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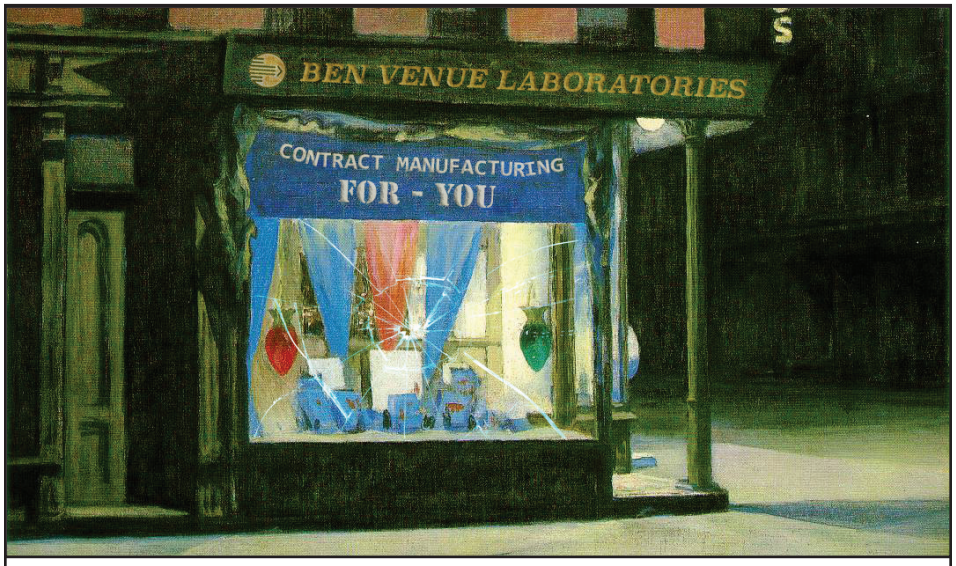

Who Makes This Drug?

Secretive Contract Manufacturing Arrangements Complicate Solutions to Shortages of Generics

By Rena M. Conti

It takes a few clicks to look up the name of a company that holds the "Abbreviated New Drug Application," or ANDA, to make a generic drug. Alas, this information is of little value.

If you want to prepare for a drug shortage or pick a high-quality manufacturer to supply drugs, you need to know about the role of a contract manufacturer, the company that makes the drug. Currently, there is simply no way for the doctors or the public to get this information.

(Continued to page 2)

In Brief

Julie Vose Elected President of ASCO

JULIE VOSE was elected president of the **American Society of Clinical Oncology** for a one-year term beginning in June 2015. She will take office as president-elect during ASCO's annual meeting in Chicago in June 2014.

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An Appreciation

Janet Rowley, "Translational Research Pioneer"

Janet Rowley, a pioneer in connecting the development of cancer with genetic abnormalities, died from complications of ovarian cancer on Dec. 17 at her home. She was 88.

Rowley was the Blum-Riese Distinguished Service Professor of Medicine, Molecular Genetics & Cell Biology, and Human Genetics at the University of Chicago.

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Knots of Overlapping Deals Lie Outside Public View

(Continued from page 1)

Even FDA can't easily determine whether a drug is made by the ANDA sponsor or a contract manufacturer.

The demise of Ben Venue Laboratories, a company that produced a big share of the generic drugs used by America's oncologists, exposes the tangled structure of the generics industry, and brings into focus the little-understood business practice of contract manufacturing.

Ben Venue, scheduled to close at the end of 2013, produced drugs and sold them under its trademark and that of a related company, Bedford Laboratories. The two firms had the same corporate parent: Boehringer Ingelheim of Germany. However, Ben Venue's principal function was to manufacture drugs under contract for a multitude of other companies that hold ANDAs.

"The lack of transparency around which company is actually manufacturing medications is incredibly frustrating," Erin Fox, director of the University of Utah's Drug Information Service, said to The Cancer Letter. "When a shortage occurs, the first action item is to determine if there are alternative sources. Currently available data makes it extremely difficult to identify if alternatives exist, or in the case of a factory or line closure, exactly which products might be affected."

It is possible to go to the FDA compendium called the Orange Book and find out which company holds the license—the ANDA—to make a drug. Yet, in practical terms, this information is useless. In addition to gaps in information about contract manufacturers like Ben Venue, there is no way to know whether ANDA sponsors have discontinued drugs without notice to FDA.

Without this information, there is no easy way for FDA officials or other stakeholders to assess the implications of changes in the supply of drugs or to easily identify available domestic capacity to make drugs needed for patient care.

Clifford Hudis, president of the American Society of Clinical Oncology, said the society supports FDA's efforts to address the problem. Nonetheless, "it appears that greater transparency at the manufacturing level is necessary to provide earlier warning about upcoming shortages," Hudis said after being briefed about the scarcity of information on contract manufacturing. "While earlier notice might not solve the shortage problem entirely, at least it would give regulators, hospitals, manufacturers, physicians, and patients additional time to plan and prepare."

Contract Manufacturing on the Rise

Contract manufacturing is an increasingly common practice throughout the branded and generic pharmaceutical industry.

Ben Venue, a Bedford, Ohio, company which closed at the end of 2013, manufactured many generic cancer drugs currently in short supply. Also, the company made the branded drug Doxil (doxorubicin hydrochloride) under contract from Johnson & Johnson.

In a report published last year, FDA noted the trend of growing reliance on contract manufacturing throughout the pharmaceutical industry (Figure 1, p. 3).

Indeed, a number of prominent manufacturers of oral tablets and capsules and physician-administered drugs, including cancer drugs currently in short supply, hold ANDAs for their own drugs and also act as contract manufacturers for others. These include including Hospira, Luitpold, and Fresenius/APP.

Thus, Ben Venue was one of a number of such contract manufacturers. Its main specialty was producing sterile injectable drugs for Bedford, its parent Boehringer Ingelheim, and other companies.

From an economic perspective, the outsourcing of production of injectibles to established contract manufacturers offers cost efficiencies to companies that hold ANDAs. Contract manufacturers can likely offer their services at a cost lower than that incurred by self-manufacturing.

