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Letter from the Editor: Milk, Bread, Eggs and 100M for a Biotech Business: The Fall of Big Pharma and Rise of Heathcare Acquisitions

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In This Issue

Mergers and acquisitions within the pharmaceutical industry are quite common and should not come as a surprise to most. However, within recent months the consolidation of the pharmaceutical industry has vastly expanded and become increasingly more frequent, as seen within the mergers of many major pharmaceutical manufacturers. A merger within the pharmaceutical industry may happen for various different reasons such as an increase or gain in market share, an acquisition for control of a blockbuster drug, access to an emerging therapeutic area, enhanced research and development productivity and/or access to new technology.[1]

Indeed, many Big Pharma products that were previously deemed to be blockbuster drugs and commonly referred to as instant money makers are now coming off of patent, forcing major drug companies to look elsewhere for profit. According to Next Generation Pharmaceutical Magazine, "between 2007 and 2012, the top 50 pharmaceutical companies are facing patent expiries on $115 billion worth of drugs."[2] For those of you unfamiliar, when a company develops a new prescription drug a patent is acquired for the medicine. A patent identifies a company as the sole distributor of the drug during the patents 20-year lifespan. Many companies obtain a patent in the early stages of drug development which is long before a drug reaches the market. Notably, many drugs never reach the market because they are unable to be developed and/or approved. However, if a drug is developed and approved, only 11-12 of the 20 years are left on the medicine's patent life.[3]

1 http://knol.google.com/k/m-a-review-pharmaceutical-biotechnology-industry#
2 http://www.ngpharma.com/article/Money-for-Nothing/
3 http://us.gsk.com/html/healthcare/healthcare-common-

Today, as many Big Pharma drugs are set to come off patent, Big Pharma companies look to acquire smaller pharma to avoid the extensive process of drug development yet increase profit and productivity. A classic example of an acquisition such as this is best demonstrated through the Pfizer and Wyeth merger in 2009. One of Pfizer's most pressing challenges and main reason behind acquisition considerations was the approaching expiration of patent rights for Lipitor. Lipitor is set to come off patent sometime this year and provided for a quarter of Pfizer's 2007 revenue of $48 billion. Although the patent expiration of Lipitor was fuel for the acquisition to occur through 2014, Pfizer faced impending patient expirations of 14 other products, totaling up to $35 billion in lost revenue to less expensive generics.[4] Other companies with patents set to expire between 2007 and 2012 include Ratiopharm, Sandoz, Merck KgaA, Actavis, Apotex, Barr, GlaxoSmithKline and Watson.[5]

Mid-to-large size Pharma are not only facing challenges with patent expirations, a lack of product pipeline is also a correlating issue fueling pharma acquisitions. Many Pharma companies are looking to smaller Pharma companies with robust pipelines and products in rare therapeutic areas to enhance their research and development productivity and revenue. Due to the extreme time and monetary commitments required for the development and approval of a new product, smaller Pharma acquisitions provide an easy solution to gain new product without the extreme time and financial burdens. Indeed, it takes on average 12 years for a new drug to pass from the development stage to pharmacy use. To put even more pressure on the Pharma industry, the U.S. Food and Drug Administration (FDA) has taken a more conservative approach on approving new medicines. Unfortunately, approximately five in 5,000, or 10 percent, of drugs that begin in the preclinical testing stage make it to human testing. And, only one in these five is ever approved human usage.[6] Not only is the drug development process difficult and time consuming, it is also extremely expensive, costing approximately $800 million to research and develop a single new medicine.[7]

Recently, rumors have swirled that Shire Pharmaceuticals is soon to be engulfed by a big pharma offer and analysts have placed Shire on their "lists of most-likely-to-be-acquired drugmakers."[8] For instance, Shire's drug for ADHD, Vyvanse, is looking at new indications such as schizophrenia, depression, binge eating and daytime sleepiness. Even without these new indications, Shire has a 31 percent increase in Vyvanse sales for the first quarter of 2011. These factors, coupled with the recent success in Shire's rare disease medicines, may make Shire ripe for the big pharma picking.[9] Additonally, Takeda recently purchased Nycomed for nearly $14 billion. Takeda has many drug patent expirations in the near future and is clearly looking to join the market of emerging drugs. With that said, Nycomed is an attractive purchase, as it has a strong and well developed reputation in the emerging market arena, in addition to a recently approved respiratory drug, Daxas.[10]

