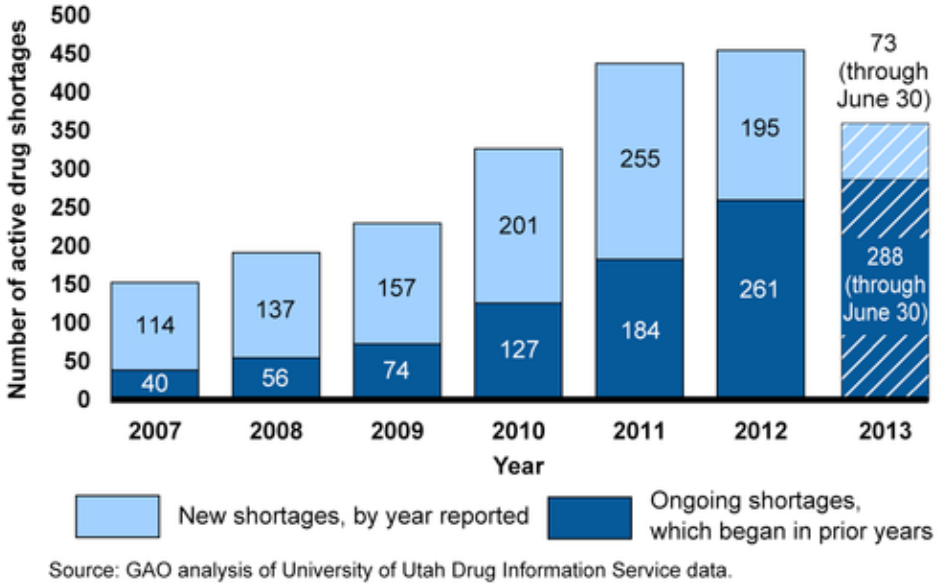
active during a given year—including both new shortages and ongoing shortages that began in a prior year—has continued to increase because many shortages are prolonged, with some spanning multiple years," said Crosse.

Douglas Throckmorton, deputy director of the FDA Center for Drug Evaluation and Research and chair of the agency's drug shortage task force, praised portions of the law and a presidential executive order that required drug manufacturers to notify FDA of problems that could lead to prolonged shortages.



Source: GAO analysis of University of Utah Drug Information Service data.

This early notification "has enabled FDA and manufacturers to prevent 170 shortages in 2013," Throckmorton told the committee. "The number of new drug shortages in the U.S. rose steadily from 60 in 2005 to an all-time high in 2011 of 251 new shortages. After a series of interventions, the number of new drug shortages has fallen to a low of 44 in 2013."

"FDA is tracking and working to resolve 97 total shortages that began in 2013 or earlier," he said.

The GAO report focused on how the FDA processes and analyzes the information it receives.

The report criticized FDA for lacking "policies, procedures, and specific training materials related to management and use of its existing drug shortage database. This lack of documentation may limit the agency's ability to communicate proper use of the existing and new databases to staff and could also ultimately lead to inconsistencies in the use of the database."

In addition, the GAO found "that FDA has not conducted routine analyses of its existing drug shortage database to identify, evaluate, and respond to the risks of drug shortages proactively."

"We determined that FDA currently uses data on an ad hoc basis to respond to specific shortages as opposed to using the data to identify trends or patterns that may help it predict and possibly prevent shortages.

"By only using the database to respond to individual shortages as they occur, FDA is missing opportunities to use the data proactively to enhance the agency's ability to prevent and mitigate drug shortages."

The GAO recommended two courses of action:

• To develop a new drug shortage information system with procedures ensuring consistent and accurate data, and

• To conduct periodic analyses using the new database to attempt to proactively identify potential shortages.

"Fundamentally we agree with the recommendations that the GAO has made," Throckmorton said to the committee. "We are putting in place a new system that's going to make the data more robust, make it more standardized, and improve our assessment of that data.

"We need to improve our communications," he said. "The communications we put on the website are looked at hundreds of thousands of times by individuals looking for information about shortages."

The FDA's drug shortage database was developed in 2011. Crosse said the GAO used information from the University of Utah Drug Information Service in its report to identify trends going back as far as 2007.

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Drug Shortages Not Going Away

Erin Fox, director of the university's drug information service, suggested several of the points regarding trends in shortages in a conversation with The Cancer Letter last October, when Ben Venue Laboratories decided to shut down its generic drug manufacturing operations in Bedford, Ohio.

