PAAS National, Inc.
Expert Third-Party Contract and Audit Advice
160 Business Park Circle • Stoughton, WI 53589 • 608-873-1342 • Fax: 608-873-4009

Hydrocodone Combination Products to Schedule C-II

What you need to know!

A whitepaper

By Edward Heckman, R.Ph.

August 26, 2014

1. Overview

The DEA has finalized their plan to move all Hydrocodone Combination Products (HCPs) into Schedule C-II on October 6, 2014. Although the DEA spelled out most of the details in their Final Rule published in the August 22, 2014 edition of the Federal Register, there are still a few scenarios that cause unanswered questions. Below are the key highlights of what you need to know as a pharmacist to implement and comply with this change. Each of the bullet points refers to a section of this whitepaper for additional details.

- As of October 6, 2014 any person who handles HCPs will be required to do so in compliance will all associated rules and regulations for Schedule C-II drugs—*with a few minor exceptions* (§ 3.2)
- Not later than October 6th, wholesalers will be required to distribute HCPs ONLY in Schedule C-II labeled packages (§4.1.1).
- After October 6, 2014, pharmacies may continue to dispense HCPs from inventory on hand in the old Schedule C-III packaging (§4.1.2).
- Any remaining refills on prescriptions for HCPs filled before October 6, 2014 may be dispensed prior to April 8, 2015 (§4.1.3).
- Beginning October 6, 2014 a DEA Form 222 or CSOS 222 will be required to order HCPs (§4.1.6)
- Any HCPs purchased in Schedule C-III packaging and returned on or after October 6, 2014 will require a DEA Form 222 (§4.1.8).
- Pharmacies will need to secure HCPs in a similar fashion as all other Schedule C-II drugs (§4.1.5).
- It is likely there may be inventory shortages (§4.1.7) or problems exceeding thresholds (§4.2) from shifts in prescribing patterns and drug utilization as well as the packaging change to C-II.

2. Background

Hydrocodone by itself has been a Schedule C-II drug since the Controlled Substances Act (CSA) was passed in 1970. The first and only single-entity hydrocodone product is Zohydro™ ER launched March 3, 2014. Hydrocodone combination products in specified amounts and combinations have been scheduled as C-III drugs.

Since 2007 HCPs have been the most frequently prescribed opioid in the United States. The IMS Institute reports that in 2013 there were 129.2 million HCP prescription filled in the United States.[1] In 2012 one HCP prescription was written for every 2.3 men, women and children in the United States.[2] The second most prescribed pain-treating opioid is the oxycodone/ acetaminophen combination at 35.9 million prescriptions in 2013, or only 28% the HCP total.

There have been slight declines in the number of HCP prescriptions in 2011 through 2013. The decline was the most pronounced in 2013, a 5% decrease from 2012. IMS attributes these decreases to the withdrawal of high dose acetaminophen products.[3]

The abuse, diversion and illicit use of prescription opioids are well documented. Yet the challenge is that opioids are the most effective drugs to treat severe pain available today.

3. Final Rule, Federal Register August 22, 2014

3.1 Final Rule published August 22, 2014

3.1.1 Federal Register

Below is information to locate the Final Rule published in the Federal Register regarding the re-scheduling of Hydrocodone Combination Products to Schedule C-II.

Department of Justice (DOJ)
Drug Enforcement Administration (DEA)
21 CFR Part 1308
[Docket No. DEA-389]
"Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products from Schedule III to Schedule II"
Action: Final Rule

[1] IMS Institute, "Medicine use and shifting cost of healthcare," April 2014, page 46, accessed at http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/IMS%20Health%20Institute/Reports/Secure/IIHI_US_Use_of_Meds_for_2013.pdf on August 22, 2014.
[2] Kroll, David, Forbes, "New Rules of Hydrocodone: What You Should Know," accessed August 22, 2014 at http://www.forbes.com/sites/davidkroll/2014/08/22/what-you-need-to-know-about-new-restrictions-on-hydrocodone-combinations/
[3] IMS Institute, "Medicine use and shifting cost of healthcare," April 2014, pages 3 and 8, accessed at http://www.imshealth.com/deployedfiles/imshealth/Global/Content/Corporate/IMS%20Health%20Institute/Reports/Secure/IIHI_US_Use_of_Meds_for_2013.pdf on August 22, 2014.