And as we all sit back and watch the industry consolidate like it has never consolidated before, the idea of jumping into the generic drug market by many is enticing. For instance, generic drug manufacturers do not incur the cost of the drug development process. Generic drug manufacturers do not undergo the burden of proving the safety and efficacy of drugs through clinical trials, as these trials have already been conducted. The cost of advertising of a drug is also extremely costly, and many generic drug companies may receive the benefit of previous marketing campaigns of the branded drug.[11] According to the FDA, a generic drug is defined as being "identical--or bioequivalent--to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use."[12] When patents expire, manufacturers are allowed to apply to the FDA to sell generic versions of a medicine. While generic drugs are chemically equivalent to the branded medicine, they are usually sold at an extremely lower price. The FDA website states that "according to the Congressional Budget Office, generic drugs save consumers an estimated $8 to $10 billion a year at retail pharmacies. Even more billions are saved when hospitals use generics."[13] Cheaper prices label

questions.html#5
4 http://www.nytimes.com/2009/01/26/business/26drug.html
5 http://www.ngpharma.com/article/Money-for-Nothing/
6 http://ca-biomed.org/pdf/media-kit/fact-sheets/CBRADrugDevelop.pdf
7 Id
8 http://www.fiercepharma.com/story/shires-growth-could-woo-big-pharma-offers/2011-05-13
9 Id
10 http://www.fiercepharma.com/story/takeda-snaps-nycomed-136b-deal/2011-05-19
11 http://en.wikipedia.org/wiki/Generic_drug
12 http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm144456.htm
13 Id

generics drugs as the more economical and cost effective choice for many consumers. However, despite the cheaper costs of generic drugs, many consumers remain loyal to branded drugs. Nonetheless, the availability of generic medicines enables populations that, in the past, may not have had access to branded drugs for their use and can now obtain proper treatment.[14]

While less expensive drug costs may be an obvious solution for consumers, they do not address issues that many pharmaceutical companies are facing. Similar to any other company, the pharmaceutical industry is driven by revenue. The loss of patents and shrinking number of blockbuster drugs decrease the amount of money in the research and development pot, which continues to reduce pipelines, creating a vicious cycle.[15] To some, the increase in use of generic drugs in not the solution. Rather, "[t]he main agenda is to reduce healthcare costs. People are paying more on healthcare than on mortgage loans. Bringing generic drugs into the market will lower the value of the original drugs; however, the government should also bring in legislation to reduce the price of branded drugs and make them affordable."[16]

Ultimately, the pharmaceutical industry is essential to all and the benefits of research and development enhance the lives of patients all around the world. Patients rely on current medicines to increase their quality of life and maintain a normal lifestyle, while many of those patients plagued with rare conditions hope a treatment can soon be developed. It is unclear what effects will stem from mergers within the pharmaceutical industry, however it is clear that pharmaceutical manufactures should strive to continue to enhance the innovation within research and development to ensure that the quality of life can be increased for all.

14 http://www.ehow.com/way_5150203_advantages-generic-drugs.html
15 http://www.ngpharma.com/article/Money-for-Nothing/
16 Shabeer Hussain, Program Leader in Pharmaceuticals for Frost & Sullivan

340B Exclusion of Orphan Drugs for Certain Covered Entities

By: Megan Campbell, Compliance Associate; Chris Cobourn, Vice President of Regulatory Affairs; Amy VanDeCar, Director of US Commercial Compliance

On May 19, 2011, the Health Resources and Services Administration ("HRSA") published a proposed rule regarding the exclusion of orphan drugs for certain covered entities under the 340B Program. Orphan status is given to drugs and biologics which, as defined by the FDA, are

> *Intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the U.S., or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug.*

In general, entities that are 340B eligible may purchase covered drugs at a discount under the PHS Program. Under the Patient Protection and Affordable Care Act (PPACA), congress extended the PHS program to additional entity types. Also under the PPACA, however, these new entity types had an "orphan exclusion," meaning that they were prohibited to purchase orphan drugs at the 340B price. This recent proposed rule provides HRSA's draft guidance on the orphan exclusion.

