Drug shortages are an increasing problem. In 2010, the number of new drug shortages reported was 211 and rose to 267 in 2011. To put this in perspective, there were only 58 drug shortages reported in 2004. A drug shortage has been officially defined as a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent.

There are many causes of drug shortages, but the most common are manufacturing difficulties. If these manufacturing problems pose a risk to public health, a recall may be initiated. This will likely cause a halt in production. If the manufacturer cannot obtain the necessary raw materials to prepare the finished drug product, a shortage can occur.

The implications of drug shortages are numerous. The obvious major impact is decreased access to lifesaving drugs. In addition, the cost of those life-saving drugs may increase as a result. For example, the cost of cancer care has escalated as generic products are in short supply and hospitals are forced to buy the brand name products. An unexpected impact has been the introduction of more errors. The Institute for Safe Medication Practices performed a survey that showed 25% of clinicians indicated an error occurred at their site directly due to a drug shortage.

This is likely because pharmacies are ordering products that are unfamiliar to hospital staff. In addition, processes for drug use may change as a result of product differences. The increased time and effort put forth by hospital staff managing drug shortages has also been noted. In a recent study in hospitals comparable to the size of Shands, the average number of hours per week spent managing drug shortages was 12 and 13 by pharmacists and pharmacy technicians, respectively. Since 2010, health care labor costs have increased by about $216 million, which has major implications on hospital budgets.

Resolution of drug shortages at the national level is headed by the Food and Drug Administration’s division of the Center for Drug Evaluation and Research (CDER). Their mission is to respond to shortages that have significant impact on public health. Drug products that are deemed medically necessary fall into that category and the CDER will work with the manufacturers to resolve the shortage. In some instances, foreign drugs may be made available via an investigational protocol.

(continued on page 4)
**Formulary Update, from page 1**

<table>
<thead>
<tr>
<th>INTERCHANGES</th>
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**Pluticasone** (Generic) for 
Ciclesonide Aerosol Nasal Spray 
(Zetonna®)

**Lactobacillus Capsules** 
(Culturelle®) and Lactobacillus 
Granules (Lactinex®)

Based on typical daily doses 
and what is tolerated

**Sitagliptin-Metformin ER** 
(Janumet XR®)

Interchanged to sitagliptin and 
regular-release metformin

<table>
<thead>
<tr>
<th>CRITERIA-FOR-USE CHANGES</th>
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**Axitinib** (Inlyta®)*

*Added in the Chemotherapy and Hazardous Drug Policies

**Ceftriaxone** (Generic)

*Single-dose for gonorrhea prophylaxis in children less than 28 days

**Vismodegib** (Erlivedge®)*

*Added in the Chemotherapy and Hazardous Drug Policies

**Boceprevir** is an antiviral with a 
labeled indication for the treatment of 
hepatitis C virus (HCV) genotype 
1 infection in adult patients who are 
treatment-naïve or who have failed 
previous interferon and ribavirin 
therapy. Boceprevir directly and 
specifically inhibits HCV NS3/4A serine 
protease, which is responsible for the 
processing of many viral proteins 
essential to HCV replication.

Boceprevir has been evaluated 
in two phase III trials. In treatment-
naïve patients, regimens containing 
boceprevir plus peginterferon alfa-2a 
and ribavirin produced sustained 
virologic response in 66% of patients, 
compared to 38% of patients taking 
only peginterferon alfa-2a and ribavi-
rin [alone].

The most common adverse drug 
reactions to boceprevir are fatigue, 
anemia, nausea, headache, and 
dysgeusia. Boceprevir is expensive, 
costing approximately $4500 per 
month. It was added in the 
Formulary in order to minimize the poten-
tial for non-compliance, which could 
contribute to resistance.

**Telaprevir** was added in the 
Formulary for the same reason as 
boceprevir. Its labeled indication and 
mechanism of action are the same as 
boceprevir.

Telaprevir has been evaluated in 
treatment-naïve subjects producing 
sustained virologic response (SVR) in 
75% of patients receiving concomi-
tant interferon and ribavirin, compared 
with 44% of those taking only peginter-
feron alfa-2a and ribavirin.

Common adverse drug reactions to 
telaprevir are rash, anemia, nausea, 
hemorrhoids, diarrhea, dysgeusia, 
fatigue, vomiting, and anal pruritus.

The biggest difference between 
boceprevir and telaprevir is cost. The 
monthly cost for telaprevir is approxi-
mately $16,740. Boceprevir has to be 
refrigerated, and telaprevir does not.