"We are seeing a decrease in the number of new shortages that are happening," Fox said. "I do believe that is because FDA is able to prevent more shortages thanks to the new FDASIA law."

"However, the shortages we have that are ongoing are not going away," she said to The Cancer Letter. "And the reason for that is the manufacturers that are involved with those shortages are still working on fixing those quality problems." (The Cancer Letter, Oct. 11, 2013).

"Existing drug shortages, especially those that have lasted for a prolonged period of time, are hard to resolve because the factors that have led to them have meant manufacturers have left that space entirely," Throckmorton told the committee. "Resolving those is going to require finding tools to encourage a new manufacturer to decide to add a product to a manufacturing line, and make a decision that that's a product they can make a profit at."

The reasons for closing down manufacturing lines can range from economic profit and loss to failing to meet FDA quality standards. While FDA hasn't weakened any of its standards during these shortages, the agency has been allowed flexibility with their regulatory authority, which generally means expediting review.

"Some of the tools we have applied include: identifying manufacturers that are willing and able to increase production of a drug in shortage, expediting FDA inspections and reviews of submissions—both from manufacturers that are currently producing, as well as manufacturers who are interested in starting new production of a drug in shortage—and finally exploring risk mitigation methods for products initially not meeting established standards to allow them to remain available safely," Throckmorton said.

For example, in one case, particulates had been found in certain doses of drugs currently in shortage. Previously, those "particulates have required the cessation of manufacturing and cessation of distribution of the product," Throckmorton said.

"Because of their critical nature, we worked with the manufacturers to find filters that could be placed in line with that product when it is administered to the patient—allowing them to continue to be used even though there is this product defect. We determined they have to be made available to the patients."

In discussing the underlying issues that can cause shortages or make them worse, both Crosse and Throckmorton agreed that more investigation needs to be done to address the economics at work.

"I've always wondered why the market itself doesn't respond to alleviate these shortages based upon a price signal," asked Rep. John Shimkus (R-Ill.). "Is there something structurally about how we—either the government in its coding, or its spending through Medicare and Medicaid, or the insurance applications of purchasing drugs—is there something that distorts the market signals for shortages?"

"Economics have to be playing a part in the decision that these manufacturers are making here," Throckmorton responded. "I think we know less about that than we might like to."

"A lot of these shortages are low-margin, generic drugs," said Shimkus. "If it's such a low margin they are making a penny on whatever the application is, and that's hard to get a price signal on a return… if you only have one plant operating at full speed producing all this product."

"[Rep. Michael] Burgess [R-Texas] mentioned Propofol… someone has said that the profit on a dose is in the tens of cents," said Throckmorton.

FDA has no authority to address most of the economic issues.

"There are things that are outside of our scope; outside of the things that the FDA is able to undertake," Throckmorton said. "There are things that the manufacturers, we believe, have a role to explore."

Richard Schilsky, chief medical officer of the American Society of Clinical Oncology, said the report "emphasizes that the FDA has made significant progress in preventing shortages by improving its responsiveness to emergent supply chain disruptions in the past two years."

"However, the GAO report determines that current FDA efforts to prevent and resolve shortages suffer from lapses in data availability and quality that prevent FDA from improving its response to drug shortages," Schilsky said in a statement. "These shortcomings hinder the FDA's ability to understand the causes of specific shortages and proactively develop strategies to prevent them from occurring."

The full 75-minute hearing is available on the House Energy and Commerce YouTube channel.

Who Makes This Drug?

Neither the GAO report nor the hearing specifically addressed the role contract manufacturing plays in drug shortages.

The entities that hold the Abbreviated New Drug Application licenses to make generic drugs can be easily looked up. However, many of the ANDA holders don't make the drugs they are licensed to market. Instead, manufacturing is often contracted out to third parties.

Since contracts are usually confidential and proprietary, it's impossible for a member of the public—including physicians and pharmacists—to determine which entity actually makes the drug. When a contract manufacturer experiences manufacturing problems—as was the case with the now defunct Ben Venue Laboratories—there is no way to predict the impact constriction of supply would have on the availability of a generic.

Though FDA technically possesses these data, they cannot be systematically accessed, even by agency staff.

In a recent story in The Cancer Letter, Rena Conti, an assistant professor of health policy and economics at The University of Chicago, focused on what FDA knows about contract manufacturing and its process:

FDA maintains records that identify which manufacturers are producing generic drugs for the U.S. market. However, these data aren't maintained in a format that makes it possible for the agency to quickly distinguish between ANDA holders and contract manufacturers of fill and finish products or base ingredients. These records aren't available for public scrutiny.