Under the proposed rule, covered entities may purchase orphan drugs at 340B prices when using the drugs to treat conditions for which they are approved or any other lawful use but they are not to be used for the rare condition or disease for which they received the status of orphan drug by the FDA. Covered entities are responsible for making sure that orphan drugs that are purchased through the 340B Program are not "transferred, prescribed, sold, or otherwise used for the rare condition or disease for which orphan drugs are designated under section 526 of the FFDCA".

Entities must provide auditable records to make certain that they are compliant with this requirement.

If covered entities chose not to or do not maintain these records, they must purchase all orphan drugs outside of the 340B Program. If this choice is made, the covered entities are required to notify the HRSA that they will be purchasing

orphan drugs outside of the 340B Program when enrolling in the program and also during re-certification.

This proposed rule could have an interesting impact on the implementation of the orphan exclusion, and in its current state could render the orphan exclusion meaningless. Manufacturers have very little insight currently in to the patient or the use of the drug purchased under the program. Manufacturers can validate 340B eligibility, using submitted Chargeback data, but this data provides no insight in to the use of the drug. So in the current state of the program, manufacturers could have little recourse or ability to question or dispute purchases. We see this now with manufacturers trying to dispute purchases under the program for potential inpatient use, or to dispute based upon patient eligibility. It is interesting that HRSA is also working on rules for the dispute resolution process. If the dispute resolution process gives the manufacturer an opportunity to dispute purchases and require documentation from the entity to demonstrate that disputed purchases are legal under the program, then maybe this draft rule can have an impact.

Additionally, in the current rule making environment, where the agency is promulgating rules to implement the terms of the PPACA, it is interesting to see proposed rules like this come out on their own. It is hard to take one part of the program on its own, and it would be good to see the proposed rules come out together, so that they can be evaluated as a whole.

Resources

1. http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/default.htm
2. http://www.federalregister.gov/articles/2011/05/20/2011-12423/exclusion-of-orphan-drugs-for-certain-covered-entities-under-340b-program#p-37

You can access more articles by going to **pharmacomplianceblog.com**

"Who Ya' Gonna Call?" (Not Ghost Busters…) v.6 - The "Joys" of Medicaid Managed Care Rebate Requirments

By: Bill Baxter, CIS Strategic Advisor, Government Affairs

As we're now painfully aware, the Patient Protection & Affordable Care Act (ACA) (http://www.healthcare.gov/law/about/index.html) requires rebates for covered drugs dispensed to Medicaid patients by Managed Care Organizations (MCO's). The change became effective for units dispensed as of 3/23/10. However, it has taken time for some states to revise their Medicaid Management Information Systems (MMIS) in order to manage the process. Many states (15) had previously carved out the drug benefit from services provided by Medicaid Managed Care Organizations (MMCO's) to Medicaid patients. Tennessee was the first, but 14 others followed its lead. For these "carve out" states, the extension of rebate obligation for MMCO patients will require no change. MCO utilization has been included in their fee-for-service (FFS) invoices for some time, depending on when these states changed their policies.

However, that is not the case for the 22 "non-carve out" (NCO) states and the District of Columbia (DC). Several NCO states have now begun invoicing for this utilization, while several others have not yet completed revisions to their MMIS operations. We are currently researching the status of all NCO states, and will have more specifics during the Compliance Implementation Services MMCO Webinar on May 5th (https://www1.gotomeeting.com/register/603836624). Additionally, there are 14 states that do not have MCO's or have chosen not to utilize them for Medicaid services. Unless and until this changes, there should be no increase in rebate claims from these states.

