Conclusions and Recommendations:

- There is moderate strength of evidence oral vancomycin is superior to oral metronidazole for clinical cure of first episode of mild to moderate *Clostridium difficile* infection (CDI).
- There is moderate strength of evidence of no difference between oral vancomycin and oral fidaxomicin in clinical cure rate of first episode of CDI. There is insufficient evidence to compare efficacy between metronidazole and fidaxomicin.
- There is high strength evidence that oral vancomycin is superior to oral metronidazole in severe or complicated CDI but there is insufficient evidence to support the use of fidaxomicin alone for complicated or fulminant CDI.
- There is moderate strength of evidence to repeat the initial antibiotic course for first recurrence of CDI, though moderate quality evidence suggests a course of fidaxomicin is superior to a course of oral vancomycin at preventing further recurrences of CDI. However, following a full-dose course of vancomycin with a slow taper or pulsed dosing over several weeks may also decrease recurrent cases of CDI.
- There is high quality evidence for 10 days of CDI treatment with insufficient evidence to support longer duration of therapy; the exception being pulsed or tapered vancomycin in cases of multiple recurrent CDI that may be given for several weeks after a full dose 10-day course is completed.
- There is insufficient evidence to support the combination of two orally administered antibiotics. Anecdotal evidence, however, suggests intravenous metronidazole or rectal enema administration of vancomycin may be helpful as adjunctive therapy in complicated or fulminant CDI, but never as monotherapy.
- No further review or research needed at this time. Review comparative drug costs in the executive session.

Previous Conclusions and Recommendations:

- There is moderate strength evidence that there is no difference in clinical cure rate between fidaxomicin, vancomycin, and metronidazole.
- There is moderate strength evidence that recurrence of CDI occurs less frequently with fidaxomicin versus vancomycin.
- There is insufficient evidence to compare efficacy or effectiveness of fidaxomicin to metronidazole.
• Make fidaxomicin a non-preferred antimicrobial for CDI and require a documented trial of appropriate therapy of vancomycin (125 mg oral four times daily) or metronidazole (500 mg orally three times daily) for first recurrence or contraindication to therapy and excluding use of fidaxomicin in patients with severe CDAD (life-threatening or fulminant infection or toxic megacolon).
• Recommend adding oral metronidazole and oral vancomycin as preferred agents on the PDL for the treatment of CDI.
• Consider requiring metronidazole as first line therapy for mild CDAD in non-hospitalized patients.

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to placebo or active controls were conducted. A summary of the clinical trials is available in Appendix 2. The Medline search strategy used for this literature scan is available in Appendix 3, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drugs, indications, and safety alerts. Finally, the AHRQ National Guideline Clearinghouse was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
Treatment of CDI
The AHRQ published on April 20, 2015, draft for public comment on an updated report of early detection, prevention and treatment of CDI. The AHRQ increased strength of evidence from moderate to high for oral vancomycin as a more effective drug than metronidazole for CDI, with moderate strength evidence of the effect regardless of disease severity. The report recognizes that the increased strength of evidence found for vancomycin should prompt changes in the next updated treatment guideline from the Infectious Diseases Society of America (IDSA), which currently supports vancomycin as the drug of choice for severe CDI and metronidazole as the drug of choice for mild to moderate CDI. In addition, there is continuing moderate strength evidence that fidaxomicin is similar to vancomycin for the initial cure of CDI, and increased strength of evidence that fidaxomicin is superior to vancomycin for the prevention of recurrent CDI. The desired outcome with CDI treatment is cure of the initial illness without subsequent recurrence, and it is well documented each episode of CDI recurrence increases the likelihood of further episodes. For these clinical reasons, evidence for fidaxomicin for initial treatment of CDI is growing, though per-course price of the drug makes treatment cost prohibitive in most cases. Lastly, there is low quality evidence that largely confirms current clinical practice that intravenous metronidazole performs significantly worse than oral metronidazole or vancomycin for treatment of CDI.