Pages 49661 through 49682

The web link to access the Final Rule is:
https://www.federalregister.gov/articles/2014/08/22/2014-19922/schedules-of-controlled-substances-rescheduling-of-hydrocodone-combination-products-from-schedule

3.1.2 Poll of Comments to Proposed Rule

Within the Final Rule the DEA responds to many comments submitted in response to the posting of the Proposed Rule on February 27, 2014. They also provide a statistical analysis of the types of comments they received. The DEA goes into great detail in their analysis. Below are two tables of information that provides a high-level view of the commenters, their opinions and the factions they represent.

In Table One, the positions of the commenters (either for or against the re-scheduling of HCPS) are tabulated. A narrow majority of the responders were in favor of the move to Schedule C-II. The DEA did not receive a clear-cut affirmation from the comments.

Table One—Poll of Positions

Number	Percent	Pro or Con Position of Commenter
573	100%	Total Comments
298	52%	Supported HCPs move to Schedule C-II
235	41%	Opposed to HCP move to Schedule C-II
40	7%	No position taken

Table Two lists the five largest sources of commenters.

Table Two—Source of Comments

Number	Percent	Five Largest Commenter Categories
250	44%	General Public
122	21%	Pharmacists and Pharmacy Students
73	13%	Physicians
35	6%	Ultimate Users
31	5%	Mid-Level Practitioners

3.2 Effective Date

The effective date of the Final Rule for HCP products to become Schedule C-IIs is October 6, 2014. This is 45 days after the publication date of the Final Rule on August 22, 2014. As of October 6, 2014 any person who handles HCPs will be required to do so

in compliance will all associated rules and regulations for Schedule C-II drugs—*with a few minor exceptions outlined in this whitepaper*.

3.3 Legal Authority

3.3.1 The DEA's Responsibility for Scheduling Drugs

The key laws associated with controlled substance scheduling are found in the Controlled Substances Act of 1970 (CSA). Pursuant to the authorities set forth in the CSA, the U.S. Attorney General delegates the responsibility for scheduling controlled substances to the Drug Enforcement Administration (DEA).

3.3.2 Purpose and Criteria for Scheduling Drugs

The purpose of the CSA and its related regulations "are to prevent, detect, and eliminate the diversion of controlled substances and listed chemicals into the illicit market while providing for the legitimate medical, scientific, research, and industrial needs of the United States."[4]

Every controlled substance is classified in one of five schedules based upon its potential for abuse, currently accepted medical use in treatment in the United States, and the degree of dependence the drug or other substance may cause. 21 U.S.C §812."[5]

3.3.3 Hydrocodone Combination Products (HCPs)

"Hydrocodone combination products (HCPs) are pharmaceuticals containing specified doses of hydrocodone in combination with other drugs in specified amounts. These products are approved for the treatment of pain and for cough suppression."[6] Until the introduction of Zohydro™ ER on March 3, 2014 as Schedule C-II, all other approved hydrocodone products in the United States were classed in Schedule C-III.

3.4 History

Below in Table Three is a chronological listing of key events leading up to the re-scheduling of HCPs to Schedule C-II. As you can see the hydrocodone issue commenced 15 years ago by a letter from a physician.

Table Three—Hydrocodone History

Date	Event
1999	Interested party petition submitted by a physician requesting HCPs to be rescheduled to C-II.

[4] Federal Register, Vol. 79, No. 163, August 22, 2014/Rules and Regulations, page 49662
[5] Ibid
[6] Ibid

Date	Event
2004	DEA submitted a request to the U.S. Department of Health and Human Services (HHS) to provide a scientific and medical evaluation of HCPs and a scheduling recommendation.
2008	HHS provided its recommendation to the DEA—HCPs should remain as Schedule C-III.
2009	DEA submitted a second request to HHS to re-evaluate their data and provide another scientific and medical evaluation and a scheduling recommendation.
July 9, 2012	The Food and Drug Administration Safety and Innovation Act (FDASIA) directed the FDA to hold a public meeting soliciting advice and recommendations regarding the scheduling of hydrocodone products.
January 24-25, 2013	FDA held a public Drug Safety and Risk Management Advisory Committee (DSaRM) meeting to discuss hydrocodone products. The DSaRM voted 19 to 10 in favor of recommending that HCPs be moved to Schedule C-II.
December 16, 2013	HHS submitted to the Administrator of the DEA its evaluation, "Basis for the Recommendation to Place Hydrocodone Combination Products in Schedule II of the Controlled Substances Act."
February 27, 2014	DEA published a Proposed Rule in the Federal Register, "Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products from Schedule III to Schedule II."
August 22, 2014	DEA published a FINAL Rule in the Federal Register, "Schedules of Controlled Substances: Rescheduling of Hydrocodone Combination Products from Schedule III to Schedule II."
October 6, 2014	Effective date to switch HCPs from Schedule C-III to Schedule C-II.