The following is general Medicaid data from 2008/2009 for a high level overview (Source: Kaiser & CMS). As you may know, data from government programs is painfully slow, but we'll update the following as more current information is available.

- Total Medicaid Spend: $339B
- Total Medicaid Eligible Population: $52M
- Medicaid Patients Enrolled in MCO's: $38M

Relative data for "Non-Carve Out" states includes:

- Medicaid Spend: $165B
- Medicaid Eligibles: $27M
- Medicaid Eligibles in MMCO's: $20M
- On average, 75% of Medicaid eligibles in non-carve out states are enrolled in MMCO's

All NCO states are currently invoicing for both FFS & MMCO utilization or are planning to do so by the end of the year. The delay for several programs is the difficulty in adapting MMIS systems to manage MMCO utilization claims. Also, a couple of states are in the process of changing data service providers and will begin invoicing when the transition is complete.

Specific NCO state info comes from CMS & individual state personnel. Note: We've personally spoken with staff from 20 of 22 NCO states, and will have surveyed all by our MMCO Webinar on May 5th. Of 22 programs, 7 states & DC are not yet invoicing. NCO information of interest includes:

- These programs have approximately half of the national total of Medicaid enrollees
- They also serve half of the national MMCO population
- The number of MCO plans (service providers) in these states range from 0 to 30+
- With approximately 75% of the Medicaid population enrolled in MMCO's in these states, expect significant increase in units & rebate claims

All NCO states will ultimately invoice for MMCO units dispensed back to 3/23/10. While most will separate FFS & MMCO invoices, they plan to use formats identical to current FFS invoices. The easiest way to stay current with individual MMCO's in each state is to Google the health department and "search" for managed care listings. Invoices will include identifiers for specific MMCO's, and virtually all will invoice for J-Code products.

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With the preceding information we know to expect an increase in rebate invoices and dollars. The question is, how can we project the need for additional reserves and staffing? Key points to consider include:

- Have you planned for expanded analytical & processing support, especially considering Medicare Part D "Coverage Gap" work load?
- Is your invoice management operation automated; are you considering such improvements?
- Do you utilize claims level detail for invoice analysis?
- What is your companies' general level of payments and disputes?
- Is your product mix used heavily in the Medicaid market?
- Do you have contracts with some and/or all of the MMCO's in a state?
- Does the wording in your MMCO contracts expose you to, or protect you from, a "double hit," i.e., discount & rebate for the same units?
- "Who ya gonna' call" for assistance & guidance?

OIG Audit Raises Concerns about Medicare Part D Plans

By: Grete Dudek, CIS Compliance Associate

Medicare Part D plans are administered by private insurance companies, known as sponsors, who are responsible for negotiating rebates with pharmaceutical manufactures to reduce the cost of the Medicare Part D program. "Rebates can substantially reduce the cost of the Part D program: however, sponsors must accurately report these rebates for the Government and beneficiaries to receive any cost savings." (2) Before each plan year, the sponsors present CMS bids containing information about the rebates they expect to receive from pharmaceutical companies. CMS uses the bids to calculate beneficiary premiums for the upcoming year. At the end of each plan year, the sponsors provide CMS with information on the actual rebates they received from the manufacturers. The OIG conducted an audit on six Medicare Part D plan sponsors, assessing their 2008 plan bids and comparing them to the actual rebates reported at the end of the plan year.

The OIG put these important findings into their report:

1. Medicare Part D sponsors reported receiving $6.5 billion in rebates in 2008. This accounts for about 10% of total gross Part D costs, on average $275 per beneficiary, or $7 per drug dispensed.

2. Sponsors underestimated the expected rebates in 69% of their bids, leading to higher beneficiary premiums in these plans and higher Government payments to the sponsors. Although the Government recoups some overpayments, beneficiaries do not. In contrast, for 29% of bids the rebates were overestimated, leading to lower beneficiary premiums. About 2% of bids were accurate.