When a company submits an ANDA to the agency, it must satisfy several requirements:

• Provide evidence substantiating bioequivalence to the already approved branded compound;

• Provide a sample of the proposed generic drug;

• Identify which FDA-approved facility will manufacture the drug (by the sponsor or outsourced to another company);

• Identify which FDA-approved facility will supply the base ingredients for the drug (by the sponsor itself, or outsourced to another company).

The agency collects and collates information that identifies the actual fill-and-finish manufacturer of a generic drug. Though these data are in the electronic format, sources said that this information doesn't contain flags that would indicate that the drug in question is manufactured by contract rather than by the ANDA sponsor.

The sponsors of ANDA are obligated to notify FDA of plans to discontinue drug manufacturing as well as any changes in manufacturing responsibilities, including the outsourcing of drug production after initial ANDA approval. FDA sources say that it's common for a firm to have to qualify a new facility to manufacture their drug due to either the loss of the old facility or due to changing market demand, which may prompt the firm to acquire additional capacity.

In these cases, ANDA holders often turn to contract manufacturers.

Even this limited information is not publicly accessible through the public web portal, Drugs@FDA, and is exempt from being released under the Freedom of Information Act. The agency generally treats non-public business relationships as confidential commercial or financial information, exempting it from public disclosure.

"U.S. courts have recognized that public disclosure of this type of information may cause substantial competitive harm to the owner of that information," FDA officials said in a statement.

"If a business relationship has been made public in a lawful manner, such as when a drug product's labeling identifies a contract manufacturer, FDA will publicly disclose in other agency records for that drug application the existence and identity of that contract manufacturer."

A proprietary data source, Thompson Reuters' RedBook, maintains more updated information on which ANDA sponsors are actively offering a drug in the U.S. market, but even this source doesn't flag contract manufacturing arrangements.

The identity and nature of base ingredient manufacturing for many drugs, also collected by FDA from ANDA sponsors, are similarly shielded from public scrutiny.

Thus, public announcements of shortages, contract manufacturing relationships and/or legal disputes among ANDA holders, fill-and-finish contract manufacturers, base ingredient sources and/or other industry stakeholders are the only way to learn about the presence and specific details of such arrangements.

Alas, even these sources are of limited value.

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Duke's Dzau Named IOM President

By Matthew Bin Han Ong

Victor Dzau, chancellor of health affairs at Duke University and president and CEO of the Duke University Health System, was named president of the Institute of Medicine.

Dzau will succeed current IOM president Harvey Fineberg effective July 1.

Dzau has served as an advisor to universities, corporations, and foreign governments, and is a member of the Board of Health Governors and chair of the Global Agenda Council on Personalized and Precision Medicine for the World Economic Forum.

"I recognize the critically important role that the IOM will have in improving the health of the nation at a time of extraordinary evolution in biomedical research and health care delivery," Dzau said in a statement. "The explosion of new data resources, novel technologies and breathtaking research advances make this the most promising time in history for driving innovations that will improve health care delivery, outcomes and quality."

In his nearly 10 years at Duke, Dzau spearheaded the creation of the Duke–National University of Singapore Graduate Medical School, as well as the Duke Global Health Institute, the Duke Institute for Health Innovation, the Duke Cancer Institute, and the Duke Translational Medicine Institute.

Under his leadership, the university's health system has undergone a transformation of its clinical information systems into a single electronic health record. Dzau also led a transformation of the Duke Medicine campus that has added the new Duke Cancer Center facility, the Duke Medicine Pavilion, the Trent Semans Center for Health Education, a new Duke University School of Nursing facility, and a Duke Eye Center building under construction.

"Victor Dzau has been a visionary leader and, in collaboration with outstanding faculty and staff, has made Duke one of the country's leading centers of biomedical research and patient care," said Duke University President Richard Brodhead. "He has guided Duke Medicine through a rapidly changing health care landscape with strength, imagination and unflagging energy.

"He has been an outstanding citizen of the university, the city, and the region, and a major voice for health care innovation globally through the World Economic Forum. We will miss him at Duke, but we appreciate the well-deserved honor of his new position at the Institute of Medicine, which will give a national scope for his leadership skills."

Dzau has maintained a research laboratory focused on the molecular and genetic mechanisms of cardiovascular disease and the development of new gene and stem cell-based therapies to regenerate and repair tissue damage from heart attack and heart disease.