Notably, they can take advantage of scale economies, producing the same drug for different ANDA sponsors using automated equipment. Furthermore,

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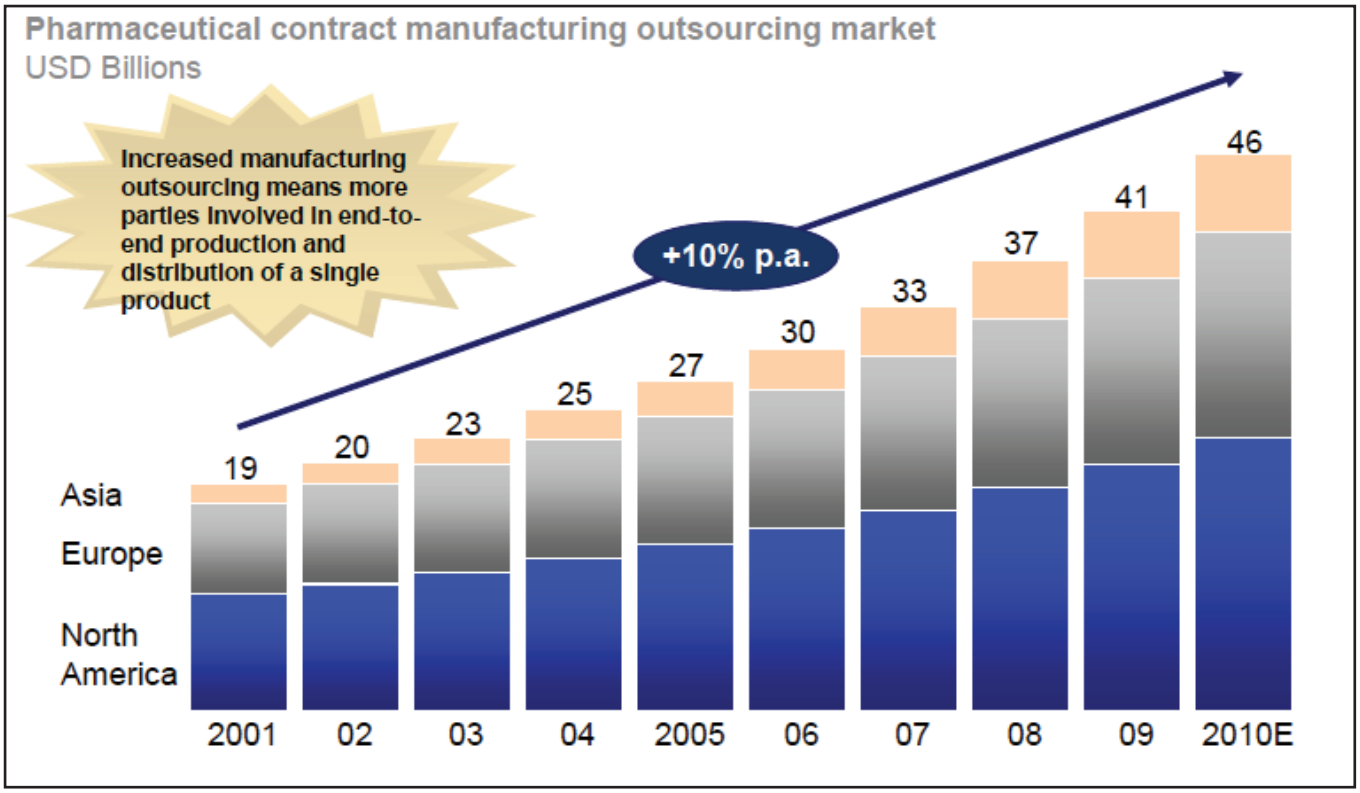


Source: U.S. FDA, Pathway for global drug safety and quality, 2013

because of scope economies, contract manufacturers likely face financial incentives to expand the portfolio of products they produce.

Contract manufacturers can pick up the slack when production by ANDA sponsors is temporarily or permanently suspended.

In the case of many drugs, the sourcing of base ingredients for drug production and the final fill and finish of the drug for sale in the U.S. may be both outsourced to different manufacturers. Here, too, supply interruptions can produce shortages.

For example, quality production problems and ongoing supply concerns in the sourcing of base ingredients outside the U.S. continue to threaten the domestic supply of heparin.

More than anything, Ben Venue is a case study in what happens when a contract manufacturer fails to adhere to manufacturing standards (The Cancer Letter, Oct. 11, 2013).

Last year, the company signed a consent decree accepting the obligation to improve quality.

Industry sources estimate that the company's owners had pumped an estimated $350 million into modernizing the plant, and that the company would need to absorb another $700 million in operating losses over the next five years to bring the plant in compliance. Negotiations between FDA and the company went on since it signed a consent agreement last January, and during that period the generic drug maker was teetering on the brink of closing the factory gates.

What FDA Knows

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.

Even when legal disputes flare up, as they did in the case of Ben Venue's production of Doxil for J&J, all the relevant details are kept under seal.

Learning from Ben Venue

In the case of Ben Venue, The Cancer Letter has more information about these arrangements than would ordinarily be publicly available.

This is the case because so many of Ben Venue's products have been in short supply.

Still, a search through company reports and news outlets produces no estimate of the number of drugs currently produced by Ben Venue for other ANDA sponsors, nor is it possible to identify those drugs using these sources or the FDA website.

However, Ben Venue's corporate sibling Bedford enumerates drugs for which it holds ANDAs and drugs known to be available through contract manufacturing by Ben Venue in its online catalog (Table 1, p. 5).

Bedford's catalog lists 66 unique generic injectable drugs manufactured by Bedford or Ben Venue.

A search through the FDA's Orange Book suggests an average of 5.4 sponsors hold ANDAs to manufacture these drugs (standard deviation 3.6).

Interestingly, there are a handful of drugs where only one ANDA holder is listed. They are: Doxil, Thiotepa and azathioprine sodium for injection. Based on this and public reports, we can surmise that Bedford/Ben Venue is likely the only manufacturer of Doxil and Thiotepa for the U.S. market.

Altogether, 53 percent of drugs listed have four or fewer ANDA sponsors.

Cross-listing Bedford's catalog with the University of Utah Drug Information Service shortages list reveals Bedford offered 25 drugs that are now in short supply and three drugs that had been in short supply in the past.

Thus, 42 percent of the drugs offered by Bedford are either currently in short supply or have been on that list. Interestingly, the average number of ANDA sponsors listed by FDA producing these drugs reported in short supply is 5.1, similar to that observed for all Bedford offered drugs.

The degree of overlap between Bedford listing and Ben Venue production isn't publicly known, but likely to be significant. Again, comparing Table 1 with Table 2 (p. 6) is revealing.

