Pharmacy News

UNIVERSITY HOSPITAL
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Special Points of Interest:

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P&T Update

Formulary Additions

- **Ocrelizumab (Ocrevus®)- Formulary addition approved.**
  Ocrelizumab is a humanized anti CD20 monoclonal antibody indicated for the treatment of adults with primary progressive or relapsing multiple sclerosis (MS). Ocrelizumab- Formulary addition approved with the following criterion:

  The medication must be approved by the patient's insurance in advance (prior authorization) and supplied to the inpatient hospital pharmacy through the patient's outpatient/specialty pharmacy.

- **Naltrexone (Vivitrol®) 380mg IM monthly - Formulary addition approved** – It is an opioid antagonist with highest mu receptor affinity. Naltrexone is restricted to Psych attending & addiction certified physicians – patients must be free of opioids 7 days prior to treatment.

- **Zoster Vaccine – Recombinant, Adjuvanted (Shingrix®) - Formulary addition- Approved with restriction to outpatient use**

Formulary Deletions

- Niacin 50mg Tablets - Formulary deletion approved
- L-Cystine HCL Injection- Formulary deletion approved
- Methocarbamol Injection- Formulary deletion approved
- All formulary deletion requests were approved for deletion (see below).
  - Adefovir Dipivoxil 10mg tablets (Hepsera®)
  - Aminosalicyclic Acid 4g granules (Paser®)
  - Amoxicillin 125mg/5mL Suspension (Amoxil®)
  - Cefuroxime Axetil 250mg tablets (Ceftin®)
  - Cephalexin 125mg/5mL Suspension (Keflex®)
  - Ciprofloxacin 750mg tablets and 20-5mg IV Solution (Cipro®)
  - Clindamycin 300mg/50mL IV solution (Cleocin®)
  - Dicloxacillin 250,500mg tablets (Dynapen®)
  - Famciclovir 125,500mg tablets (Famvir®)
  - Griseofulvin Microsize 125mg/5mL suspension (Grivulvin V®)
  - Isoniazid-Rifampin 150-300mg tablets (Rifamate®)
  - Isoniazid/Rifampin/Pyrazinamide 50-120-300mg tablets
  - Itraconazole 250mg IV Kit (Sporonax®)
  - Lopinavir-Ritonavir 200-50mg Tablets (Kaletra®)
  - Micafungin 50mg IV (Mycamine®)
  - Nitrofurantoin Macrocrystals 50,100mg tablets (Macrodantin®)
  - Penicillin V Pot 125mg/5mL, Penicillin V Potassium 250mg Capsules (Veetids®)
  - Phenazopyridine 200mg tablets (Pyridium®)
  - Quinine Sulfate 200, 260, 325mg Capsules
  - Naphazoline Eye Drops (Naphcon®)
  - Edrophonium for injection (Enlon®)

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P&T Updates

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Line of Extension - approved

- Rilpilvirine and cobicistat are part of combination therapy in HAART – having the individual therapies will allow for more individualized therapy.
- Rilpilvirine 25mg tablets (Edurant®) – in combination therapy as part of Complera® (emtricitabine, rilpivirine, tenofovir).
- Cobicistat 150mg tablets (Tybost®) – plays the same role as ritonavir. Cobicistat part of co-formulated drugs.
- Valacyclovir 500mg, 1g tablets (Valtrex®) – used often as non-formulary. From efficacy perspective, no major difference in efficacy except that acyclovir requires higher frequency.

Policies & Procedure/Floor stocks

- 707-500-101 Non - Approved Abbreviations 2017-2018 - approved
- High Risk High Alert & Look Alike/Sound Alike Handout 2018 - approved
- Intravenous Medication Administration Guideline 2018 - approved
- Alaris® Drug Library Update - approved
- UH Drug Formulary - approved
- 707-500-122 Automatic Therapeutic Exchange - approved
- 707-600-127 Refrigerator Units and Temperature Monitoring - approved

  This is a revision to UH Policy #707-600-127 – Refrigeration Units and Temperature Monitoring, Validation and Documentation. Updated within the policy is the addition of a -80 degrees Celsius. Investigational Drug Freezer. All investigational drugs requiring storage at -80 degrees Celcius. have the temperature recorded every 15 minutes with the Sensoscientific Inc. system and every 10 minutes with the MadgeTech Datalogger. Data from both devices is downloaded monthly. The Temperature Control Log was also updated to reflect the addition of this refrigerator.