Dzau is a past chairman of the Association of Academic Health Centers and has published widely on the need to transform America's academic medical and health centers. He has also served in leadership roles on voluntary community and statewide boards in North Carolina, and will continue to reside in Durham.

Dzau presided over the controversy touched off by Duke genomics researcher Anil Potti and his mentor Joseph Nevins. That scandal triggered an investigation by IOM.

The Duke Institute for Genome Sciences & Policy may be shuttered, according to an insider report following a review conducted late last year.

Duke University officials did not confirm or deny the allegations.

"Faculty and administration are working on a range of options to ensure that Duke continues to be a leader in genome research and its many applications to society," said Michael Schoenfeld, vice president for public affairs and government relations, in an email to The Cancer Letter. "We expect to announce a plan in the spring."

The institute garnered national attention when The Cancer Letter uncovered a genomics scandal involving Duke researcher Anil Potti and his mentor Joseph Nevins, who retired last August (The Cancer Letter, Oct. 18, 2013).

It is not publicly known whether the debacle was factored in the institute's latest review.

A similar review appears to have been conducted in 2011, in which three of six IGSP centers were phased out, including the center run by Nevins and Potti.

At the time, institute director Huntington Willard wrote in a memo that the review would "assess whether [the institute's] current organizational structure and intellectual balance is optimal for the future of the genome science and policy."

The "dismantling" of the institute is inexplicable, the independent blog Duke Check reports, because there is no other university with a similar genome institute.

"The scholarly activities of the institute are

self-supporting, winning major grants regularly that have now total more than a quarter billion dollars," the report states.

"The institute does get, according to a source in PTP's office with knowledge of budgetary matters, about $2.5 million a year for administrative and teaching expenses, but in return the university and its various divisions keep multiples of that sum from the overhead money that is tagged onto every grant."

In Brief

NCI's Czajkowski Takes Job At Harvard Medical School

JOHN CZAJKOWSKI, NCI deputy director for management, has accepted a position as executive dean of administration at Harvard Medical School. His start date will be June 2.

"Needless to say, this has been a tough decision," Czajkowski wrote in an email to NCI staff. "I care deeply about this organization, and I have the deepest respect for all of you as my colleagues. But the Executive Dean position presents a great opportunity for me and my family, and we ultimately decided that it is something we should pursue."

ISSAM MAKHOUL was named the inaugural recipient of the Laura F. Hutchins, M.D. Distinguished Chair for Hematology and Oncology at the **University of Arkansas for Medical Sciences**.

Makhoul is director of the Division of Hematology/Oncology in the UAMS Winthrop P. Rockefeller Cancer Institute. Hutchins holds the Virginia Clinton Kelley Endowed Chair for Clinical Breast Cancer Research. She is a professor of medicine in the Division of Hematology/Oncology, where she served as division director from 1998 until September 2013.

"I cannot think of anyone better suited to hold the distinguished chair honoring Dr. Hutchins than her long-time colleague Dr. Makhoul," said UAMS Chancellor Dan Rahn.

Funding for the chair was made possible by a donation of $1 million from an anonymous donor, proceeds from the institute's 2012 Gala for Life fundraiser, and private donations. The chair holder uses the interest proceeds for research, teaching, or service activities.

Makhoul's research focuses on the role on antiangiogenic therapy and targeting cancer-initiating cells in breast cancer, as well as quality of life and survivorship. He joined the UAMS faculty in 2002, is an associate professor in the UAMS College of Medicine, and was named director of the Division of Hematology/Oncology in 2013. He has also served as director of the division's Hematology/Oncology Fellowship Program since 2008.

MARGARET DIMOND was named president of the **Karmanos Cancer Hospital**, effective immediately.

She will report directly to Gerold Bepler, president and CEO of the Barbara Ann Karmanos Cancer Institute.

Dimond will manage all clinical operations at Karmanos' main campus in Detroit as well as its Farmington Hills and Monroe locations and work with the leadership teams at Karmanos, Detroit Medical Center, McLaren Health Care, and Wayne State University.

Prior to coming to Karmanos, Dimond served as president and CEO of the McLaren Medical Group since 2008. There she was responsible for the ambulatory services network consisting of more than 250 primary and specialty physicians over an 18-county area.

She continues to hold faculty appointments at Michigan State University's College of Human Medicine and College of Social Sciences. She previously held a faculty appointment at Wayne State University's School of Social Work from 1990-2002.

NORTH SHORE-LIJ CANCER INSTITUTE opened a $47 million radiation therapy facility.