**Imipenem** was the first carbapenem 
antibiotic. Imipenem is combined with 
cilastatin (imipenem-cilastatin) to slow 
the metabolism of imipenem. Carba-
penems are broad-spectrum antibiot-
ics that are often streamlined to more 
narrow-spectrum antibiotics once the 
or ganism and its sensitivities are 
known.

In July 2010, the P&T Committee 
 voted to make imipenem nonformulary 
and not available. Doripenem [Dori-
bax®] was added in the Formulary as the 
primary carbapenem because it 
may be less likely to be selected for 
carbapenem-resistant pseudomonas 
isolates.

Since that time, interest in imipe-
 nem use for the management of non-
tuberculosis mycobacterial disease has 
increased. Most reports about treating 
non-TB mycobacterial disease are with 
imipenem. Therefore, the Mycobacte-
riology Division requested the re-
addition of imipenem-cilastatin in the 
Formulary. Imipenem-cilastatin was 
added in the Formulary and restricted 
to approval by Infectious Diseases, the 
Antimicrobial Management Program, or 
mycobacteriology physicians.

**Tenofovir** is a nucleoside reverse 
transcriptase inhibitor (NRTI) with a 
labeled indication for the treatment of 
HIV as part of highly active antiretrovi-
ral therapy (HAART) and for the treat-
ment of chronic hepatitis B in adults. A 
40-mg-per-scoop tenofovir powder was 
recently approved.

The typical adult dosage for both 
indications is 300 mg once daily. Pediatric 
dosing for patients age 2 and 
above for HIV-1 is 8 mg/kg body 
weight, up to a maximum of 300 mg 
daily, administered as oral powder or 
tablets.

Tenofovir powder was added in the 
Formulary consistent with the philoso-
phy of ensuring availability of HAART 
to provide continuity of treatment.

**C1-esterase inhibitor** (Berinert®), 
ecallantide, and icatibant are drugs 
designed to treat acute attacks of 
hereditary angioedema (HAE) caused 
by C1-esterase deficiency and dysregu-
lation of complement and coagulation 
systems. These agents were design-
ated nonformulary and not available 
after determining that they would not 
be used at Shands UF. Cinyryze® brand 
of C1-esterase inhibitor was design-
ated a high-priority nonformulary 
drug in January 2009 because it is only 
available by a restricted distribution 
program. Patients must supply their 
own drug when used in the hospital 
for the prevention of HAE attacks.

Berinert® and Cinyryze® replace the 
deficiency of C-1 esterase in patients 
with HAE. Ecallantide is a kinin 
inhibitor. Icatibant is a bradykinin B2 
receptor antagonist.

Berinert® has been shown to be 
effective in reducing the time to onset 
of symptom relief for abdominal and 
facial HAE attacks. Ecallantide was 
shown to be effective in improvement 
of symptoms from baseline. Icatibant 
was shown to be effective in reducing 
the time to clinically significant relief 
of symptoms against an active com-
parator, but there was no difference 
compared with placebo. Only ecallan-
tide has been used for laryngeal 
attacks in clinical trials.

The C1-esterase inhibitors and ecallan-
tide are contraindicated in patients 
with a history of hypersensitivity to 
the respective products. There are no 
known contraindications for icatibant. 
Most of the adverse events for these 
medications are mild and temporary. 
The most common adverse events 
seen in clinical trials include injection 
site reactions, nausea, dizziness, and 
headache. Icatibant has been associ-
ated with elevated liver enzymes and 
fever. Subsequent HAE attacks and 
diarrhea have been reported with 
Berinert®. There is also a risk of prion 
or virus transmission with C1-esterase 
inhibitors because they are derived 
from pooled human plasma. Adverse 
reactions with ecallantide include 
fever and nasopharyngitis.

These products are expensive. 
Berinert® costs more than $4000 per 
dose for a 70-kg patient. Ecallantide 
costs over $8000 per dose, while a 
dose of icatibant costs nearly $7000 
per dose.

These agents were considered 
for nonformulary not available designa-
tion because HAE is a rare disease (ie, 
6,000 to 10,000 people in the US), the 
self-limiting nature of most acute 
attacks, and the high acquisition costs 
of these drugs.

Patients are rarely admitted to 
Shands UF with acute HAE. It is 
unlikely that patients would be diag-
nosed quickly enough to benefit from 
these agents. These drugs would 
likely expire before being used.