- **Naloxone Rescue Kit Distribution Protocol-approved**

  This is a new ED initiative to give those patients who are at high-risk of opioid overdose upon discharge a take-home naloxone kit. Section 4a of the protocol details patient selection criteria including those who received emergency medical care involving opioid intoxication or poisoning, have suspected opioid abuse or concerning therapeutic opioid use, and recent incarceration/ release from prison with history of opioid use. Patients not meeting the criteria but at risk of opioid overdose can be offered a prescription for naloxone to be filled at an outpatient pharmacy.

  The provider would place an order in the patient's profile under the entry: "Naloxone Kit for Discharge." The provider must document and conduct education before dispensing the kit to the patient upon discharge. The kit includes 2 naloxone 1mg/mL 2 mL luer-lock prefilled syringes for intranasal administration, 2 mucosal atomization devices, and educational materials. The kit will be loaded in select Pyxis machines or delivered from pharmacy. This policy is proposed to be piloted in the ED. The cost of a kit is approximately $75. An estimated 60 patients/month may be candidates for the naloxone kit.

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P&T Updates

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Additional strategies to tackle opioid overdose/use include;

A guideline has been developed in the ED for ED use to treat patients in acute pain who are opioid-naïve with non-opioid analgesics.

Possible opioid/pain stewardship may be implemented in the future to address on-going opioid usage.

- Medication Overrides from an Automated Dispensing Cabinet – New Policy-approved

  The purpose of this policy is to address the need for medication overrides from automated dispensing cabinets (ADC) and describes the types of medication overrides that will be reviewed for appropriateness and the frequency of the reviews.

Alzheimer's Disease in Physicians

The stigma, or the negatively preconceived notion, associated with Alzheimer's makes people in certain positions, such as those in the medical field, reluctant to seek help and diagnosis. In an article in the New England Journal of Medicine, *Alzheimer's Disease in Physicians – Assessing Professional Competence and Tempering Stigma*, Dr. Devi Gayatri further explains what physicians with Alzheimer's disease face and the measures that could be taken to both lessen the stigma and assist physicians with Alzheimer's disease.

Alzheimer's disease is characterized by an inevitable decline in cognitive function, that can have a varied course and magnitude between patients. While data on physicians with Alzheimer's disease is not available, statistics about the overall prevalence of Alzheimer's can be utilized to postulate the number of physicians with Alzheimer's.[1] According to the Alzheimer's Association, about 5.5 million people age 65 and older have Alzheimer's disease, which makes up about 10% of people age 65 and older.[2] Therefore, an assumption can be made that 10% of practicing physicians age 65 and older have some degree of Alzheimer's disease. However, diagnosis of Alzheimer's disease does not imply that a physician must stop practicing. The Mini Mental State Exam (MMSE) can be used in Alzheimer's patients to assess their cognitive status and rate of decline in cognitive function.[3] Patients with aggressive Alzheimer's disease see a decrease of about five points in their yearly MMSE score (maximum score of 30), whereas patients with slowly progressive Alzheimer's disease see a decrease in their MMSE score by about one point every year.[1] On the contrary, typically people who have jobs that require a high level of cognitive function tend to perform well on the MMSE despite cognitive decline because the questions are fairly basic, such as "count backward from 100 by sevens" and "take the paper in your right hand, fold it in half, and put it on the floor."[1,2]

