On Wednesday, November 27th, President Obama signed into law H.R. 3204. We have compiled the following Frequently Asked Questions document as a resource for members and to answer questions that have arisen since the passage and signing of the bill. A more detailed legal analysis will also be prepared.

Q. When will H.R. 3204 go into effect?

A. Technically, H.R. 3204 went into effect as soon as the President signed the bill. However, for the vast majority of the law, the FDA will be required to engage in rulemaking processes on how they will administer and regulate the law as it is written. Much work will need to be done by the FDA to write these rules, both for “traditional” (“503A pharmacies”) and for outsourcing facilities. While the FDA is expected to move quickly to fully implement 503A and 503B, a firm timeline has not been released by the agency. Congressional oversight on how the law is implemented by the FDA is anticipated.

Q. What is an Outsourcing Facility?

A. H.R. 3204 lays the foundation for a new type of pharmacy/manufacturer – the Outsourcing Facility (OF). In fact, this new type of FDA-regulated business has feet planted in both the pharmacy and the manufacturing worlds. An excellent overview of OFs can be found here (provided by Hyman, Phelps & McNamara, P.C.). Some of the bigger items to keep in mind:

- An OF is defined as a facility in one geographic location that is engaged in the compounding of sterile products, has voluntarily elected to register as an OF with the FDA, and complies with the requirements of section 503B (text can be found in H.R. 3204).
- OFs may or may not obtain prescriptions for identified individual patients. (Therefore, OFs may compound for office use in a non-patient specific manner.)
- An OF must be directly supervised by a pharmacist but is not required to be a registered pharmacy with the State in which it is located.
- OFs may only compound with bulk drug substances (active pharmaceutical ingredients or APIs) that:
  - Are ingredients in medications appearing on the FDA’s drug shortage list or
  - Are on a list established by the FDA (a so-called “positive list”)
- Ingredients other than bulk drug substances (inactives or non-APIs) must comply with USP/NF or other compendium recognized by the FDA.
- Independent wholesaling of medications compounded by OFs is prohibited.
• OFs must register, pay an annual fee, comply with current Good Manufacturing Practice regulations, provide reports to FDA on drugs they compound and be subject to inspections by the FDA.

Q. What is a “503A pharmacy”?

A. A “503A pharmacy” is a “traditional pharmacy” engaged in compounding that will need to comply with regulations in FDCA section 503A. Although states will be the primary regulator of “traditional compounders,” deviations from section 503A will subject the pharmacy to federal inspection or enforcement action (i.e., for violations of FDA’s cGMP or distribution of misbranded or unapproved drug products). Highlights of section 503A include:

• Compounded medications must be for an identified individual patient on receipt of a valid prescription or order.
• Anticipatory compounding is allowed, but in “limited quantities,” based on historical prescription orders.
• APIs used in compounding must:
  o Comply with USP/NF monographs (if they exist) or
  o Be a component of an FDA-approved drug or
  o Appear on a list issued by the FDA (“positive list”)
• Non-APIs must comply with USP/NF monographs, if they exist.
• Drugs removed or withdrawn from the market because they are unsafe or not effective (“negative list”) may not be used in compounding.
• A compounded medication may not be “essentially a copy” of an FDA-approved drug, unless the change to that copied product produces a significant difference for the patient.
• FDA is charged with developing a “demonstrably difficult to compound” list. Items appearing on this list will not be allowed to be compounded.
• Unless a state enters into a Memorandum of Understanding (MOU) with the FDA, a pharmacy may not ship compounded medication in excess of 5% of total prescription orders outside of the state the pharmacy resides in (see below).
• Compounded medication must be compounded pursuant to the standards set forth in USP (i.e., chapters <795>, <797>):

Q. So, what is all this I am hearing about the 5% rule?

A. As outlined in the last bullet point above, a 503A pharmacy cannot ship out of state compounded products in excess 5% of their total prescription orders compounded within the state. So, what does this mean?

Let’s take a look at what exactly section 503A says. Drugs may be compounded only if:

“...Such drug product is compounded in a State—
(i) that has entered into a memorandum of understanding with the Secretary which addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a State agency of complaints relating to compounded drug products distributed outside such State; or

(ii) that has not entered into the memorandum of understanding described in clause (i) and the licensed pharmacist, licensed pharmacy, or licensed physician distributes (or causes to be distributed) compounded drug products out of the State in which they are compounded in quantities that do not exceed 5 percent of the total prescription orders dispensed or distributed by such pharmacy or physician.”

NOTE – NOWHERE does it say “sterile” or “office use.” So, absent the state entering into an MOU with the FDA, the pharmacy can only ship “5% of the total prescription orders” outside of their state in which they are compounded. That’s ALL prescription orders and applies to ALL compounded products – sterile, non-sterile, office-use or otherwise.

So, what’s the definition of “prescription order”? Is it a prescription? Total number of doses dispensed? Prescription revenue? At this point, we don’t know, but a strict interpretation would be A PRESCRIPTION (regardless of number of doses dispensed or revenues generated). So, given that interpretation, if a pharmacy is filling 100 prescriptions per day (all prescriptions, compounded and non-compounded), ONLY 5 compounded prescriptions (5%) could be shipped out of state. Please note that this is the interpretation currently and is subject to change. PCCA and other stakeholders will need to watch closely as to what the FDA defines as a “prescription order.”

Q. What about this “negative list” everyone is talking about? Won’t the FDA just put all bulk drug substances on the negative list?