Among all drugs in Table 1 listed as being currently in short supply and manufactured by Bedford in their

Table 1

Drug Name	Offered by Bedford (source: Bedford's catalog)	Number of ANDA Holders (source: DRUGS@FDA)	In current short supply (source: University of Utah)
Acetazolamide Injection	Ben Venue Laboratories, Inc.	3	yes
Acyclovir Injection	Ben Venue Laboratories, Inc.	3	
Adenosine Injection	Ben Venue Laboratories, Inc.	10	yes
Allopurinol Sodium	Ben Venue Laboratories, Inc.	13	
Amikacin Sulfate Injection	Bedford Laboratories	2	
Atracurium Besylate Injection	Ben Venue Laboratories, Inc.	5	
Azathioprine Sodium for Injection	Ben Venue Laboratories, Inc.	1	
Bumetanide Injection	Ben Venue Laboratories, Inc.	3	yes
Buprenorphine Hydrochloride Injection	Ben Venue Laboratories, Inc.	4	
Butorphanol Tartrate Injection	Ben Venue Laboratories, Inc.	3	
Cafcit (Caffeine Citrate)	Ben Venue Laboratories, Inc.	6	
Chloroprocaine HCl Injection	Ben Venue Laboratories, Inc.	3	
Cladribine Injection	Bedford Laboratories	4	
Cyclosporine Injection	Bedford Laboratories	3	yes
Cytarabine Injection	Ben Venue Laboratories, Inc.	5	yes
Dacarbazine Injection	Ben Venue Laboratories, Inc.	5	yes
Dactinomycin Injection	Bedford Laboratories	3	yes
Daunorubicin HCl injection and Cerubidine for Injection	Ben Venue Laboratories, Inc.	3	yes
Deferoxamine Mesylate for Injection	Ben Venue Laboratories, Inc.	5	
Dexrazoxane for Injection with Sodium Lactate Injection	Ben Venue Laboratories, Inc.	4	
Dihydroergotamine Mesylate Injection	Ben Venue Laboratories, Inc.	4	yes
Diltiazem HCl Injection	Ben Venue Laboratories, Inc.	6	
Dobutamine Injection	Ben Venue Laboratories, Inc.	4	yes
Doxapram HCl Injection	Ben Venue Laboratories, Inc.	3	
Adriamycin® (Doxorubicin HCl) for Injection	Bedford Laboratories	1	
Doxycycline Injection	Bedford Laboratories	3	
Enalaprilat Injection	Ben Venue Laboratories, Inc.	4	yes
Esmolol Hydrochloride Injection	Bedford Laboratories	4	
Etomidate Injection	Ben Venue Laboratories, Inc.	5	
Etoposide Injection*	Bedford Laboratories	5	
Famotidine Injection	Ben Venue Laboratories, Inc.	5	yes
Floxuridine Injection	Ben Venue Laboratories, Inc.	2	
Fluconazole Injection	Ben Venue Laboratories, Inc.	9	yes
Flumazenil Injection	Ben Venue Laboratories, Inc.	6	
Haloperidol Lactate Injection IR	Ben Venue Laboratories, Inc.	10	
Indomethacin for Injection	Ben Venue Laboratories, Inc.	3	
Ketamine HCl Injection	Bedford Laboratories	4	
Ketorolac Tromethamine Injection	Ben Venue Laboratories, Inc.	8	yes
Labetalol Hydrochloride Injection	Bedford Laboratories	5	
Leucovorin Calcium for Injection	Ben Venue Laboratories, Inc.	4	
Levocarnitine Injection	Ben Venue Laboratories, Inc.	4	yes
Mesna Injection	Ben Venue Laboratories, Inc.	7	yes
Methotrexate for Injection	Bedford Laboratories	7	
Metoprolol Tartrate Injection	Bedford Laboratories	9	
Midazolam HCl Injection	Ben Venue Laboratories, Inc.	9	
Milrinone Lactate Injection	Ben Venue Laboratories, Inc.	9	
Mitomycin Injection	Ben Venue Laboratories, Inc.	3	yes
Norepinephrine Bitartrate Injection	Ben Venue Laboratories, Inc.	3	
Octreotide Acetate Injection	Bedford Laboratories	8	
Ondansetron Injection	Bedford Laboratories	18	yes
Orphenadrine Citrate Injection	Ben Venue Laboratories, Inc.	5	yes
Paclitaxel Injection	Ben Venue Laboratories, Inc.	9	yes
Pamidronate Disodium for Injection	Bedford Laboratories	11	
Pentostatin for Injection	Ben Venue Laboratories, Inc.	2	
Phentolamine Mesylate for Injection*	Ben Venue Laboratories, Inc.	3	
Polymyxin B Injection	Bedford Laboratories	4	
Prochlorperazine Edisylate Injection	Bedford Laboratories	3	yes
Propranolol Hydrochloride Injection	Ben Venue Laboratories, Inc.	5	
Ranitidine Injection*	Ben Venue Laboratories, Inc.	3	
Rifampin for Injection	Bedford Laboratories	4	yes
Terbutaline Sulfate Injection	Ben Venue Laboratories, Inc.	5	yes
Thiotepa for Injection	Ben Venue Laboratories, Inc.	1	yes
Valproate Sodium Injection	Bedford Laboratories	3	yes
Vecuronium Bromide for Injection	Ben Venue Laboratories, Inc.	7	
Vinblastine Sulfate for Injection	Ben Venue Laboratories, Inc.	2	
Vinorelbine Injection	Ben Venue Laboratories, Inc.	11	