4. Ramifications of the Change—Concerns

4.1 What happens on October 6, 2014?

4.1.1 C-III vs C-II Package Labeling. By October 6th, wholesalers will be required to distribute only HCPs labeled as Schedule C-II drugs. Wholesalers must flush out their entire HCP inventory of Schedule C-III labeling and build adequate inventory levels of stock with Schedule C-II package labeling. The DEA believes that wholesalers will swop their C-III excess inventories with manufacturers for the new C-II packaging.

4.1.2 Pharmacies may continue to dispense from Schedule C-III packages. After October 6, 2014, pharmacies may continue to dispense HCPs from inventory on hand in the Schedule C-III packaging, but keep in mind prescriptions filled after this date must comply with the rules and regulations associated with Schedule C-II drugs.

4.1.3 What about HCP Prescriptions with refills remaining? If a prescription for a HCP is issued before October 6, 2014 and authorizes refills, the refills may be dispensed as long as they occur prior to April 8, 2015. All prescriptions written on or after October 6, 2014 are Schedule C-II and must comply in all respects including no refills.

This area of the Final Rule raises unanswered questions. The Rule states "Any prescriptions for HCPs that are issued before October 6, 2014, and authorized for refilling, may be dispensed."[7] The key here is whether the DEA meant dispensed or simply written and dated prior to October 6, 2014?

- Does this mean an original date of fill for a HCP prescription, pre-October 6th dated, that has refills can occur after October 6th and the refills are valid?
- Does this mean that a patient could hang onto a HCP prescription with refills dated prior to October 6, 2014 and wait to get it filled it later and still be eligible to obtain the refills?
- Should a HCP prescription written with refills prior to October 6th, but is filled after October 6th be filled as Schedule C-III or Schedule C-II?
- Will physicians backdate prescriptions they write to circumvent the "no-refill" rule for C-IIs?
- Will transfers of prescription copies from one pharmacy to another of HCPs be valid after October 6, 2014, with refills remaining?

These are unanswered questions that emanate from the Final Rule. Until the DEA provides further guidance, the most conservative and safest approach is to only honor refills on HCP prescriptions with original fill dates in your pharmacy prior to October 6, 2014.

4.1.4 NDC Questions. A major question and area of concern will be whether manufacturers replace the C-III HCP package NDC numbers with new ones as C-IIs. If new NDCs are issued there could be some confusion in billing the old NDC versus the new one which will create audit situations and chargebacks. The C-II NDCs could show up as refills (because wholesalers can only distribute HCPs with C-II labeling)—and could be disallowed because the NDC submitted is a Schedule C-II drug, which cannot be refilled.

4.1.5 Should Pharmacies change security measures with HCPs? Yes, the security of HCPs in the pharmacy will need to be similar to any other Schedule C-II drug stocked and must meet any state and federal requirements. While the DEA or CSA does not require retail pharmacies to place Schedule C-II drugs in vaults or safes, many pharmacies do. When the DEA enacted the rule that allows Schedule C-II inventory to be dispensed throughout the pharmacy—the main security risk and concern was after hours break-

[7] Ibid page 49681

ins. The rationale was that Schedule C-IIs dispersed would be tougher for a burglar to find. But the rampant increase over the last few years of armed robberies during store hours has caused many pharmacies to revert back to safes or vaults.

4.1.6 Ordering. A DEA Form 222 or a CSOS 222 is required with pharmacy orders invoiced or delivered on or after October 6, 2014. It is unclear what will happen if a wholesaler runs out of the old C-III packaging prior to October 6, 2014 and only have the new C-II packaging in stock. My assumption is that the wholesaler would require a DEA Form 222 from a pharmacy to order the C-II labeled product. So the C-II process may actually commence prior to October 6, 2014.