**Ingenol mebutate** is a topical gel 
for the treatment of actinic keratosis, 
a cutaneous neoplasm that develops 
on-sun-damaged skin. The likelihood 
of progression of an individual actinic 
keratosis to squamous cell carcinoma 
is varied but usually low. Estimates 
of annual rates of transformation have 
ranged from 0.03% to 20%. Multiple 
modalities have been used for the 
management of these lesions, includ-
ing physical or chemical destruction, 
(continued on next page)
Formulary Update, from page 2
topical medication, and photodynamic therapy.

Ingelni mebutate is applied once daily for three consecutive days. Because this is not an acute clini-
cal condition and treatment can be administered on an outpatient basis, it was designated nonformulary and not available.

Brentuximab vedotin is a CD30-di-
rected antibody-drug conjugate with labeled indications for the treatment of patients with Hodgkin’s lymphoma after failure of autologous stem cell transplant or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not stem cell transplant candidates and for the treatment of patients with sys-
temic anaplastic large cell lymphoma after failure of at least one prior multi-
agent chemotherapy regimen. The approved dose for both indications is 1.8 mg/kg/dose (max of 100 kg) IV given every three weeks for up to 16 cycles, or until disease progression or treatment toxicity. Dose adjustments are needed for both neutropenia and peripheral neuropathy.

Patients should be monitored for infusion-related reactions and tumor lysis syndrome, however, inpatient administration is not necessary. It is given as a 30-minute infusion and generally does not require pre-med-
ication. Pertinent drug interactions may occur with potent CYP3A4 and CYP3A5 inhibitors and inducers, as brentuximab vedotin is both a sub-
strate and an inhibitor of CYP3A4 and CYP3A5.

Post-market drug safety informa-
tion was recently issued by the FDA on brentuximab vedotin. The report warns healthcare professionals of new cases of progressive multifocal leukoencephalopathy (PML), a brain infection, which has been associ-
ated with brentuximab vedotin use. Though rare, PML can result in death, and the FDA threatened the FDA to add a new Boxed Warning of this risk to the drug label. The FDA has also added a warning against combined brentux-
imab vedotin and bleomycin use due to the increased risk for pulmonary toxicity; combined use is considered contraindicated.

A full treatment course of brentux-
imab for a 70-kg patient receiving 16 cycles of therapy is estimated at $168,000.

Brentuximab vedotin was designat-
ed a high-priority nonformulary drug for use in inpatients, although use should be rare. If needed, there is suf-
cient time to acquire drug before its administration would be needed. This designation would allow for screening when a patient’s routine dose occurs during a hospitalization and prevents use of repeated doses that should be administered in the outpatient setting.

Glucarpidase is a recombinant bacterial enzyme used as a rescue therapy to inactivate methotrexate, thus providing an alternate route of elimination to renal excretion. In Jan-
uary 2012, FDA approved glucarpidase injection with a labeled indication for the treatment of toxic plasma metho-
trexate concentrations in patients with delayed methotrexate clearance due to impaired renal function. It is not a substitute for and must be used in conjunction with leucovorin.

A proactive review of glucarpidase was completed and it was designated a high-priority nonformulary drug. The EPIC entry for this drug will include instructions on the process needed to obtain this drug to facilitate timely acquisition. Currently it is only available as part of an investigational drug protocol. Once it becomes com-
nercially available, this designation will be re-evaluated.

Zetonna® is an aerosol version of ciclesonide nasal spray with a labeled indication for the treatment of symp-
toms associated with seasonal and perennial allergic rhinitis in adults and adolescents 12 years of age and older. Its dosage is one 37-mcg actuation per nostril once daily, differing from the other ciclesonide nasal dosage form in its concentration per actuation. Omna-
riss® nasal spray is available as 50-mcg per actuation.

Omnaris® was designated nonfor-
mulary and not available in August 2009, and an interchange was approved to generic fluticasone one or two sprays per nostril daily.

Consistent with the previously approved interchange, Zetonna® was designated nonformulary and not avail-
able with an interchange to generic fluticasone nasal spray. Fluticasone spray will be given as one spray per nostril daily. Patients are permitted to use their own supply of Zetonna®.

Lactobacillus is an acid-producing probiotic bacterium that is a normal bowel inhabitant. It is used to attempt to reestablish the normal physiologic and bacterial flora of the intestinal tract, and has been used to treat antibiotic-associated diarrhea.