Table 2

Drug Name	Offered by Bedford (source: Bedford's catalog)	Reasons for shortage (source: University of Utah)
Acetazolamide Injection	Ben Venue Laboratories, Inc.	Ben Venue has stopped production in its plant and will close in early 2014.
Adenosine Injection	Ben Venue Laboratories, Inc.	Astellas had Adenoscan on back order due to increased demand. Ben Venue has stopped production in its plant and will close in early 2014. Sagent has adenosine syringes on shortage because the company is transferring suppliers of raw materials. Teva has discontinued their adenosine injection. Wockhardt discontinued their adenosine 3 mg/mL 2 mL and 4 mL syringes.
Bumetanide Injection	Ben Venue Laboratories, Inc.	Bedford has bumetanide injection on shortage due to manufacturing delays. Astellas had Adenoscan on back order due to increased demand. Ben Venue has stopped production in its plant and will close in early 2014. Baxter discontinued bumetanide 0.25 mg/mL 2 mL vial in early-2011. Hospira had bumetanide on shortage due to manufacturing delays.
Cyclosporine Injection	Bedford Laboratories	Perrigo discontinued cyclosporine injection in late-November, 2011. Bedford has cyclosporine injection on shortage due to manufacturing delays. Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014.
Cytarabine Injection	Ben Venue Laboratories, Inc.	APP has cytarabine on shortage due to increased demand. Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014.
Dacarbazine Injection	Ben Venue Laboratories, Inc.	Teva had dacarbazine on back order due to manufacturing delays. Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014.
Dactinomycin Injection	Bedford Laboratories	Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014.
Daunorubicin HCl injection and Cerubidine for Injection	Ben Venue Laboratories, Inc.	Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014. Teva states the reason for the shortage is demand exceeding available supply.
Dihydroergotamine Mesylate Injection	Ben Venue Laboratories, Inc.	Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014. Paddock cannot provide a reason for the shortage of dihydroergotamine mesylate injection.
Dobutamine Injection	Ben Venue Laboratories, Inc.	Baxter has dobutamine on back order due to increased demand. Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014. Hospira has dobutamine on shortage due to manufacturing delays.
Enalaprilat Injection	Ben Venue Laboratories, Inc.	Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014. Teva has discontinued both of their products.
Famotidine Injection	Ben Venue Laboratories, Inc.	Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014. West-Ward (formerly Baxter) could not provide a reason for the shortage.
Fluconazole Injection	Ben Venue Laboratories, Inc.	Teva has fluconazole injection on shortage due to manufacturing delays. Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014.
Ketorolac Tromethamine Injection	Ben Venue Laboratories, Inc.	American Regent discontinued all ketorolac injection presentations in 2010. APP states the shortage was due to manufacturing delays. Baxter could not provide a reason for the shortage. Cura filed for bankruptcy in 2010. Hospira states that shortages are due to manufacturing delays and increased demand. Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014. West-Ward has ketorolac injection on shortage due to manufacturing delays. FDA imposed an import ban in mid-2013 on several Wockhardt products including ketorolac.
Levocarnitine Injection	Ben Venue Laboratories, Inc.	American Regent has levocarnitine injection on back order due to manufacturing delays. Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014. Teva could not provide a reason for the shortage.
Mesna Injection	Ben Venue Laboratories, Inc.	Teva has a shortage of mesna injection due to manufacturing delays. Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014.
Mitomycin Injection	Ben Venue Laboratories, Inc.	Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014. Accord states the reason for the shortage was increased demand.
Ondansetron Injection	Bedford Laboratories	Caraco temporarily discontinued ondansetron injection. West-Ward acquired Baxters ondansetron vials for injection and discontinued product offering. Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014. Hospira has ondansetron on shortage due to manufacturing delays. Teva is temporarily discontinuing ondansetron 20 mL injection. Wockhardt has ondansetron injection on shortage due to an FDA import alert.
Orphenadrine Citrate Injection	Ben Venue Laboratories, Inc.	Watson stated the shortage was due to production delays. Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014.
Paclitaxel Injection	Ben Venue Laboratories, Inc.	APP had paclitaxel on shortage due to increase demand for the product. Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014. Teva had paclitaxel on shortage due to manufacturing delays. Sandoz has paclitaxel on back order due to a raw material shortage. Hospira had paclitaxel on back order due to increased demand for the product. Sagent has paclitaxel on shortage due to increased demand for the product.
Prochlorperazine Edisylate Injection	Bedford Laboratories	Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014.
Rifampin for Injection	Bedford Laboratories	Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014. Pfizer has rifampin injection on back order due to a manufacturing issue resulting in potential for product discoloration and possible impurities or potency issues.
Terbutaline Sulfate Injection	Ben Venue Laboratories, Inc.	Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014. Akorn has discontinued terbutaline injection.
Thiotepa for Injection	Ben Venue Laboratories, Inc.	Bedford has thiotepa injection on shortage due to manufacturing delays.
Valproate Sodium Injection	Bedford Laboratories	APP has valproate sodium injection on shortage due to increased demand. Ben Venue has stopped production in its plant in Bedford, Ohio and will close in early 2014.

catalog, the closure of Ben Venue facilities is always listed as one public rationale for shortages reported to the University of Utah Drug Information Service. The University of Utah researchers offer the following rationale for the shortage:

"Ben Venue has stopped production in its plant in Bedford, Ohio, and will close…Ben Venue supplies multiple sterile injectable products for Bedford Laboratories. Supplies of product that has already been manufactured will continue to be released until inventory is depleted. Bedford Laboratories has a small number of products manufactured elsewhere that are not affected by this closure."

Assessing America's Drug Supply

The knot of undocumented, overlapping outsourcing arrangements has two important implications for patients, physicians, hospitals, insurers and other manufacturers.

First, these arrangements make it hard for these stakeholders to predict exactly what the supply of drugs will be after mergers, acquisitions and/or closures of contract manufacturing facilities supplying drugs to the U.S. market.

For example, among the drugs listed in Table 1, it is unclear which manufacturers have the existing capacity to continue to make the drugs after the closing of Ben Venue. It is plausible that every one of the drugs listed in Table 1 had been outsourced to one or more contract manufacturers.

"Currently, if you hear of a closure at a specific facility, you have to wait and see what products might be impacted," Fox said.

Perhaps of more immediate concern, the public lacks information regarding the number and probable capacity of current suppliers of drugs in short supply. Indeed, one implication of Table 1 and Table 2 is that the number of companies with adequate capacity to manufacture generic injectable drugs for the U.S. market, including those affected by shortages, is likely much smaller than previously documented.

University of Utah's Fox predicts that the exit of Ben Venue will make drug shortages stretch another four years or longer. This comes at a time when the rate at which shortages emerge has been dropping, but the absolute number of shortages is on the rise.

Second, under these arrangements, public stakeholders are unable to quickly assign blame when supply or quality lapses occur.

Thus, drug purchasers cannot effectively choose manufacturers with a demonstrated commitment to quality production or reassure patients of supply meeting quality standards.

"FDA's new strategic plan around drug shortages recommends that purchasers use available data regarding the quality of manufacturers when making purchasing decisions," Fox said.

"This is currently difficult to do as the only available quality data from FDA are MedWatch alerts, warning letters, and '483' inspection forms. In some cases, these data may document concerns regarding quality, yet a list of products manufactured on site is not publicly available."

The author is an assistant professor of health policy and economics at the University of Chicago. Paul Goldberg and Will Craft contributed to this story.

Report to the Nation

Death Rates Continue to Decline In All Cancers, Major Sites

Death rates continued to decline for all cancers combined for men and women of all major racial and ethnic groups and for most major cancer sites, according to the Annual Report to the Nation on the Status of Cancer. Rates for both sexes combined decreased by 1.5 percent per year from 2001 through 2010.

The report was published online in the journal Cancer.

Overall incidence rates decreased in men and stabilized in women. The prevalence of comorbidity was similar among cancer-free Medicare beneficiaries (31.8 percent), breast cancer patients (32.2 percent), and prostate cancer patients (30.5 percent); highest among lung cancer patients (52.9 percent); and intermediate among colorectal cancer patients (40.7 percent).