Studies of diagnostic testing and treatment of CDI published in English between January 1978 and October 31, 2014 were identified in a 2015 systematic review. Appropriate diagnostic testing and markers of disease severity were reviewed but will not be detailed here. The odds ratio of antibiotic use and CDI risk is reported to be 3.2 for third-generation cephalosporins and 2.86 for clindamycin. Other beta-lactam antibiotics (penicillins and cephalosporins) are also particularly associated with risk of CDI. Fluoroquinolones are associated with increased risk of the BI/NAP1/027 strain. Historically, antibiotic withdrawal was a stand-alone treatment option as about 15% of patients recover after the offending antibiotic is stopped. However, the effectiveness of antibiotic withdrawal for mild CDI is remains unclear, but it is clear that failure to stop the offending antibiotics is associated with CDI recurrence.

Metronidazole vs. Vancomycin
Author: A. Gibler, Pharm.D.  Date: May 2015
Metronidazole and vancomycin have been primary therapies for CDI since the 1980s. Early studies suggested that oral metronidazole and oral vancomycin had equivalent efficacy and relapse rates, but newer data suggest higher treatment failure rates when metronidazole is used in severe or complicated CDI. However, there are conflicting data whether oral metronidazole treatment failures have increased after the emergence of BI/NAP1/027. For mild CDI, cure rates for oral metronidazole and oral vancomycin were not statistically different (73-90% vs. 81-98%, respectively). However, among patients with severe CDI, differences in cure rates were more pronounced and fair better for vancomycin (79-97%) compared to metronidazole (66-76%). Overall, treatment failures with oral metronidazole have been higher than with oral vancomycin from 2001-2010 (22.4% vs. 14.2%; p=0.002) but recurrence rates remained similar (27.1% vs. 24.0%; p=0.26). Patients receiving metronidazole also have a longer time to symptomatic improvement than patients receiving vancomycin. Factors associated with metronidazole failure include age older than 60 years, presence of fever or leukocytosis, hypoalbuminemia, ICU admission and abnormal abdominal CT imaging findings. Oral vancomycin is typically well tolerated as both oral and rectal administration is rarely systemically absorbed. Metronidazole is associated with gastrointestinal adverse effects, a disulfiram-like reaction when ingested with alcohol, and peripheral neuropathy with prolonged therapy.2

Mild to Moderate CDI
For mild to moderate CDI, oral metronidazole 500 mg 3-times daily for 10 days remains the preferred therapy, in part because of its low cost. For patients unable to take oral medications, metronidazole may be administered intravenously as adjunctive therapy, but not as monotherapy since CDI recurrence is common when the intravenous dose is given as monotherapy. Newer evidence is shifting away from metronidazole to oral vancomycin and it is reasonable to consider oral vancomycin 125 mg orally 4-times daily for 10 days for mild to moderate CDI. Randomized studies demonstrate similar cure rates between fidaxomicin 200 mg orally twice daily for 10 days (87.7-88.2%) and oral vancomycin (85.8-86.8%) but fidaxomicin may be associated with fewer recurrences (15.4% vs. 25.3%; p=0.005). When antibiotics cannot be discontinued because of ongoing infection, clinical cure rates for concomitant CDI are higher with fidaxomicin than with vancomycin. However, fidaxomicin is not considered first-line therapy for mild or uncomplicated CDI because of its higher cost.2

Severe or Complicated CDI
Vancomycin is the preferred therapy for severe or complicated CDI. The recommended dose is 125 mg orally 4-times daily for 10 days but expert opinion often favors higher doses in severe or complicated cases. Vancomycin may be administered rectally in the setting of ileus, as an adjunctive therapy, though evidence is limited to case reports. Rectally administered vancomycin is not typically used alone because the drug may not reach the entire affected area. In severe or complicated CDI, or in cases when rectal vancomycin must be given, it may be appropriate to give intravenous metronidazole as adjunctive therapy since this route can achieve detectable levels of drug throughout the colon. However, evidence for this practice is remains very limited. No data support the use of fidaxomicin in complicated or fulminant CDI.2