3. The audited sponsors had complex relationships with Pharmacy Benefit Managers (PBMs) that sometimes lacked transparency. The lack of transparency could be troubling for sponsors, who may not always have enough information to oversee compliance of the PBM with CMS requirements, for which the sponsor is responsible.

4. Sponsors can receive rebates at the plan level or at the sponsor level. If they are received at the sponsor level, the sponsors must allocate the rebates per plan. The OIG found that different sponsors used different methods to allocate the rebates across plans. Since the actual rebate amounts are used to determine the amount that the Government pays each sponsor for providing the benefit, the method the sponsor uses to allocate the rebates across plans can affect the amount the Government pays to the sponsor providing the benefit.

Based on these findings, the OIG recommended the following to CMS:

1. CMS should take steps to ensure that sponsors more accurately include their expected rebates in their bids. The OIG recommends that CMS work with sponsors who have the largest difference between expected rebates in the bids and actual rebates to ensure that the differences do not occur again.

2. CMS should require sponsors to use a method it determines to be reasonable to allocate rebates across plans. If CMS does not recommend a method (or several), sponsors can strategically allocate rebates across plans to increase their payments from the Government.

3. CMS should ensure that sponsors have sufficient audit rights and access to rebate information so that they can accurately report rebates.

4. CMS should ensure that sponsors appropriately report the fees that pharmacy benefit managers collect from manufacturers and needs to clarify when these fees should be reported as rebates. CMS should monitor the fees that are required to be reported (starting in 2009) as bona fide service fees.

CMS agreed with the first recommendation, that it should ensure sponsors more accurately include rebates in their bids and may consider adding to its bid review a comparison of rebates in the bid to rebates actually received. CMS did not agree that sponsors should use specific methods to allocate rebates, but will continue to

review the methods used by sponsors to determine whether more guidance would be appropriate. CMS also believes that it has taken steps to promote transparency of the rebate information the sponsors report to CMS, and does not agree with the third recommendation. Finally, CMS partially agreed with the last recommendation, to ensure that sponsors correctly report fees that PBMs collect. Although the OIG found that bona fide service fees were being reported differently by sponsor, CMS does not believe that more specificity is needed in the definition of these fees.

"The industry group America's Health Insurance Plans sees it this way: The Part D program is highly competitive so plans have an incentive to offer the lowest bid and, therefore, the most affordable premiums to attract beneficiaries.… It is also important to keep in mind… that Part D bids are based on projections of future costs, which are inherently uncertain. As the report notes, Part D plans reconcile rebates estimated in their bids with the amounts actually collected…. (3)". Although it may be worthwhile for CMS to help sponsors with the biggest differences between their estimates and actual rebates, Part D premiums are well below estimates of cost from when the program was enacted.

Resources

1. Concerns With Rebates in the Medicare Part D Program. http://oig.hhs.gov/oei/reports/oei-02-08-00050.asp
2. Concerns With Rebates in the Medicare Part D Program (full report). http://oig.hhs.gov/oei/reports/oei-02-08-00050.pdf
3. OIG Audit Raises Concerns About Medicare Part D Plans. http://www.healthleadersmedia.com/content/LED-263408/OIG-Audit-Raises-Concerns-About-Medicare-Part-D-Plans

An Update from CMS on the Medicare Part D Coverage Gap Program

By: Kaelyn DeConti, Compliance Consultant

This past Wednesday (May 4, 2011), the Centers for Medicare & Medicaid Services (CMS), along with their third party administrator (TPA), Palmetto GBA, held a webinar to provide Pharmaceutical Manufacturers with information and developments in relation to the Medicare Part D Coverage Gap Program.

CMS Quarter 1 (Q1) invoices have officially been distributed as of April 30th, 2011. Manufacturers must pay Part D Sponsors by June 7th, 2011 and confirm payment by June 12th, 2011. The dispute timeline is as follows:

April 30, 2011 – Manufacturer Data Report distributed
May 1, 2011 – 60-day Dispute Window begins
May 1, 2011– June 29, 2011 – Dispute Submission Files date range for Q1 Data Reports
June 17, 2011 – CMS receives Dispute Submission Files
August 28, 2011 – Data Q1 Disputes will be resolved

Currently, no low volume invoices have been distributed and CMS has not decided on when low volume will be invoiced. Low volume means 10 or fewer beneficiaries with the same NDC 9 drug dispensed by the pharmacy.