Among all cancer patients, and especially for patients diagnosed with local and regional disease, age and comorbidity levels were important influences on the probability of dying of other causes and on overall survival. For patients diagnosed with distant disease, the probability of dying of cancer was much higher than the probability of dying of other causes, and age and comorbidity had a smaller effect on overall survival.

The report is a collaboration of NCI, the American Cancer Society, the Centers for Disease Control and Prevention, and the North American Association of Central Cancer Registries. These entities have been publishing annual reports since 1998.

The latest report shows that the rate of death from lung cancer, which accounts for more than 25 percent of cancer deaths, has been dropping at a faster pace than in previous years. The report suggests that the decline is likely the result of decreased cigarette smoking prevalence over many years, and is now being reflected in mortality trends.

Additional declines in colorectal, breast, and prostate cancer death rates have also helped drive decreases in death rates for all cancers types combined, a trend that began about 20 years ago.

The decreased death rates for these four cancers accounted for more than two-thirds of the overall reduction in cancer death rates in the period 2001-2010. The report shows that death rates increased for some cancers, including cancers of the liver and pancreas for both sexes, cancers of the uterus in women, and, in men only, melanoma of the skin and cancers of the soft tissue in this 10-year period.

The special feature of this year's report highlights the prevalence of other disease conditions, including diabetes, chronic lung disease, cardiovascular disease, and 13 others, in cancer patients over 65 years of age, and how they affect survival.

The report shows that one-third of patients in this study population have comorbidities, with a higher frequency of comorbidities in patients with lung or colorectal cancer, and that survival is influenced by the presence of other medical conditions as well as the type of cancer, stage at diagnosis, and age.

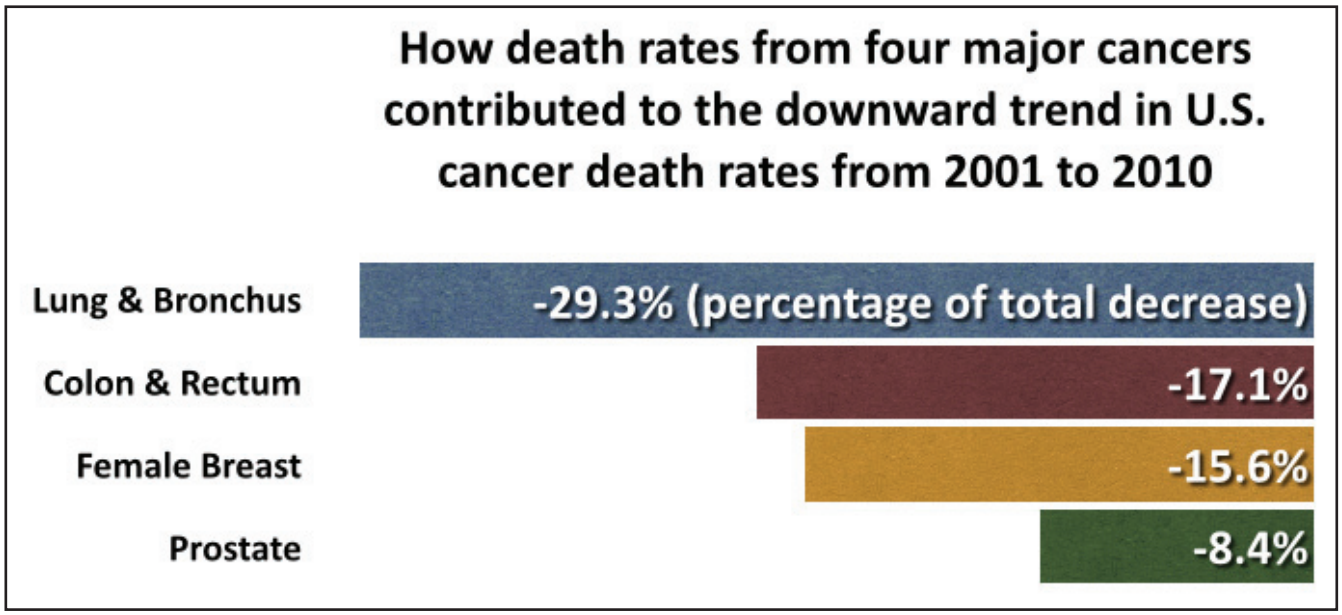
The latest report found that from 2001 through 2010, death rates for all cancers combined decreased by 1.8 percent per year among men and by 1.4 percent per year among women.

Death rates among children 14 years of age and younger decreased by 1.9 percent per year. Death rates among men decreased for 11 of the 17 most common cancers (lung, prostate, colon and rectum, leukemia, non-Hodgkin lymphoma, esophagus, kidney, stomach, myeloma, oral cavity and pharynx, and larynx) and increased for melanoma of the skin, soft tissue cancers, and cancers of the pancreas and liver.

During the same 10-year period, death rates among women decreased for 15 of the 18 most common cancers—lung, breast, colon and rectum, ovary, leukemia, non-Hodgkin lymphoma, brain, myeloma, kidney, stomach, cervix, bladder, esophagus, oral cavity and pharynx, and gallbladder—and increased for cancers of the uterus, pancreas, and liver.

The report found that lung cancer death rates for men dropped 1.9 percent per year during the period 1993-2005 and fell by 2.9 percent per year from 2005-2010. For women, rates declined 1.4 percent per year during the period 2004-2010, which was a turnaround from an increase of 0.3 percent per year during the period 1995-2004. These shifts have been attributed to many factors that have reduced the prevalence of cigarette smoking in the U.S.

Of particular note is the smaller drop in lung



cancer death rates for women, most probably due to a later decline in cigarette smoking rates among females.

"The sustained fall in death rates for most cancers is an important indicator of our success in controlling this large set of complex diseases but is not as fast as we'd like," NCI Director Harold Varmus said in a statement. "In addition, the report emphasizes the need to consider the entire health status of cancer patients since many have other significant medical conditions that may affect their survival."

Incidence rates may presage changes in mortality outcomes however.

During the period of 2001-2010, overall cancer incidence rates decreased by 0.6 percent per year among men, were stable among women, and increased by 0.8 percent per year among children (ages 0 through 14 years), continuing trends from recent annual reports.

During the 2001-2010 period, incidence rates decreased for six of the 17 most common cancers among men (prostate, lung, colon and rectum, stomach, larynx, and brain and other nervous systems) and increased for eight others (kidney, pancreas, liver, non-Hodgkin lymphoma, thyroid, leukemia, melanoma of the skin, and myeloma). Among women, incidence rates decreased for six of the 18 most common cancers (colon and rectum, bladder, cervix, oral cavity and pharynx, ovary, and stomach), and increased for eight others (thyroid, melanoma of the skin, kidney, pancreas, leukemia, liver, myeloma and uterus).