Recurrent CDI
Recurrent CDI is more common in older patients and in those with concomitant antibiotic use, presence of comorbidities, concomitant use of proton pump inhibitors, and if the initial CDI is severe. Repeating the initial therapy of oral metronidazole or vancomycin is reasonable for the first recurrence of mild to moderate CDI. However, growing evidence suggests vancomycin 125 mg orally 4-times daily for several weeks using pulsed or tapering doses, or fidaxomicin 200 mg orally twice daily for 10 days, are preferred for any subsequent recurrences. In patients with a recurrence rate of 45%, one study found a slow tapering or pulsed courses of vancomycin lower the recurrence rate by 31% (p=0.01) and 14.3% (p=0.02), respectively. Fidaxomicin may be a reasonable option for recurrent CDI or when administered immediately after a course of vancomycin in patients with multiple CDI recurrences. Use of rifaximin as an adjunctive therapy for recurrent CDI after standard therapy is limited to anecdotal evidence only and monotherapy should be avoided given its propensity for resistance. Evidence is also limited for use of nitazoxanide as an adjunctive therapy for recurrent CDI. Fecal microbiota transplantation restores gut microbiota diversity via the instillation of donor stool into the gastrointestinal tract and has good clinical response without reports of adverse events for refractory or recurrent CDI.2

Author: A. Gibler, Pharm.D.  Date: May 2015
Treatment of Recurrent CDI

A 2014 systematic review of studies of the treatment of recurrent CDI (RCDI) without language or date publication restrictions was performed. Ultimately, 105 studies were analyzed for the review.3

Vancomycin
Evidence supporting the use of vancomycin is moderate. There is considerable variability in dosing and duration for RCDI, but it is currently the standard of care in treating RCDI. Examining high-quality trials using vancomycin, three studied a metronidazole comparator and two fidaxomicin. The metronidazole comparator studies included 179 patients given metronidazole compared to 310 receiving vancomycin. Using sustained response (e.g., no recurrence), vancomycin was as efficacious as metronidazole (relative risk (RR) 1.08; 95% confidence interval (CI), 0.85 to 1.35; I²=0%, p=0.53). Studies comparing fidaxomicin to vancomycin, discussed further below, included a total of 79 patients in each arm, and appeared slightly more efficacious than vancomycin (RR 1.86; 95% CI, 1.04–3.31; I²=0%, p=0.04). Pulsing or tapering doses of vancomycin has demonstrated efficacy in small studies and subgroups, and has been adopted as part of the current guidelines but has not yet been evaluated in large RCTs. Tapering vancomycin involves a prolonged regimen where the dose is slowly reduced over several weeks. Pulsing involves a dose of vancomycin every 3 days for several weeks following completion of a full 10-day course.3

Metronidazole
All of the identified studies of metronidazole were of high quality, and found a fairly consistent efficacy, similar to vancomycin. Current Infectious Disease Society of America (IDSA) guidelines endorse one repeat course of metronidazole as the standard of care for the first recurrence. A temporal correlation of treatment failure has been noted since the emergence of the BI/NAP1/027 strain. It is not recommended beyond a first recurrence because of the risk of accumulation of neurotoxic metabolites. A total of 283 patients were treated with metronidazole-containing regimens, with a second recurrence in 86 patients (29%). Rates of initial response were between 77 and 100%. One study concluded that metronidazole was non-inferior to vancomycin in a first relapse, while two favored vancomycin regimens.3

Fidaxomicin
Evidence for fidaxomicin is moderate in light of two positive, high-quality studies. Fidaxomicin is the only drug other than vancomycin approved by the U.S. Food and Drug Administration (FDA) for CDI. Both of the existing studies on fidaxomicin compared the drug to vancomycin and found non-inferiority, with pooled results showing the slight superiority of vancomycin. Both studies were presented to the OHA Pharmacy & Therapeutics committee in 2012. It is worth noting that this medication is considerably more expensive than oral vancomycin, and may have decreased activity against the BI/NAP1/027 strain.6