Many of you may have noticed the strange characters at the end of the amounts in the invoice and detail data. Please remember to refer to the "Overpunch Character Map" provided on the Palmetto GBA website (or click the underlined hyperlink abovee). Please feel free to contact Ms. Lisa McNair if you have additional questions regarding this mapping,

With this program, the same drugs could be covered under Part B or Part D depending on patient and/or setting specifics. Note however, that Part D does NOT cover drugs that are covered under Medicare Part B as prescribed and dispensed or administered with respect to that individual. Medicare Part B coverage categories include: Durable Medical Equipment (DME) Supply Drugs, Immunosuppressants, Oral Antineoplastics, Oral Antiemetics, IVIG, and "Not usually self administered" drugs furnished incident to physician's service.

CMS highlighted clarification on the D08-Early Fill Validation, as they have received numerous questions about this topic. They emphasized that the validation needs to be determined with appropriate prescription history.

The below example was given by CMS and illustrates that an Early Fill cannot be determined without appropriate prescription history:

Fill Number	RX Fill Date	Day's Supply	Date fill should run out	Date fill actually runs out
1	2/1/2011	30	3/2/2011	3/2/2011
2	2/20/2011	30	3/21/2011	4/1/2011
3	4/2/2011	30	4/1/2011	5/1/2011

- Initially, we expect fill 2 on March 2nd. Instead, this fills occurs 10 days early on February 20th. However, fill 3 on 4/2 explains the refill pattern.
- A total of 90 days' supply was dispensed in a 90 day interval.
- The average monthly supply is equal to 30 days.

During the webinar, CMS introduced a new format called the Dispute Return Format. This is another inbound data format and is used by Palmetto and CMS to notify the manufacturer of the disposition of the disputed script line items submitted via the Dispute (Data) Report. The Return Format is similar to the Dispute report with the addition of a number of dispute edit codes and additional information that is required. Examples of the Dispute File Layout can be found here: Dispute File Layout.

The final topic was on Dispute Submission File Creation. For this, you will need the Manufacturer Data Report and the Dispute Submission File Layout; both of which are posted on the CMS website. The creation and overview are as follows:

<u>Creation</u>
Manufacturer Data Report
- Extract rows for dispute

Detailed Dispute Information
- Use Record Type Code DETCG
- Add Dispute Reason Code as field 18
- Add supporting dispute information in fields 19-22
- Field 23 is reserved space

Add Headers and Trailers
- Headers – use Record Type Code TPAMH
- Trailers – use Record Type Code TPAMT

<u>Overview</u>
Detailed Dispute Return File
- Record Type Code – Field 1
- Fields 2-22 match Dispute Submission File
- Disputes not accepted for dispute consideration
- Disputes accepted for dispute consideration

The last bit of information, that I would like to add, is that as of this most recent webinar, there is still no guidance as to the 1099 reporting status. We will make this information available as soon as we hear something.

Palmetto GBA anticipates holding monthly webinars the first Wednesday of every month to discuss outstanding issues such as the dispute resolution process which still under construction, audit processes, any file or report changes and to address questions. The next scheduled

webinars will be held on Wednesday, June 1, 2011 from 4:00pm-5:00pm ET and Wednesday July 6, 2011 from 4:00pm-5:00pm ET.

Pharmaceutical manufacturers and interested parties are encouraged to register with the Palmetto GBA to receive email updates at www.csscoperations.com. Customer support will be provided via the CSSC Help Line, Monday thru Friday from 8:00am to 7:00pm (EST) at 877-534-2772 from or inquiries may be submitted to the Help Line at csscoperations@palmettogba.com.