"Similar to death rates, the overall decrease in cancer incidence rates among men was driven in part by declines in lung cancer, mainly reflecting the success of tobacco control interventions," said John Seffrin, CEO of the American Cancer Society. "We are particularly heartened to see that in the most recent time period, from 2005 to 2010, lung cancer incidence rates dropped among women. Nonetheless, lung cancer remains by far the leading cause of cancer death in both men and women."

Comorbidities and Cancer

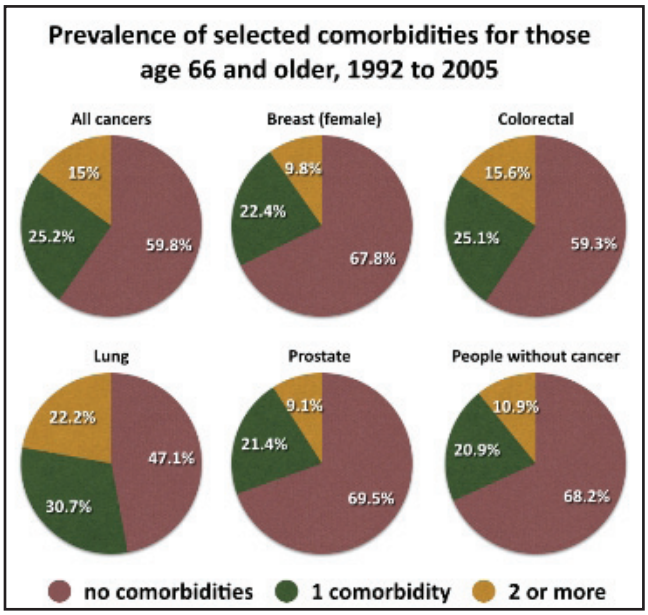
The special feature section of the report discusses the prevalence of comorbidities among Medicare beneficiaries with lung, colorectal, breast, and prostate cancer and how these conditions influence survival due to a person's cancer and other illnesses. Forty percent of patients 66 years of age or older, with any of these four cancers, had at least one comorbidity.

Measures of comorbidity can contribute to understanding how multiple diseases work together to affect outcomes. For cancer patients, incorporating comorbidity measures into treatment planning may lead to better decisions about the potential risks and benefits of treatment options.

The authors linked cancer registry data from NCI with Medicare claims data that identified the presence of comorbidities in patients ages 66 or older, one year prior to their diagnosis of cancer.

Cancer stage was included in this survival model because patients with late-stage cancer have higher death rates than those diagnosed with earlier stage cancer, even after accounting for comorbidity.

The cancers with a high prevalence of comorbidities were lung cancer (52.9 percent) and colorectal cancer (40.7 percent), while the prevalence of comorbidities for those with breast cancer (32.2 percent) or prostate cancer (30.5 percent) was similar to that seen in non-cancer patients (31.8 percent).



Sixteen comorbidities were identified in patients in the year prior to cancer diagnosis, including acute myocardial infarction (heart attack), AIDS, stroke, chronic kidney failure, chronic hepatitis, and others. The four most common comorbidities include diabetes, chronic obstructive pulmonary disease, congestive heart failure, and cerebrovascular disease.

Some of the more notable associations of comorbidities and survival included:

• For women with breast cancer diagnosed at an early stage of the disease, five-year survival varied by age and comorbidity level. For example, for women ages 66-74 with early stage disease, the probability of death for low or moderate comorbidity levels was almost double the probability of death compared to women with no comorbidity, while for women with severe comorbidity levels, the likelihood of dying was nearly triple compared to women with no comorbidity.

Comorbidity levels were associated with a similar impact on five-year survival among men ages 66-74 with prostate cancer diagnosed at an early stage. By contrast, comorbidity levels had relatively little or modest impact on the survival of women diagnosed with advanced breast cancer or men with advanced prostate cancer.

• For colorectal cancer, comorbidity and age were associated with decreased five-year survival among men and women with early stage disease, but not among patients with advanced disease.

• For lung cancer, the influence of comorbidities on survival was relatively small, probably because prognosis is often poor, even at early stages of the disease.

In Brief

Julie Vose to be ASCO President; Breakthrough Winners Named

(Continued from page 1)

Julie Vose
Source: ASCO.org

Vose is the Neumann M. and Mildred E. Harris Professorial Chair and Chief of the Oncology/Hematology Division in the Department of Internal Medicine at the University of Nebraska Medical Center, and the associate director of clinical research and co-chair of the Lymphoma Program at the Fred and Pamela Buffet Cancer Center. Since joining ASCO in 1991, she has served on the board of directors, as chair of the Cancer Education Committee, and is the current chair-elect of the Integrated Media and Technology Committee. She is also a member of the board of directors for the University of Nebraska Medical Center Physicians Group, co-chair of the NCO Lymphoma Steering Committee, and serves on the FDA Oncologic Drugs Advisory Committee.

Additionally, four members were elected to the ASCO board of directors, and two members were elected to the ASCO nominating committee. The following physicians will begin four-year terms as members of ASCO's Board of Directors starting in June 2014:

• **Linda Bosserman** was elected to a community oncologist seat. She is president of the Wilshire Oncology Medical Group, Inc. Since joining ASCO in 1990, Bosserman has served on the Quality Care Symposium Planning Committee and Practice Guidelines Implementation Network. She was a member of the White House Physician Forum on Health Reform in 2009.

• **David Khayat** was elected to an international oncologist seat. He is the head of the Department of Medical Oncology at Pitié-Salpêtrière Hospital in Paris. Since joining ASCO in 1987, he has served as chair of the International Affairs Committee, on the Cancer Education Committee, and as associate editor of the Journal of Clinical Oncology. He has served as president

of the French National Cancer Institute and the French Federation of Medical Oncologists.

• **Walter Curran** was elected to a radiation oncologist seat. He is the executive director of the Winship Cancer Institute of Emory University and the Lawrence W. Davis Professor and chairman of Emory's Department of Radiation Oncology. Since joining ASCO in 1988, Curran has served on the Cancer Research Committee, the Cancer.Net Editorial Board, and the Conquer Cancer Foundation Advanced Clinical Research Award in Glioma Subcommittee. He is one of three founding principal investigators of the new NCI-funded cooperative group NRG Oncology and the founding chair of the NRG Oncology Foundation Board.

• **Charles Blanke** was elected to an undesignated specialty seat. He is a professor of medicine at the Oregon Health & Science University Knight Cancer Institute in the Division of Hematology and Medical Oncology. Since joining ASCO in 1995, Blanke has served as chair of the Cancer Education Committee, co-chair of the Gastrointestinal Cancers Symposium Program Committee, and on the Journal of Clinical Oncology editorial board. He is the chair of SWOG.