The institute's Department of Radiation Medicine has relocated from LIJ Medical Center in New Hyde Park, N.Y., to the health system's Center for Advanced Medicine, an outpatient care complex in Lake Success, N.Y.

Services provided include: stereotactic radiosurgery, stereotactic body radiation therapy, intensity-modulated radiation therapy, and image-guided radiation therapy, as well as a brachytherapy program.

The new facility is the first phase of a major expansion of cancer services at the Center for Advanced Medicine. The Monter Cancer Center is doubling in size to 80,000 square feet, with construction expected to be completed this spring as part of a $45 million expansion.

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THE DUKE-NUS GRADUATE MEDICAL SCHOOL Singapore has partnered with **ImaginAb Inc**. to establish a joint corporate laboratory to develop new in vivo molecular imaging agents to study cancer biology and immune function.

ImaginAb is a U.S. clinical-stage company that develops agents based on a proprietary antibody fragment technology platform.

The two will establish protein engineering and molecular imaging capabilities designed to interface with Duke-NUS's Signature Research Programs in cancer and stem cell biology, cardiovascular and metabolic diseases, neurobiology and immunology. The new facilities will also be used to support ImaginAb's research and development.

The 10th annual **ST. JUDE THANKS AND GIVING CAMPAIGN** raised more than $97 million last holiday season to support the **St. Jude Children's Research Hospital**, a projected increase of more than 31 percent over the previous year. Since 2004, the campaign has raised nearly $485 million.

For the fifth consecutive year, Kmart was the top corporate fundraising partner. During the 2013 holiday season, Kmart raised $21.9 million, nearly tripling the $7.5 million the company raised in 2012.

More than 60 companies and brands, including ANN Inc., AutoZone, Brooks Brothers, Claire's, CVS/pharmacy, Dick's Sporting Goods, Dollar General, Domino's, GNC, Gymboree, HomeGoods, HSN, Kay Jewelers, Kmart, Marshalls, New York & Company, Target, and Williams-Sonoma—as well as new partners Best Buy, Christopher & Banks, GameStop, Justice & Brothers, Stage Stores, Tommy Hilfiger, and many others—asked shoppers to support St. Jude through in-store and e-commerce initiatives, specialty merchandise, and social media engagement.

A roster of celebrities helped to promote the campaign, including Jennifer Aniston, Robin Williams, Michael Strahan, Sofia Vergara, Shaun White, Luis Fonsi, Brad Paisley, Darius Rucker, Sabrina Soto, Olivia Holt, Jennette McCurdy, and many more, as well as a week-long exposure on NBC's Today Show, which featured several in-depth stories chronicling the journeys of St. Jude patients.

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ROSWELL PARK CANCER INSTITUTE will collaborate with **GenomOncology** to develop an informatics solution that enables the association of next-generation sequencing results with knowledge resources to define actionable mutations.

The two will work to develop a software platform that integrates laboratory information management systems, electronic health records, information technology and bioinformatics and that provides a workflow enabling genomic analysts and pathologists to create actionable reports.

GenomOncology will be demonstrating this software platform at two upcoming conferences, Advances in Genome Biology & Technology in February, and at the U.S. & Canadian Academy of Pathology in March.

ROCHE SERVICIOS S.A., a Roche affiliate, and **Cancer Genetics Inc.** have entered into a three-year agreement to expand molecular diagnostic cancer testing in Central America and the Caribbean.

Under the agreement, CGI will be the exclusive provider of molecular diagnostic cancer testing for Roche Servicios, covering multiple disease categories, including testing for lung cancer, breast cancer, and lymphoma. CGI first began offering such testing for Roche Servicios in late 2012. CGI will use Roche's cobas platform.

CGI will initially focus on cobas-based testing starting with the epidermal growth factor receptor mutation test, intended to help select non-small cell lung cancer patients for treatment with EGFR inhibitors. The partnership allows for expansion into other cancer categories and regions as mutually decided by CGI and Roche.

NOVARTIS acquired **CoStim Pharmaceuticals Inc.**, a portfolio company developing monoclonal antibody drugs, for an undisclosed amount. The acquisition was announced by MPM Capital and Atlas Venture.

CoStim was founded in 2012 by Luke Evnin, MPM's managing director, and Robert Millman, the managing director for operations. Millman was initially president of CoStim, and Evnin became chairman of the board.

CoStim has assembled a portfolio of agents directed at multiple T cell regulatory targets through relationships with the Dana Farber Cancer Institute, Harvard Medical School, Boston Children's Hospital, Brigham and Women's Hospital, and Immutep SA.