Compliance Implementation Services (CIS) offers Medicare Part D Coverage Gap Program assistance to pharmaceutical manufacturers, which includes receiving and processing quarterly reports, preparation of confirmation reports, payment processing and when the time arrives, dispute resolution assistance. Please contact Lisa C. McNair at lisamcnair@cis-partners.com for additional information.

Resources

1. http://www.cms.gov/PrescriptionDrugCovGenIn/05_Pharma.asp#TopOfPage
2. http://www.cms.gov/PrescriptionDrugCovGenIn/01_Overview.asp#TopOfPage
3. http://www.palmettogba.com/palmetto/palmetto.nsf/DocsCat/Home
4. http://www.csscoperations.com/internet/Cssc.nsf/files/CG_Manufacturer_Dispute_Edits_050411.xls/$FIle/CG_Manufacturer_Dispute_Edits_050411.xls
5. http://www.csscoperations.com/internet/Cssc.nsf/files/May%202011%20Manufacturers%20Webinar%20Slides.pdf/$FIle/May%202011%20Manufacturers%20Webinar%20Slides.pdf

New Proposed Rule on Disqualification of Clinical Investigators

By: Karen Chaney, Clinical Compliance Specialist

On April 13, 2011 the Food and Drug Administration (FDA) proposed a new rule that would expand the scope and consequences of clinical investigator disqualification. "Under this proposal, when the Commissioner of Food and Drugs determines that an investigator is ineligible to receive certain test articles (drugs, devices, or new animal drugs), the investigator also will be ineligible to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by the FDA."[1] The proposed rule orientates from the 2009 Government Accountability Office's (GAO) report on the FDA's oversight of clinical investigators which recommended for the FDA to take stronger action to prevent clinical investigators engaged in serious misconduct from doing so again.

The proposed rule is also intended to harmonize 21 CRF parts 312 (drugs and biologics), 511 (animal drugs) and 812 (devices). 21 CRF Parts 312 and 511 will be updated to include requirements similar to Part 812 that the FDA will notify clinical investigators in writing once the FDA receives notification that a clinical investigator has repeatedly or deliberately failed to comply with current regulations or submitting false information. At that time a clinical investigator can provide written justification to the violations and if deemed acceptable the disqualification process will cease. If the Commissioner determines the written justification is not acceptable the clinical investigator can request an informal hearing to determine if he/she will be eligible to receive certain test articles and/or conduct clinical investigations for research and marketing applications.

When a Clinical Investigator is disqualified, the new proposed rule requires notification, including specific evidence and reasoning for disqualification, to be sent to the applicable Institutional Review Boards (IRB), sponsor, and investigator. Reinstatement of a Clinical Investigator can occur if the Commissioner determines the Clinical Investigator has provided adequate assurances that they

1 U.S. Food & Drug Administration (April 13, 2011). "FDA Proposes New Rule on Disqualification of a Clinical Investigator". Press Release. Retrieved 2011-04-14.

can conduct clinical investigations in compliance with current regulations.

The FDA expected benefits of the proposed rule include:

- "This proposed action of explicitly extending a disqualified investigator's ineligibility to receive any FDA-regulated test article would help to reduce the risk of additional violations in other FDA-regulated investigations and thus, would help to ensure the integrity of clinical trial data and help reduce the risk to human subjects who participate in FDA-regulated investigations."[2]
- "This proposed rule may also lead to improved public confidence in the clinical data supporting FDA decisions."[2]

This new proposed rule creates increased requirements for the sponsor company to screen potential investigators and monitor active investigators more closely. A key area of improvement for pharmaceutical companies conducting clinical trials is not only screening investigators during pre-trial activities and periodically throughout the life of the trial, but to clearly document the screening process and the resulting findings. CIS commonly notes sponsor oversight for evaluating Clinical Investigator compliance trends across trials/protocols/products. Implementing these procedures requires a risk-based approach to developing quality systems, which is a new approach also being adopted by the FDA. The proposed rule shows increased attention by the FDA on areas of non-compliance and adequate clinical trial oversight. The risk in failing to adequately screen clinical investigator compliance could result in findings from the FDA that could result in the discontinuation of a trial or marketing approval. Comments on the proposed rule are due to the FDA by July 12, 2011. Comments can be submitted electronically on the Federal eRulemaking Portal at http://www.regulations.gov or written submissions can be faxed to 301-827-6870 or mailed to Division of Dockets Management [HFA-305], Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All submissions should include Docket No. FDA-2011-N-0079 and/or RIN number 0910-AG49.