A. The “negative list” was referenced in 503A when FDAMA first passed in 1997. This is a list that the FDA maintains of medications that have been removed or withdrawn from the market for safety or efficacy reasons. The FDA has continued to maintain this list over the past 15+ years and while they could start placing many bulk drug substances on the list, we doubt that they would do so. Placing a bulk drug substance on the list would also disallow other medications to be manufactured by drug companies (so, for instance, ketoprofen would not be listed, as by doing so, all manufactured ketoprofen drugs would have to be removed from the market).

One could argue that FDA could also use this list to stop the compounding of some hormone replacement therapy, namely estriol. However, the FDA has tried to do this twice in the past decade and has run up against major public resistance to the listing. Therefore, we don’t anticipate the FDA using this list as an avenue to outlaw certain types of compounding.

Also, on December 2, 2013, FDA issued a pre-publication notice that it intends to develop and publish a list of drug products or categories of “demonstrably difficult to compound” drugs that cannot be compounded. FDA will seek input for the “difficult to compound list” and then issue the list as a regulation pursuant to notice and comment.
Q. OK – so that’s the negative list. What about this “positive list” I have been hearing about?

A. Actually, there are two “positive lists” – one for 503A pharmacies and one for OFs. Remember, OFs are much more limited in what they can compound with regards to both APIs and non-APIs. OFs may only compound with:

- APIs that are in drugs appearing on the FDA’s drug shortage list.
- APIs that appear on the “positive” list, put forth by the FDA.
- Non-APIs must comply with USP/NF monographs or other compendia recognized by the FDA.

On December 2, 2013, the FDA issued a pre-publication notice in the Federal Register stating that it is preparing to develop a list of bulk drug substances that OFs may use to compound drug products.

- FDA is seeking nominations from interested groups for inclusion of bulk substances on the OF list.
- Nominations should include:
  - Complete information about the bulk product, including whether the substance is recognized in foreign and domestic pharmacopeia;
  - A bibliography of safety and efficacy data (which FDA recognizes is not of the type and amount required of an NDA);
  - Explanation of clinical need;
  - Information about the compounded product (including dosage form, strength, route of administration, past and proposed use, available stability data).
- Nominations supported by the most complete and relevant information will be considered first. Groups will be able to petition the FDA for amendments after the list is published.

503A pharmacies, on the other hand, may compound with:

- APIs that have a USP/NF monograph.
- APIs that are in FDA-approved products.
- APIs that appear on a “positive list,” put forth by the FDA.
  - On December 2, 2013, the FDA issued a draft guidance document that states that until a bulk drug substance list is published, human drug products should be compounded only using APIs that are components of FDA-approved drugs OR have a USP/NF monograph.
- Non-APIs must comply with USP/NF monographs if applicable.

Therefore, 503A pharmacies are able to compound with more bulk substances (APIs and non-APIs) than what OFs are allowed to compound with. We estimate that a very high percentage of bulk substances
that compounding pharmacies use today will automatically be allowed under the new rules of 503A. OFs, on the other hand, will be much more limited in what they can compound with.

Q. So, why are people calling this the “new” 503A?

A. This stems from the fact that in H.R. 3204, Congress basically recycled a part of a law that was passed in 1997 (FDAMA - the FDA Modernization Act of 1997), but removed (or “severed”) the ban on advertising and marketing that several courts had found unconstitutional. Some courts had previously struck down section 503A in its entirety and some struck down just the unconstitutional advertising provisions. To remove any ambiguity as to whether Section 503A would now be enforceable, Congress removed the unconstitutional provisions when it passed H.R. 3204.

Q. What does this mean for 503A pharmacies and how they can advertise their compounding products and services?

A. Our interpretation of the new law is that 503A pharmacies (and OFs) may advertise that they engage in compounding and can also advertise specific medications that they compound. However, advertising must be truthful and making medical claims about compounded medication or using “trade names” of medications in advertising will continue to be prohibited by the FDA. The statute specifically states that prohibited acts include “advertising or promotion of a compounded drug [that] is false or misleading in any particular.”

Q. How will inspections be handled once this law takes effect?

Let’s start with the easy one – OFs. Since OFs register with the FDA, they are agreeing to register and be inspected by the FDA. In addition, since an OF is not required by H.R. 3204 to be a pharmacy, the OF is not forced to register with the State Board of Pharmacy. Therefore, OFs will be inspected by the FDA and these facilities will be expected to implement and enforce current Good Manufacturing Practices.

Now, onto 503A pharmacies. We all must remember that the FDA has the authority to inspect any facility or business that sells or stores medication. This authority has not changed with the passage of H.R. 3204. Also, the statue does not directly address how the FDA should continue with their inspections of “traditional” compounding pharmacies. The FDA has the authority to continue with the risk-based approach that they have implemented over the last 12 months. The FDA has stated in draft Guidance released December 2, 2013 that FDA intends to continue to cooperate with State authorities to “address pharmacy activities that may be in violation” of the FDCA, including section 503A. The FDA expects to “employ a risk based enforcement approach.” It will give highest enforcement priority to compounded drugs and FDCA violations that pose the greatest health risk – which sounds like the approach that FDA has used since commencing its April 2013 Pharmacy Inspection Assignment.
On December 2, 2013, the FDA released several documents pertaining to the implementation of both 503A and 503B. PCCA is reviewing the documents and will publish additional information about them in the coming weeks.