The following two members of the ASCO Nominating Committee will serve three-year terms beginning in June 2014:

• **Gregory Reaman** is the associate director of the FDA Office of Hematology and Oncology Products, a professor of pediatrics at The George Washington University School of Medicine and Health Sciences, and an adjunct professor of oncology and pediatrics at Georgetown University School of Medicine. Since joining ASCO in 1978, he has served on the board of directors, the Cancer Survivorship Committee, and as chair of the Membership Committee, among other activities. He is a past chair of the Children's Oncology Group.

• **David Spriggs** is head of the Division of Solid Tumor Oncology and the Winthrop Rockefeller Chair of Medical Oncology at Memorial Sloan-Kettering Cancer Center and a professor of medicine at Weill Cornell Medical College. Since joining ASCO in 1986, he has served on the Scientific Program Committee, chair of the Grants Selection Committee, and as an associate editor of the Journal of Clinical Oncology. He serves as an associate editor of the New England Journal of Medicine. Spriggs will serve as the 2016-2017 chair of the Nominating Committee.

The winners of the **2014 BREAKTHROUGH PRIZE** in fundamental physics and life sciences were announced Dec. 12 at the NASA Ames Center, in Mountain View, Calif.

The prizes have a total awarded amount of $21 million.

The Breakthrough Prize in Life Sciences recognizes excellence in research aimed at curing intractable diseases and extending human life.

The 2014 recipients are:

• **James Allison**, of MD Anderson Cancer Center, won for the discovery of T cell checkpoint blockade as an effective cancer therapy.

• **Robert Langer**, the David H. Koch Institute Professor at the Massachusetts Institute of Technology, for discoveries leading to the development of controlled drug-release systems and new biomaterials.

• **Michael Hall**, of the University of Basel, for the discovery of Target of Rapamycin and its role in cell growth control.

• **Alexander Varshavsky**, of the California Institute of Technology, for discovering critical molecular determinants and biological functions of intracellular protein degradation.

• **Mahlon DeLong**, of Emory University, for defining the interlocking circuits in the brain that malfunction in Parkinson's disease. This scientific foundation underlies the circuit-based treatment of Parkinson's disease by deep brain stimulation.

• **Richard Lifton**, of Yale University and the Howard Hughes Medical Institute, for the discovery of genes and biochemical mechanisms that cause hypertension.

The Breakthrough Prize in Fundamental Physics recognizes transformative achievements in the field of fundamental physics, with a focus on recent developments.

The 2014 winners are **Michael Green**, of the University of Cambridge, and **John Schwarz**, of California Institute of Technology, for opening new perspectives on quantum gravity and the unification of forces.

ANDREA SLOAN, an ovarian cancer patient whose efforts to get access to a BioMarin drug attracted national media attention, died from complications of pneumonia Jan. 1 (The Cancer Letter, Nov. 8, 2013). Sloan, an Austin attorney, was 45.

An Appreciation

UChicago's Janet Rowley, 88

(Continued from page 1)

Before her, few scientists suspected that chromosomal aberrations caused cancer. Beginning in the 1970s, Rowley made a series of fundamental discoveries demonstrating that specific chromosomal changes caused certain types of leukemia.

Rowley's discoveries changed the way cancer was understood, opened the door to development of drugs directed at the cancer-specific genetic abnormalities and created a model that still drives cancer research.

"Janet Rowley's work established that cancer is a genetic disease," said Mary-Claire King, professor of genetics and medicine (medical genetics) at the University of Washington and president of the American Society of Human Genetics. "She demonstrated that mutations in critical genes lead to specific forms of leukemia and lymphoma, and that one can determine the form of cancer present in a patient directly from the genetic changes in the cancer. We are still working from her paradigm."

For years, Rowley struggled to convince fellow researchers. "I became a kind of missionary," she would often recall, preaching that chromosome abnormalities were important and hematologists should pay attention to them. "I got sort of amused tolerance at the beginning."

But thanks to her persistence and a long list of related discoveries, her ideas gained credence. Eventually, they brought her widespread recognition, including the Lasker Award, the National Medal of Science and the Presidential Medal of Freedom.

"Janet Rowley is a hero to many, including me," said Brian Druker, director of the Oregon Health & Science University Knight Cancer Institute. "Her groundbreaking work on the identification of the reciprocal translocation between chromosomes 9 and 22 in patients with chronic myelogenous leukemia allowed the development of the life-saving treatment Gleevec for this disease."

Her work also had a powerful influence on the research of other scientists.

"Janet Rowley was a pioneer in what is now called 'translational research,' the direct application of laboratory studies to understanding and treating human disease." said Richard Schilsky, a former UChicago colleague and now chief medical officer of

the American Society of Clinical Oncology.

"She laid the foundation for personalized cancer care and targeted therapy."

"She developed the Rosetta Stone that has enabled us to begin to dissect leukemias and lymphomas, to understand their progression and how they respond to treatment," said blood cancer specialist Richard Larson, professor of medicine at the University of Chicago. "Within my practice lifetime, her discoveries have led to the development of medicines that dramatically altered the management of fatal diseases like chronic myelogenous leukemia. We can now treat those patients on an outpatient basis with oral drugs that are well tolerated and highly effective."

Also, Rowley had an impact on the relationship between medical research and public policy. President Jimmy Carter appointed her to the National Cancer Advisory Board (197984). President Bill Clinton awarded her the National Medal of Science (1998). From 2002 to 2009, she served on George W. Bush's President's Council on Bioethics.

In 2009, she stood next to President Barack Obama when he lifted the federal moratorium on funding for stem cell research, and she returned to the White House later that year to accept the Presidential Medal of Freedom.

Rowley was often cited as a strong example of independent thinking and perseverance.

"Janet has been a mentor for her colleagues as well as her trainees and an ongoing example of scientific wisdom and imagination combined with impeccable professional and personal style," said colleague Michelle Le Beau, director of the University of Chicago Medicine Comprehensive Cancer Center. "She received just about every imaginable honor. Yet she remained breathtakingly humble, giving most of the credit to her colleagues, her students and luck."

Janet Davison Rowley was born April 5, 1925 in New York City, the only child of Hurford and Ethel Davison. Her parents, both UChicago graduates, moved to Chicago when she was 2. Her father taught retail store management at the college level and her mother taught English in the public high schools.

In 1940, after two years at a Catholic girls' high school, Rowley, then 15, won a scholarship to enroll in the Hutchins College at the University of Chicago, which combined the last two years of high school with the first two years of college. "The U of C," she later recalled, "taught me to stick to my convictions if I really thought that I was correct, even when others disagree."