Pharmacists often receive requests from nursing to interchange lactobacil-
lus capsule and powder formulations when a patient’s ability to tolerate one changes. This is consistent with the policy for many other medications available as solid and liquid oral dosage forms. Lactobacillus introduces confusion because there is no standard interchange designation of capsule and pow-
der for liquid administration. The “conversion” is to switch from the recommended daily dose of one product to that of the other. The “standard” dosage of Culturelle® is one capsule twice a day. The “standard” dosage of Lactinex® is one packet three times a day.

Janumet XR® is a dipeptidyl-pep-
tidase-IV (DPP-IV) inhibitor [sitagi-
litin] and biguanide antidiabetic agent [extended-release metformin] combination product with a labeled indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. It dif-
ers from Janumet® by its inclusion of extended-release rather than regular-
release metformin.

Janumet® was designated nonfor-
mulary and not available in March 2008 and interchanged to its individ-
ual ingredients. Additionally, in July 2010, extended-release metformin was designated nonformulary and not available, with an interchange approved between 850-mg dose increments of regular release met-
formin and 750-mg increments of the extended release.

<table>
<thead>
<tr>
<th>Metformin ER Dosage</th>
<th>Metformin IR Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 mg daily</td>
<td>500 mg twice a day</td>
</tr>
<tr>
<td>1500 mg daily</td>
<td>500 mg in the AM &amp; 850 mg in the evening</td>
</tr>
<tr>
<td>2000 mg daily</td>
<td>1000 mg twice a day</td>
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</tbody>
</table>

Janumet XR® was designated nonformulary and not available and will be interchanged to an equivalent sitagliptin dosage and regular-release metformin, consistent with previously approved interchanges. (see chart on page 6)

Axitinib and vismodegib are new chemotherapy drugs that were added in the Chemotherapy and Hazardous Drug Policies. These agents were not added in the Formulary, but are included in these policies to assure safe handling in case of nonformulary use.

Axitinib is an oral kinase in-
hibitor indicated for the treatment of advanced renal cell carcinoma after failure of one prior systemic therapy. Progression-free survival was significantly improved with axitinib compared with sorafenib in a multi-
center, randomized, phase III study in patients with progressive renal cell cell carcinoma after one first-line therapy including a sunitinib-, temsirolimus-, or cytokine-based regimen or bevacizumab plus interferon alfa. Patients will usually use their own supply of this drug.

Vismodegib is an oral hedgehog path-
way inhibitor indicated for basal cell carcinoma (BCC), a common skin cancer with low metastatic potential. It is also indicated for use in patients with metastatic BCC or in patients with locally advanced BCC that has recurred following surgery. Vismo-
degib is also indicated for patients with locally advanced BCC who are (continued on page 6)
available when they meet FDA standards.

On a local level, there are many processes in place at Shands to lessen the impact of drug shortages for our patients. The Pharmacy Department tracks all current shortages likely to impact Shands. When a shortage has been identified, staff looks for product at other manufacturers to try and keep our supply stable. If there are no other supply options, product will be moved to key areas in the hospital. For example, during an etomidate shortage, product was removed from all crash carts and redistributed to areas of high use. If there are therapeutic equivalents or different route options available, staff will be encouraged to increase the use of alternatives. In the case of the intravenous lorazepam shortage, orders were changed to oral lorazepam, when appropriate. Restrictions may also help maintain supply of certain products. Intravenous pantoprazole supply was preserved due to efforts to uphold the criteria for use set in place by the P&T Committee, restricting it for nonvariceal upper gastrointestinal bleeds and patients under strict NPO orders.

Hospital staff notifications of drug shortages usually occur shortly before a change is implemented. Some prescribers ask why they do not receive advance notice when changes are necessary. If all possible shortages were passed on to physician and nursing staff, they would be overwhelmed with the amount of shortages that are reported. Frequently, shortages are resolved at the last minute, so it is difficult to determine when to sound the alarm and implement contingency plans. For instance, our supply of ondansetron injection was previously declining but the manufacturer was able to resume supply before a critical low was hit. Therefore, the medical staff are only notified of a shortage when the situation is critical.

Drug shortages will likely increase and continue to have a major impact on patient care. With new laws being introduced such as the Preserving Access to Life-Saving Medications Act, the FDA will hopefully gain the necessary tools to regulate shortages on a national level. This law would make it a requirement for manufacturers to report actual or potential interruptions in supply, develop criteria to identify drugs vulnerable to shortage, revisit the FDA definition of “medically necessary,” and improve communication among FDA, manufacturers, and health systems. Necessary resources will continue to be utilized at Shands to effectively manage these shortages.