The current evidence for nitazoxanide and rifaximin for RCDI remain weak.3

Treatment Failure and Recurrence of CDI Following Treatment with Vancomycin or Metronidazole
The objective of this 2012 review was to evaluate the frequency of treatment failure and recurrence of CDI following treatment with vancomycin or metronidazole in studies performed in the last 10 years. In total, 39 articles (7005 patients) were selected for inclusion in the systematic review. However, the follow-up period was short for most studies: up to 1 month in 6 studies, 1 to 2 months in 12 studies, 2 to 3 months in 12 studies, 6 months in 2 studies and an unknown length of follow-up for the remainder of studies. In addition, the definitions of treatment failure and recurrence were not identical in 53.8% and 15.4% of the studies, respectively. All studies required the presence of symptoms (diarrhea, abdominal pain, fever) and a positive stool test for C. difficile toxin A or B for the diagnosis of CDI. Sixteen studies reported treatment failure with metronidazole (22.4%) and 8 studies reported treatment failure with vancomycin.

Author: A. Gibler, Pharm.D. Date: May 2015
Recurrence of CDI after initial treatment with metronidazole was demonstrated in 18 studies (27.1%) and in 8 studies with vancomycin (24.0%), a significant difference (p=0.26). Fourteen studies did not provide outcomes for metronidazole and vancomycin separately, but reported the outcomes of the entire population. In all studies combined, mean treatment failure and incidence of recurrence were similar for metronidazole (22.3%) and vancomycin (22.1%). However, there were studies that reported very high (66.7%) or very low (2.9%) failure or recurrence depending on the study design. Mean treatment failures and recurrences in RCTs were 16.0% and 19.4%, respectively. In prospective observational cohort studies, the mean treatment failure was 26.8% (p<0.001, higher compared with RCTs) and the mean recurrence was 19.0% (p=0.86, similar to that of RCTs). In retrospective studies, the mean treatment failure was 22.7% (p=0.002, higher compared with RCTs) and the mean recurrence was 23.3% (p=0.03, higher compared with RCTs). There was no significant difference in the mean treatment failure between observational prospective and retrospective studies (p=0.06), but significantly more recurrences were reported in retrospective than observational prospective studies (p=0.005).

New Guidelines:

The European Society of Clinical Microbiology and Infectious Disease (ESCMID)

Recommendations in the recently updated ESCMID guideline were based on a systematic assessment of the quality of evidence. The Grades of Recommendation Assessment, Development and Evaluation (GRADE) system was used to grade the strength of our recommendations and the quality of the evidence. Strength of recommendations (SoR) followed the standard grades (A=strong; B=moderate; C=marginal; D=against). The guideline followed the Appraisal of Guidelines Research and Evaluation Collaboration (AGREE) self-assessment tool. The objectives of the guideline were to: 1) provide an overview of currently available CDI treatment options and 2) develop an evidence-based update of treatment recommendations. The following definitions were used in reviewing the evidence and developing their recommendations:

Treatment response is present when either stool frequency decreases or stool consistency improves and parameters of disease severity (clinical, laboratory, radiological) improve and no signs of severe disease develop. All other cases are considered treatment failure.

Recurrent CDI is present when CDI re-occurs within 8 weeks after the onset of a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment.

In cases of non-severe CDI (no signs of severe colitis) in non-epidemic situations and with the CDI clearly induced by the use of antibiotics, it may be acceptable to stop the inducing antibiotic and observe the clinical response for 48 hours, but patients must be followed very closely for any signs of clinical deterioration and placed on therapy immediately if this occurs. Metronidazole 500 mg orally 3-times daily for 10 days is recommended as the first antibiotic-of-choice for treatment of initial CDI in mild/moderate disease (Grade 1; SoR A). Alternative therapy options include vancomycin 125 mg orally 4-times daily or fidaxomicin 200 mg orally 2-times daily for 10 days (Grade 1, SoR B). There may be marginal benefit in using a higher dose of vancomycin 500 mg orally 4-times daily but data are limited (Grade 1, SoR C). There is no evidence to support the practice of extending anti-CDI therapy for the duration of therapy if the patient is also on a non-CDI antibiotic.