4.1.7 Inventory Shortages. There could possibly be inventory shortages of either the C-III labeling prior to October 6th or the C-II labeling after October 6th. While the DEA expects a completely smooth transition and no interruptions in the supply chain, minor hiccups between manufacturers and wholesalers may disrupt the supply chain.

4.1.8 Returns of C-III labeled HCPs after October 6, 2014. Any HCPs purchased in Schedule C-III packaging and returned on or after October 6, 2014 will require a DEA Form 222.

4.1.9 Wholesaler Security. This change also means that wholesalers are required to stock the new Schedule C-II inventories in their vaults rather than in less restrictive controlled substance cages in their distribution centers. For the time being we will assume that wholesalers have adequate space in their vaults to house HCPs.

4.1.10 Manufacturer Quotas. Manufacturers are required to obtain quotas for the amounts of a Schedule C-II drug they can manufacturer. As of October 6, 2014 manufacturers will be required to obtain quotas to continue manufacturing HCPs, with the following exception:

A manufacturer who is authorized to package both Schedule C-III and Schedule C-II drugs may re-label packages labeled C-III without obtaining procurement quotas if:

1. The re-labeling occurs prior to December 8, 2014.
2. If the manufacturer is re-labeling HCPs returned to the manufacturer and the manufacturer returns the same quantity and strength of HCPs with the new C-II labeling.
3. An invoice or DEA Form 222 (as applicable) documents that the return and redistribution occurred as a result of the Final Rule.

4.2 Changes in Prescribing Patterns and Thresholds

Some of the comments submitted voiced concerns that with HCPs in Schedule C-II, prescribers might write for other Schedule C-II opioids that are “stronger” such as Percocet, Endocet or

Oxycodone. I believe the commenters have a legitimate concern and there will almost certainly be shifts in utilization patterns. Now that HCPs will be Schedule C-II, if a doctor has to go to the extra effort to write a C-II prescription they might as well make sure the drug prescribed will be strong enough to effectively mitigate a patient's pain.

There are some doctors who refuse to prescribe any Schedule C-II drugs—this is a policy in many Emergency Rooms. Doctors and hospitals do not want to shoulder the added liability associated with Schedule C-II drugs. Will the rescheduling of HCPs change practitioner policies or will HCPs simply become less available?

If such shifts come to fruition, wholesaler threshold limits are going to be out of alignment for a period of time. This could present problems for pharmacies to be able to acquire adequate quantities of some drugs to take care of legitimate patients.

4.3 Impact on Patient Access

Patient access to HCPs will decrease. There is no doubt that moving HCPs to Schedule C-II will decrease utilization and impact patient access, whether for legitimate or illegitimate patients. In the case of the later, this is obviously a good thing, reducing the amount of opioids that fall prey to diversion and abuse is a positive. The challenge is that this move will also prove to be more restrictive for patients with legitimate medical conditions.

When extra steps or hurdles are added to any process, fewer people are willing to "go to the extra trouble" and forgo the more burdensome process. This will surely be the case with HCPs. It may mean that patients who run out of medication on weekends or that live in rural areas will suffer until they can connect with their physicians.

The DEA reports in the Final Rule that they received many comments voicing concerns that the increased administrative burdens placed upon pharmacists with Schedule C-II HCP prescriptions will be a distraction to patient care, counseling and safety. The DEA's response was "The processes and procedures associated with dispensing a controlled substance are not relevant factors to the determination of whether a substance should be controlled or under what schedule a substance should be placed if it is controlled."[8]

5. Conclusion

While prescription opioids are the most highly abused class of drugs, they are also the most effective drugs available to control severe pain. In a perfect world any patient with a legitimate medical purpose would be able to easily obtain their pain medications while abuse, diversion and illicit trafficking would be curtailed. The challenge is that the two objectives are

[8] Ibid, page 49674

misaligned. With the move of HCPs to Schedule C-II the balance shifts away from ease of access in favor of mitigation of abuse.

The change of HCPs from Schedule C-III to Schedule C-II will be impactful—pharmacists must make proactive plans to accommodate this change now. There are several unanswered questions that could cause problems. My advice is to take the most conservative approach possible and stay out of trouble.