Specifically, with physicians, Alzheimer's can exhibit clinical variability which can imply either minimal or extreme impact on cognitive functioning. Patients have varying levels of both healthy nerve cells and brain networking strength, which affects symptoms and disease course.[1] It is possible to see patients with a steady, consistent decline in cognitive function, but it is also possible to see patients whose cognitive function declines at a slow enough rate that they are able live into the 90s without any noticeable symptoms of Alzheimer's disease.[1] However, the stereotype associated with Alzheimer's disease makes severe complications appear to be the norm. The stigma and fear make most people, including physicians, hesitant to get evaluated which often results in later diagnoses, which make treating the disease more difficult.[1] Fear of Alzheimer's disease also comes with fear of how people may perceive you after diagnosis. Renowned professors have even been put on disability because of the preconceived notion that they would not function well and impair the education of their students. Similarly, physicians are afraid of being diagnosed with Alzheimer's because of the social and legal issues that could arise regardless of their ability to show strong cognitive function.[1]

There are ways to make diagnosis less scary that allow physicians to continue working in their profession, and protect the public. The American Medical Association believes that periodic cognitive evaluations after the age of 70, with maintenance-of-certification exams, can assess the physician's

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Alzheimer's Disease in Physicians

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cognitive function and up-to-date knowledge.[1] Similar practice is seen in the legal workforce with judges. To maintain the integrity of the physician and their practice, cognitively-impaired health professionals can work with independent groups who oversee the physician's work as a final checkpoint.[1] By accepting the degree of variability of Alzheimer's disease, along with supporting physicians rather than stigmatizing them, we can help decrease the fear associated with Alzheimer's disease and help physicians continue practicing as long as their cognitive function remains strong enough to provide proper, safe, and efficient care to patients.

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Public Health and Pharmacy: A Health-System Pharmacist Role in Public Health

As pharmacists have moved beyond solely dispensing and distributing medications, the role of a pharmacist has evolved to providing more patient-oriented, administrative as well as public health services. A pharmacist's pharmacotherapy expertise, access to care and preventative services can benefit many functions of public health.[1]

Despite the potential impact, the role of a pharmacist in public health is not clearly defined, recognized or promoted by healthcare professionals including educators and public health organizations. However, both national pharmacy organizations American Society of Health-System Pharmacists (ASHP) and American Pharmacists Association (APhA) have created policies and statements to provide guidance and help promote pharmacists' role in public health.[1,2]

Public health involves two levels of services: macro-level planning and micro-level implementation. The macro level involves the well-being of a population, focusing on assessing and prioritizing a community's health-related needs as well as planning to address those needs. This can involve formulating community health programs as well as managing, administering and evaluating community health-promotion programs. The micro level involves all the activities surrounding the activities required to implement public health initiatives, whether on a provider-to-patient or a program-to-population basis.[2]

Health-system pharmacists play a vital role in maintaining and promoting public health. ASHP believes that all health-system pharmacists have a responsibility to "participate in global, national, state, regional, and institutional efforts to promote public health and to integrate them into their practices and that health-system pharmacists should be involved in public health policy decision-making and in the planning, development, and implementation of public health efforts".[2] The major areas that health-system pharmacists can be involved with public health is direct involvement in infection control, substance abuse prevention, education and treatment, immunization, tobacco cessation, direct patient health education as well as emergency preparedness and response. Participation in pharmacy and therapeutic committees as well as medication use evaluation is also an opportunity to practice population based care.[2,3]

In the future, pharmacists' role will continue to be important in public health as advancements in technology and an increasing abundance of information for improving human health will result in both population-and patient-specific clinical data. The increasing amount of data will allow for population-specific disease management programs, many of which can be managed by pharmacists.[3]

With increasing awareness and education of the role of a pharmacist in public health, it is the hope that pharmacists will assume not only to have the responsibility of participating and integrating public health into their practice, but also to ensure involvement in policy decision making as well as planning, development and implementation of those efforts.[1,2]

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CAR-T cell therapy and the Management of Cytokine Release Syndrome

CAR T-cell therapy is an immunotherapy in which T-cells are genetically engineered to express chimeric antigen receptors.[1] This targets tumor-associated antigens on malignant cells and simulates a T-cell antitumor response.[1] The CAR T-cell administration consists of a novel and complicated process. First, the patients T-cells are extracted via leukapheresis and reprogrammed into CAR T-cells with the insertion of genes through a viral vector.[1] Next, the CAR T-cells are proliferated and expanded in a process that can take several weeks.[1] Finally, before the patient can be infused with the CAR T-cell therapy, the patient is given lymphodepleting chemotherapy.[1]