By Brianna Franklin, PharmD

REFERENCES
4. Gatesman ML, Smith TJ. The shortage of essential chemo-
For decades, the Physician’s Desk Reference or PDR has been perceived as the “go-to” reference for “official” drug information. In other words, a manufacturer’s official prescribing information (labeling) could readily be found in the PDR. With changes in drug use and the availability of alternative sources of the same information, the future of this reference, which is now in its 66th edition, has to be in doubt.

The business model for the PDR has been to publish only the official prescribing information for brand name drugs for which there is not generic competition. Manufacturers paid to have their drug listed in the PDR. You could consider a listing in the PDR as a form of advertising. In the past, the PDR was commonly distributed by drug manufacturers’ sales representatives as a promotional item. Some people, including consumers and librarians purchased the PDR.

When most drugs prescribed were brand name drugs, the PDR contained most of the official prescribing information for the commonly prescribed drugs. However, times have changed. By 2015, it is estimated that 90% of all prescriptions will be for generic drugs. Thus, the PDR would only include 10% of the drugs prescribed. As more drug patents expire, fewer drugs are listed in the PDR. In the last 3 years, the size of the PDR has decreased.

What is the best alternative? Drug labeling information for most prescription and some non-prescription drugs can now be found in a reference called DailyMed. It is available at www.dailymed.nlm.nih.gov. As the URL suggests, this is an official governmental publication of the FDA and the National Library of Medicine.

Unlike the PDR, DailyMed lists the official labeling for brand name and generic drugs. It contains current prescribing information for most drugs, including recently approved drugs and labeling information that has been recently changed.

The information is also presented in a standardized format that makes it easy to find information in the labeling. Do you need dosage information? You can click on the Dosage & Administration tab. Other tabs include Description, Clinical Pharmacology, Indications & Usage, Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage, How Supplied, Patient Counseling Information, Boxed Warnings, and Medication Guide. Each label has a permanent link (URL) that can be referenced and will not change.

Best of all, DailyMed is available free with no advertising or potential conflicts of interest. It even archives old versions of a product’s labeling, so you can see how a label has recently changed. We will continue to keep old PDRs in the Drug Information Center for historical purposes, but there does not appear to be a continued need for print versions of the PDR.
Formulary Update, from page 3

not candidates for surgery or radiation therapy. It is the first FDA-approved drug for metastatic BCC.

Vismodegib labeling contains a boxed warning concerning the possibility of embryo-fetal death and severe birth defects.

Again, patients will usually use their own supply of this drug.

Ceftriaxone is an injectable third-generation cephalosporin with activity against gram-positive and gram-negative bacteria. Its long half-life allows for once-daily dosing.

Co-administration of calcium-containing intravenous solutions within 48 hours of ceftriaxone is contraindicated. This includes parenteral nutrient preparations. Use of ceftriaxone with calcium can lead to tissue crystallization and potentially patient harm.

Ceftriaxone is contraindicated in neonates age 28 days or younger and newborn infants at risk for hyperbilirubinemia. Risk for hyperbilirubinemia is defined as the high-intermediate to high risk zone on the algorithm as outlined by the American Academy of Pediatrics.

The Division of Pediatric Infectious Diseases requested one-time doses of ceftriaxone be allowed in children less than 28 days old for the prophylaxis of gonorrhea if they do not have another contraindication. The benefits of ceftriaxone outweighed any possible risk in this group provided the patient is not at risk for hyperbilirubinemia and has not recently received IV calcium within 48 hours. Cefotaxime is used in this age population for other uses or when patients are at risk for hyperbilirubinemia or who have received calcium-containing products.

<table>
<thead>
<tr>
<th>Janumet® XR Daily Dosage (Sitagliptin/Metformin ER)</th>
<th>Dosages for Interchanged Products (Sitagliptin + Metformin IR)</th>
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</thead>
<tbody>
<tr>
<td>Sitagliptin 100 mg– Metformin XR 1000 mg</td>
<td>Sitagliptin 100 mg Once Daily + Metformin IR 500 mg Twice Daily</td>
</tr>
<tr>
<td>Sitagliptin 50 mg– Metformin XR 1000 mg</td>
<td>Sitagliptin 50 mg Once Daily + Metformin IR 500 mg Twice Daily</td>
</tr>
<tr>
<td>Sitagliptin 50 mg– Metformin XR 500 mg</td>
<td>Sitagliptin 50 mg Daily + Metformin IR 250 mg Twice Daily</td>
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</tbody>
</table>