Vancomycin 125 mg orally 4-times daily for 10 days (Grade 1, SoR A) is considered superior to metronidazole 500 mg orally 3-times daily (Grade 1, SoR D) in severe CDI based on clinical evidence, largely due to its pharmacokinetic properties. The use of high doses of vancomycin 500 mg orally 4-times daily (Grade 3, SoR B) was included in the Infectious Diseases Society of America/Society for Healthcare Epidemiology of America treatment guidelines for management.
of severe complicated CDI as defined by the treating physician. However, there is insufficient evidence to support the use of doses higher than 125 mg 4-times daily in the absence of ileus. Fidaxomicin is non-inferior to vancomycin for initial cure of CDI, but there are no data available on the efficacy of this drug in severe, life-threatening disease (Grade 1, SoR B).5

Vancomycin 125 mg orally 4-times daily or fidaxomicin 200 mg orally 2-times daily for 10 days (Grade 1, SoR B) is recommended for both treatment of mild or moderate CDI with risk for recurrent CDI, or for treatment of first recurrence of CDI. The incidence of a second recurrent of CDI after treatment of a first recurrence with oral metronidazole or vancomycin is similar. Fewer secondary recurrences are reported with oral fidaxomicin compared to vancomycin after treatment of a first recurrence. However, the evidence on fidaxomicin for this specific subgroup of CDI patients is limited to two phase 3 studies and based on a retrospective subset analysis of data and a limited number of patients. There are no prospective RCTs performed with metronidazole, vancomycin or fidaxomicin for this specific subgroup. In addition, fidaxomicin was not associated with fewer recurrences of CDI due to the BI/NAP1/027 strain. Therefore, based on the evidence currently available, the SoR for treating a first recurrence of CDI with oral vancomycin or oral fidaxomicin is considered equal, unless the disease has progressed from non-severe to severe. There may be some marginal benefit to adding metronidazole or higher doses of vancomycin (Grade 3, SoR C for both).5

In non-severe second (or later) recurrences of CDI, oral vancomycin or fidaxomicin is recommended. Vancomycin and fidaxomicin are equally effective in resolving CDI symptoms (Grade 2, SoR B for both), though fidaxomicin may lower likelihood of CDI recurrence after a first recurrence. However, there are no prospective RCTs investigating the efficacy of fidaxomicin in patients with multiple recurrence of CDI. In these cases, vancomycin is preferably administered using a pulsed regimen (125 mg 4-times daily for 10 days, followed by 125-500 mg per day every 2-3 days for at least 3 weeks) or tapered regimen (125 mg 4-times daily for 10 days, then gradually decreasing the dose to 125 per day) (Grade 2, SoR B for both).5

When oral administration is not possible, intravenous metronidazole 500 mg 3-times daily for 10 days (Grade 2, SoR A) may be added to vancomycin 500 mg/100 mL 4-times daily via oral/nasogastric tube for 10 days (Grade 3, SoR B). Alternatively, vancomycin 500 mg/100 mL can be given 4-times daily as a retention enema for 10 days (Grade 3, SoR B).5

The American College of Gastroenterology
The American College of Gastroenterology published evidence-based guidelines for the diagnosis, treatment and prevention of CDI. The Grades of Recommendation Assessment, Development and Evaluation (GRADE) system was used to grade the strength of our recommendations and the quality of the evidence.6 The guideline is designed to complement the ESCMID guidelines reported previously and the IDSA guidelines which are currently being updated.