There are currently two approved CAR T-cell therapies: Kymriah® (tisagenlecleucel) and Yescarta® (axicabtagene ciloleucel) which target CD-19 on malignant B-cells in relapsed/refractory leukemia and lymphoma. Yescarta® was approved based on the results of the ZUMA-1 pivotal trial for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.[2] At a minimum of 6 months of follow up, the objective response rate (ORR) was 82%, and the complete response rate (CRR) was 54%.[2] This is in comparison to a historically control with an ORR of only 20%.[2] Response rates were also sustained at later follow up with an overall survival rate at 18 months of 52%.[2] Kymriah® was approved based on the results of the ELIANA trial for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.[3] Relapse-free probability was 75% at 6 months and 64% at 12 months among responders.[3] In addition, the probability of survival was 89% at 6 months and 79% at 12 months.[3] Overall, both treatments demonstrate efficacy for refractory/relapsed hematologic malignancies, which previously had severely limited options.

Both treatments were also associated with high rates of a unique toxicity known as cytokine release syndrome (CRS). In the ZUMA -1 trial, CRS any grade occurred in 93% of patients and Grade ≥ 3 in 13% of patients.[2] Similarly, in the ELIANA trial, CRS any grade occurred in 78% of patients and Grade ≥ 3 in 48% of patients.[3] CRS is an on target effect of CAR T-cell therapy in which activated T-cells and bystander immune cells release inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor - (TNF-α), and interferon-y (IFN-y).[4] The resulting hyper-inflammatory state is characterized by high fevers, hypotension, hypoxia, and multi-organ toxicity.[4] Management of mild-moderate CRS consists of supportive care such as acetaminophen, vasopressors, oxygen, and mechanical ventilation.[4] Tociluzumab (Actemra®) is a monoclonal antibody against IL-6 receptor that is FDA approved for severe/life-threatening CAR T-cell therapy induced CRS.[5] Treatment with tociluzumab has the potential benefit of being less toxic to T-cells compared to other cytokine targets or corticosteroids.[4] Therefore, corticosteroids are typically reserved for use following failure of tocilizumab in refractory CRS cases.[4] Due to the high rates of severe CRS, both therapies are available through a Risk Evaluation and Mitigation Strategies (REMS) program at certified healthcare facilities. A minimum of two doses of tociluzumab must be readily available for each patient within two hours of CAR T-cell infusion.[2,3]

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Increasing Rate of Antibiotic-Resistance Infections

Antibiotic resistance is an ongoing concern in the medical community, especially in the hospital setting. Antibiotic resistance costs the healthcare system billions of dollars annually and puts patients at an increased risk of morbidity and mortality. The clinical and economic outcomes of resistant infectious strains put the healthcare community at odds with empiric treatment and the utilization of "big gun" antimicrobials. Infections caused by resistant bacteria lead to up to two-fold higher rates of adverse outcomes compared with similar infections caused by susceptible strains.[1] Since 2002, the cost due to antibiotic resistance has more than doubled with a rise of 165% and not only has the cost increased, but the prevalence of antimicrobial resistant infections has doubled as well. Currently the CDC is reporting a total of 18 drug-resistant threats, three of which are considered urgent threats; Clostridium difficile (C. difficile), carbapenem-resistant Enterobacteriaceae (CRE) bacteria, and Neisseria gonorrhoeae. According to Thorpe et. al, the incidence of infections have not significantly increased. However, the proportion of infections that were antibiotic resistant rose dramatically, from 5.2% to 11.0%.[2]

With resistant antimicrobial infections on the rise, it is the responsibility of hospitals to ensure that their patients receive the appropriate medications for their individual infections. The overuse of antibiotics, as well as the empirical use of broad-spectrum antibiotics drives antimicrobial resistance. Epidemiological studies have demonstrated a direct relationship between antibiotic consumption and the emergence and dissemination of resistant bacteria strains.[3] The implementation of Antimicrobial Stewardship Programs (ASP) in hospitals throughout the country aim to decrease the prevalence of antimicrobial resistance. There are several professional, accrediting, and regulatory organizations that support ASPs including The Joint Commission and the CDC. The success of implementing an Antimicrobial Stewardship Program will demonstrate the importance of pharmacist involvement in antibiotic regimens, improved patient outcomes, and decrease the incidence of resistant infections.