She completed a bachelor of philosophy degree in 1944 and was accepted into the University's medical school, but the quota—three women out of a class of 65—was already filled, "so I had to wait nine months," she said in an interview. "I was only 19 at the time, so it wasn't a great tragedy."

On Dec. 17, 1948, at age 23, she graduated from medical school. The next day, she married fellow medical student Donald Rowley, who would become a professor of pathology at the University of Chicago. They completed their internships at the United States Public Health Service's Marine Hospital in Chicago in 1951 and had four boys. She spent the next 20 years raising them while working three days a week at various sites, including a Chicago clinic for children with Down syndrome, a genetic disorder caused by an extra chromosome 21.

Her interest in chromosomes and cancer gained focus in 1962, after a year at Oxford University, where she learned newly developed techniques of chromosome analysis. Back in Chicago, Leon Jacobson, a colleague and mentor, suggested she apply those techniques to the study of chromosomes from patients with leukemia. He offered some laboratory space, a microscope and a salary of $5,000 a year. For the next decade, she labored over the microscope, searching amid the seeming genetic chaos of leukemic cells for consistent chromosome abnormalities.

She made her first big discovery at home. After a second sabbatical in Oxford from 1970 to 1971 to learn new staining techniques to highlight the different stripes or "bands" on chromosomes, Rowley began to photograph the chromosomes of leukemia patients using the fluorescence microscope.

She would take the pictures home to examine. Her children often teased her about getting paid to play with paper dolls as she sat at their dining room table, cutting each chromosome out of the photographs and carefully arranging them in pairs.

In the spring of 1972, in her Hyde Park home, Rowley "lined up the chromosomes from leukemia cells on a table and told my kids not to sneeze."

She noticed that the chromosomes of a patient with acute myeloid leukemia had two abnormalities. Chromosomes 8 and 21 appeared to have made a trade. Part of 21 had broken off and moved to chromosome 8, and part of 8 had moved to chromosome 21—an exchange now known as a "translocation." When she looked at more patients with this same kind of leukemia, she saw the same process.

Later that year she noticed that patients with a different disease, chronic myelogenous leukemia, had a different translocation. One end of chromosome 22 had been exchanged for a piece of chromosome 9. Because of this transfer from one chromosome to another, important genes that regulated cell growth and division were no longer located in their normal position, resulting in uncontrolled cell growth of cancer.

The two consistent translocations—one in AML and one in CML, both published in 1973—argued that such translocations were tied to specific types of leukemia, but because the chromosomes of patients with either AML or CML could be highly variable, many scientists remained skeptical. In 1977, Rowley and colleagues identified a third chromosome example, the 15;17 translocation that causes acute promyelocytic leukemia, a rare disease but one where every patient had the same genetic flaw.

"That made me a believer," she later recalled. "That was the frosting on the cake."

Understanding the 9;22 translocation eventually led to the development of the drug imatinib (Gleevec), one of the most successful targeted cancer therapies to date. Gleevec blocks the function of the abnormal protein produced by that translocation. Her discovery

of the acute promyelocytic leukemia translocation led to effective treatment with high-dose retinoic acid, a vitamin A derivative.

Picking up on her lead that specific translocations defined specific forms of cancer, scientists around the world joined the search for chromosomes that either exchanged genetic material or duplicated genetic material, or lost it altogether. Others used the translocations as roadmaps to find specific genes disrupted by chromosome damage, thus opening up the current era of cancer genetics. By 1990, more than 70 translocations had been identified and linked to different cancers.

"This was a time of excitement and wonder that is hard to describe," she wrote in an essay. At age 47, after publishing the AML and CML studies, her 17th and 18th publications, her career took wing. Her resume now lists 508 publications in leading scientific journals. More recent discoveries include cloning a gene rearrangement that occurs in many infant leukemias and the recognition of deletions of parts of chromosomes 5 and 7 associated with therapy-related leukemia in patients previously treated with particular anti-cancer drugs.

She rose quickly through the ranks at UChicago, rising from research associate (assistant professor) in 1962 to associate professor in 1969, professor in 1977 and distinguished service professor in 1984.

The awards began in the early 1980s, including the Lasker Award and the National Medal of Science, the nation›s highest scientific honor, in 1998; the Presidential Medal of Freedom, America's highest civilian honor, in 2009; a Lifetime Achievement Award from the American Association for Cancer Research in 2010; the Japan Prize for Healthcare and Medical Technology in 2012; and the Albany Medical Center Prize in 2013. She has received honorary doctor of science degrees from 14 institutions, including Oxford, Harvard University, Yale University, the University of Pennsylvania and Dartmouth College.

She was elected as a member of numerous scientific and honorary societies including the National Academy of Sciences, the Institute of Medicine, the American Philosophical Society and the American Academy of Arts & Sciences.

Rowley, who continued to bicycle daily from her Hyde Park home to her laboratory in her late 80s, routinely advised young investigators not to give up.

"Take risks," she had said. "Do something different if it looks interesting… I didn't do anything noteworthy until I was 50. Success often involves a great deal of luck. Some people don't like to hear that because it means there are things out of their control. But that's the way it is."

"She has inspired a generation of translational research scientists, impacted hundreds of thousands of lives, and her spirit will live on in all of the people who have benefitted from her work," Druker said. "I have always admired her unrelenting curiosity and graceful humility."

An avid gardener, Rowley spent her rare free moments converting her city lot near campus into a flower and vegetable garden, the place where she claimed to have done some of her best thinking. Her other interests include the opera and traveling worldwide to hike, camp, observe wildlife, and become acquainted with the indigenous peoples. She also enjoyed spending time with her family at their cottage along Lake Michigan.

"Both my parents served as exemplary role models for their approaches to science, to life, to others and to family," said David Rowley, one of her sons. "My mother was an inspiration to all of her family through her generosity and her caring, and doing whatever was in her power to help each of us achieve our own individual goals. She will be dearly missed by her family, including five grandchildren."

Her husband, Donald, died in 2013. She is survived by three of their four sons, David, Robert and Roger; and grandchildren Jason, Jenny, Gia, Anra and Ian.

Rowley and her family have established a number of funds at the University of Chicago, including seeding an endowment fund to support training of an advanced hematology/oncology fellow interested in translational research in hematologic malignancies. There are also a number of funds named in her honor, including the recently announced Janet Davison Rowley Professorship Fund. Memorial gifts can be sent to:

Medicine and Biological Sciences Development
Attn.: Callie Johnston
130 E Randolph, Suite 1400
Chicago, IL 60601

Source: University of Chicago.