In the management of mild, moderate and severe uncomplicated CDI, any inciting antibiotic agents should be discontinued (strong recommendation, high-quality evidence). However, there is no evidence to support the practice of extending anti-CDI treatment beyond the standard duration of therapy if non-CDI antibiotics cannot be discontinued. Patients with mild or moderate CDI should begin on metronidazole 500 mg orally 3-times daily for 10 days (strong recommendation, high-quality evidence). Failure to respond to metronidazole after 5-7 days should prompt a change to vancomycin 125 mg 4-times daily for 10 days (strong recommendation, moderate-quality evidence). Patients with severe CDI should be initially treated with vancomycin 125 mg 4-times daily for 10 days (conditional recommendation, moderate-quality evidence). Vancomycin may be delivered via enema in patients unable to take oral routes of administration (conditional recommendation, low-quality evidence).6

Vancomycin 125 mg orally 4-times daily plus intravenous metronidazole 500 mg 3-times daily is the treatment of choice in patients with severe and complicated CDI who have no significant abdominal distention (strong recommendation, low-quality evidence). In patients with complicated CDI with ileus or toxic colon

Author: A. Gibler, Pharm.D.  Date: May 2015
and/or abdominal distension, vancomycin 500 mg orally 4-times daily or 500 mg/500 mL per rectum 4-times daily plus intravenous metronidazole 500 mg 3-times daily are recommended (strong recommendation, low-quality evidence).  

The first recurrence of CDI can be treated with the same regimen that was used for the initial episode. However, if the recurrence is severe, vancomycin should be used. The second recurrence should be treated with a pulsed vancomycin regimen (conditional recommendation, low-quality evidence). However, fecal microbiota transplant should be considered if there is a third recurrence after using a pulsed vancomycin regimen (conditional recommendation, moderate-quality evidence). 

**New FDA Drug Approvals:**
None identified.

**New Formulations/Indications:**
None identified.

**New FDA Safety Alerts:**
None identified.

**References:**


Appendix 1: Current Status on Preferred Drug List

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Appendix 2: New Clinical Trials

Fifty-one potentially relevant articles were evaluated from the literature search. After further review, all articles were either post-hoc analyses of older trials, meta-analyses of select studies, or studies without evaluation of clinical outcomes, and were therefore excluded.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to March Week 5 2015

1 exp Clostridium difficile/ 5041
2 vancomycin.mp. or exp Vancomycin/ 15403
3 metronidazole.mp. or exp Metronidazole/ 8154
4 fidaxomicin.mp. 133
5 2 or 3 or 4 22851
6 1 and 5 937
7 limit 6 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) 156
8 limit 7 to (english language and yr="2012 -Current") 51
Appendix 4: Current Prior Authorization Criteria

**Fidaxomicin (Dificid®)**

**Goal(s):**
- To optimize appropriate treatment of *Clostridium difficile*-associated diarrhea.

**Length of Authorization:**
10 days

**Requires PA:**
- Fidaxomicin (Dificid®)

**Covered Alternatives:**
Preferred alternatives listed at [www.orpdl.org](http://www.orpdl.org)

### Approval Criteria

<table>
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<tr>
<th>1. What diagnosis is being treated?</th>
<th>Record ICD9 code.</th>
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</thead>
<tbody>
<tr>
<td>2. Does the patient have a diagnosis of <em>Clostridium difficile</em>-associated Diarrhea (CDAD)? (ICD-9 008.45)?</td>
<td>Yes: Go to #3. No: Pass to RPH; Deny (medical appropriateness)</td>
</tr>
<tr>
<td>3. Will the prescriber consider a change to a preferred antibiotic?</td>
<td>Yes: Inform Provider of covered alternatives in class. No: Go to #4</td>
</tr>
<tr>
<td>Message: Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee.</td>
<td></td>
</tr>
<tr>
<td>4. Does the patient have a documented trial of appropriate therapy with vancomycin or metronidazole for a first recurrence or contraindication to therapy?</td>
<td>Yes: Go to #5. No: Pass to RPH; Deny (medical appropriateness)</td>
</tr>
<tr>
<td>5. Does the patient have severe, complicated CDAD (life-threatening or fulminant infection or toxic megacolon)?</td>
<td>Yes: Pass to RPH; Deny (medical appropriateness) No: Approve for up to 10 days</td>
</tr>
</tbody>
</table>

**P&T / DUR Action:** 5/15; 4/12

**Revision(s):**
Initiated: 7/12

Author: A. Gibler, Pharm.D.  Date: May 2015