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Code Sepsis: The Introduction of the Hour-1 Bundle

Sepsis is a life threatening complication of an infection constituted by organ dysfunction caused by a dysregulation in a host response. Since the Surviving Sepsis Campaign published the first evidence based guideline in 2004, there have been many updates to reflect the evolving literature surrounding sepsis.1 The most recent guideline was published in 2016, which provides updates from the previous 2012 publication. Notable changes from the 2012 to 2016 guidelines are the differences in the definitions of sepsis, outlined in Table 1. The 2012 Surviving Sepsis Guidelines differentiate sepsis, severe sepsis, and septic shock based on systemic inflammatory response syndrome (SIRS) criteria, which remained largely unchanged from the previous twenty years.2

In 2016, the Sepsis-3 Update removed the definition of severe sepsis and defined sepsis and septic shock based on a different assessment tool known as the sequential organ failure assessment (SOFA) score.3 The reason behind the change being that the SIRS criteria did not necessarily indicate a life-threatening response to infection, but encompassed a hosts response to inflammation. The SOFA score was deemed a more appropriate assessment tool for determining the level of sepsis-induced organ dysfunction. The 2016 Surviving Sepsis Guidelines adopted the new definitions and it is currently recommended to identify septic patients based on SOFA score.4 Because the SOFA score contains many variables that are not readily available at the time of patient presentation, a shortened form called the quick SOFA (qSOFA), offers predictive validity similar to that of the full SOFA score for initial triage.

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Code Sepsis: The Introduction of the Hour-1 Bundle

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Table 1. Comparison of Surviving Sepsis Guidelines Definition of Sepsis

	2012 Surviving Sepsis Guideline[2]	2016 Surviving Sepsis Guidelines[4]
Assessment tool	SIRS (2 or more of the following): - T > 38.3˚C or < 36˚C - HR > 90 beats/min - RR >20 breaths/min - WBC < 4,000/mm^3 or > 12,000 mm^3	qSOFA (2 or more of the following) - Hypotension (SBP <100 mmHg) - Altered mental status (GCS <15) - Tachypnea (> 22 breaths/min)
Sepsis	SIRS + source of infection	SOFA + source of infection
Severe Sepsis	Sepsis + organ dysfunction	Definition removed
Septic Shock	Sepsis induced hypotension persisting despite adequate fluid resuscitation	Sepsis and vasopressor therapy needed to elevate MAP ≥ 65 mmHg and lactate >2 mmol/L in the absence of hypovolemia

Sepsis bundles have been implemented and encouraged in many hospital settings as a form of quality improvement since the first Surviving Sepsis Guideline was published. Bundles promote appropriate, immediate management in the initial hours after the development of sepsis. Recent studies have confirmed the relationship between compliance with sepsis bundles and patient survival.5 The literature has lead both the New York State Department of Health and the Center for Medicaid Services to have mandated public reporting of sepsis bundle compliance.6

The criteria included in the sepsis bundles has changed over time based on literature published. In 2012, early goal directed therapy (EGDT) was the mainstay sepsis treatment and made up the components of the sepsis bundle. EGDT was based on the landmark trial in 2001 by Rivers and colleagues, which consisted of protocolized resuscitation efforts. This included early insertion of a mixed venous oxygen saturation (ScvO2) catheter, titration of interventions based central venous pressure (CVP), mean arterial pressure, urine output, and ScvO2, and also included recommendations for treatment with red blood cells or inotropes as indicated.7 This EGDT strategy showed improvement in mortality compared to standard therapy. The 2016 Surviving Sepsis Guidelines challenged the series of "goals" recommended in the previous guideline due to three large randomized controlled trials that failed to show mortality reduction with EGDT compared to standard care: ARISE trial, ProCESS trial, and ProMISe trial.8-10 In place of EGDT, the 2016 guidelines recommends a 3-hour bundle and a 6-hour bundle, which are comprised of the components shown in Table 2.