CIS is experienced in developing and implementing procedures for clinical programs and follows all regulatory updates to ensure a high level of compliance with our clients. We will be watching the development of this change in regulation and will post updates as they become available.

2 Federal Register/Vol. 76, No. 71, pages 20575 - 20588 http://www.gpo.gov/fdsys/pkg/FR-2011-04-13/pdf/2011-8786.pdf

Clinical Quality Management Systems – Regulatory Agency Emphasis

By: Billy Grimme, Project Manager, Global Clinical R&D

Regulators continue to raise the expectations for Sponsors and Contract Research Organizations (CROs) to develop a Risk-based Clinical Quality Management System (QMS) to foster GCP compliance and quality across a clinical development organization. As my colleague, Karen Brown, stated in her recent blog "Clinical Quality Management System – Something Borrowed", this concept has been adapted from what has traditionally been a Good Manufacturing Practice (GMP) approach in ICH Q8, Q9, and Q10.[1]

The Food and Drug Administration (FDA) acknowledges that the concept of a QMS addresses challenges in product manufacturing, but has since stated that the approach of a Clinical QMS provides a model for "maximally efficient, nimble clinical development programs that produce high quality data and protect trial participation without extensive regulatory oversight."[2] A Clinical QMS consists of "coordinated activities that collectively permit sponsors and CROs to appropriately direct and control their clinical trials and clinical development programs in compliance with applicable statutes and regulations".[3]

The regulatory agencies, specifically the FDA, acknowledge there is no specific requirement for a Clinical QMS, while clearly articulating the shift in Agency expectations for sponsors' oversight of clinical trials. This shift in expectations was reinforced by Janet Woodcock, MD, Director, Center for Drug Evaluation and Research (CDER) on October 13th, 2010 at "A Clinical Trials Transformation Initiative (CTTI) Expert Meeting", Leslie Ball, MD, Director, Department of Scientific Investigations (DSI) on January 18th, 2011 at "Developing CAPAs in the GCP Environment", and by Ann Meeker-O'Connell, Officer, DSI in April 2011 at "Proactive GCP Compliance".

The best approach for sponsors to accommodate this shift in expectations is to develop a Clinical QMS, as defined above, and that includes the following risk-based approach: [2, 3, 4]

- Build quality into clinical development programs, i.e. protocol development
- Apply risk management principles to effectively target oversight resources to activities that present a greater risk to data integrity and human subject protection
- Define controls to:
  - Prevent errors
  - Identify potential problems and intervene before issues become endemic

Ms. Meeker-O'Connell further developed this concept, during the April 2011 Exl Pharma Conference "Proactive GCP Compliance", and provided further justification for the development of a Clinical QMS. She informed the audience of a recent DSI review of marketing applications received from Q1 2010 to Q1 2011 and provided two lessons learned:[2]

- Despite the resources devoted to monitoring and other, often retrospective quality activities, problems persist.
- Systemic errors can render trial data unreliable and may be unrelated to activities at the clinical investigator site.

These lessons learned hit at the very need to develop a Clinical QMS to proactively implement quality standards that cannot be addressed in a retrospective approach.

1 http://www.pharmacomplianceblog.com/blog/?p=3475, Karen Brown, "Clinical Quality Management System – Something Borrowed".

2 Ann Meeker-O'Connell, "Using Risk-based Quality Frameworks to Facilitate Clinical Development", April 5, 2011.

3 Janet Woodcock, MD, "Quality Risk Management for Clinical Trials", October 13, 2010.

4 Leslie Ball, MD, "Regulatory Expectations for Clinical CAPAs: FDA Perspective", January 18, 2011.