In April 2018, Critical Care Medicine published The Surviving Sepsis Campaign Bundle: 2018 Update, which recommends combining the 3-hour and 6-hour bundle into a single hour-1 bundle.6 The components of the hour-1 bundle can be found in Table 2.

The intent of the hour-1 bundle is to emphasize early recognition and initiation of resuscitation and antibiotics for patients with sepsis or septic shock. Although all resuscitative efforts may not be complete within the hour time frame, initiating treatment is recommended to begin immediately. Lactate measurement serves a surrogate marker of tissue hypoperfusion. If the initial lactate is > 2 mmol/L, a repeat level should be drawn in 2-4 hours to help guide resuscitative efforts. In addition to measuring a lactate, it is important to attempt to identify the source of infection, draw cultures, and administer appropriate antibiotics as soon as possible. If feasible, blood cultures should always be drawn prior to antibiotic administration because of the possibility of sterilization that could occur within minutes of antibiotic administration. However, antibiotic therapy should not be delayed in order to obtain blood cultures. Fluid resuscitation in addition to antibiotics is the cornerstone of initial sepsis management to stabilize sepsis induced shock. Patients should receive 30 mL/kg of crystalloid solution within three hours of recognition. Additional fluid administration should be guided by patient response to initial fluid resuscitation. If the blood pressure is not restored with fluid management, addition of vasopressors should be applied in order to try to restore tissue perfusion to vital organs.

The Sepsis Committee at University Hospital is working to implement this bundle and educate hospital staff on recognizing sepsis as a medical emergency. In the future, we hope to implement a Code Sepsis to aid in addressing all requirements included in the hour-1 bundle. This bundle should serve as the next iteration of the Surviving Sepsis Campaign to help improve outcomes and reduce the overall burden of sepsis.

Table 2. Surviving Sepsis Campaign Bundles of Care*

2016 Surviving Sepsis Guideline[4]	2018 Surviving Sepsis Update[6]
3 hour bundle: - Measure lactate level - Obtain blood cultures prior to antibiotic administration - Administer broad spectrum antibiotics - Rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L	Hour-1 bundle: - Measure lactate level (remeasure in 2-4 hours if lactate > 2 mmol/L) - Obtain blood cultures prior to administration of antibiotics - Administer broad spectrum antibiotics - Rapidly administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L - Apply vasopressors if patient hypotensive during/after fluid resuscitation to maintain MAP ≥ 65 mm Hg
6 hour bundle: - Repeat lactate (if initial lactate > 2 mmol/L) - Apply vasopressors (for hypotension that does not respond to fluid resuscitation to maintain MAP > 66 mmHg) - In the event of hypotension despite volume resuscitation o rinitial lactate >4 mmol/L: (1) measure CVP and (2) measure ScvO2	

* "Time zero" is defined as the earliest chart annotation consistent with sepsis or septic shock.

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Code Sepsis: The Introduction of the Hour-1 Bundle

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Mr. Andre Emont
Certified Consultant Pharmacist (CCP®)

Congratulations to Mr. Emont on passing the CCP® examination and becoming a Certified Consultant Pharmacist (CCP®). Most recently, Mr. Emont enhanced his professional career by becoming a Certified Joint Commission Professional (CJCP®)

The examination consisted of questions related to Federal and State regulations, and various clinical situations that may be encountered while working as a consultant pharmacist. The Joint Board for Certification of Consultant Pharmacists (CCP) was formed in 1982 to create an educational process that would certify consultant pharmacists as specialists in the long-term care field. Since 1982, consulting pharmacy has grown to include diverse areas such as correctional facilities, ambulatory surgical centers, end stage renal disease dialysis centers, residential and out-patient substance abuse facilities, adult and pediatric day health services, assisted living, residential health care facilities, hospice and hospitals. Certification is a highly regarded professional credential and is currently listed as an Advisory Standard in the New Jersey Department of Health and Senior Services' manual of Standards for Licensure of Long-Term Care Facilities.

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