

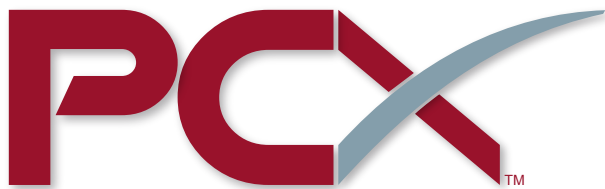
## Guest Letter from the Editor: An Update on the Pending AMP Rule - Are the Rumors True?

By: Chris Cobourn, Vice President of Regulatory Affairs

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In a recent Pink Sheet article, Joe Fine, the technical director for the pharmacy division of the CMS Center for Medicaid, CHIP, Survey & Certification, quoted from a speech at NCPA on May 23, stating that the CMS AMP rule is written and forwarded on for two levels of review. He added that Health and Human Service officials are now considering the document and, once done, will pass it on to the White House Office of Management and Budget, which has up to 90 days for its review.

In my recent blog article, I spoke to rumors of the time which suggest an Infirm Final AMP rule around Memorial Day, see my blog article<sup>1</sup> for more information on what an “Interim Final Rule” could mean.

I cannot say for sure that we should expect an Interim Final Rule, as the Pink Sheet article also stated that the “...document will be published as a notice of proposed rulemaking, with opportunity for public comment...” but it also suggested an effective date of October, which could be very aggressive for a public comment period.

The rule should prove interesting reading, and will have a lot of scrutiny by both manufacturers and the retail industry. Addressing one key area of complexity, Fine is quoted in the article “...CMS has heard “in droves” from manufacturers demanding to know, “How can we tell once the wholesaler buys it, where it goes? And this is something that we have had to work out, and we discuss it in the rulemaking...”

Manufacturers had to modify their AMP calculations as of October, 2010, in 2 key areas, the first in making adjustments

<sup>1</sup> <http://www.pharmacomplianceblog.com/blog/?p=3719>

for Class of Trade to include only sales to Retail Community Pharmacies, the second in determining an Alternative AMP for products that were a 5i drug and not generally sold to retail. There were many other gray areas in the limited legislative language of the PPACA, such as the new Bona Fide Service Fee language, and specific definitions on Line Extensions.

There was talk by some that the PPACA language suggests a “build up methodology,” as opposed the gross to net exclusion approach developed by most manufacturers and adhered to for the history of the program. Most manufacturers did not make this major methodology shift in October, as they did not feel as though there was clear guidance to do so, and there simply was not the data available to do the calculation this way. Judging by Fine’s quote above, this was probably one of the key areas discussed in the rulemaking.



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## Evaluating the Impact of Medicaid Managed Care Rebates on 340B Service Providers

By: Bill Baxter, Strategic Advisor, Government Affairs

As all of us that qualify to be called “GP Geeks” know, the Patient Protection and Affordable Care Act (ACA) has brought on many changes, with more to come. They have impacted virtually every aspect of health care and every provider. A significant change is the extension of Medicaid rebates to Managed Care Organizations (MCOs) that provide prescription drug services for Medicaid patients. A key area of recent interest we are hearing is the effect the requirement for such rebates will have on contractual and reimbursement arrangements between MCOs and 340B service providers.

Currently there are many more questions than answers. However, this is a topic that will be discussed in depth at the upcoming 340B Annual Coalition Meeting being held in Washington, DC on July 11 – 13. You may recall Chris Cobourn’s recent blog article “Why Manufacturers Should Consider Attending”<sup>1</sup> Background and registration information for the conference may be found at [www.340bcoalition.org](http://www.340bcoalition.org).

As Chris says in his blog, if you are interested in attending, CIS partners will receive a \$150 discount on their conference registration. This discount is the same as (not in addition to) the Drug Discount Monitor subscriber rate. To receive your discount, go to [www.340bcoalition.org](http://www.340bcoalition.org). Under “Please select your registration category from the following list,” choose the third option: “Industry Drug Discount Monitor Subscriber or Contracted Supplier of the 340B Prime Vendor Program.” Respond to the next questions as you normally would, then select the option for “CIS” under “How did you hear about the conference?” Please note you must select “CIS” in order to receive the discount. If you have questions, please contact Bridgette Joye at 202-552-5861 or [Bridgette.joye@snhpa.org](mailto:Bridgette.joye@snhpa.org).

<sup>1</sup> <http://www.pharmacomplianceblog.com/blog/?p=3808>

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## Incentive-Based BPAs: The End of an Era

By: Jeff Blake, FSS Project Manager

In the past, the less than stringent Federal requirements surrounding the competitive bidding process for orders placed under GSA Federal Supply Schedule (FSS) contracts have allowed Federal agencies to “circumvent” the process through the use of Blanket Purchase Agreements (BPA). These agreements are typically incentive-based contracting vehicles that offer additional price concessions to FSS eligible entities outside of the statutory pricing requirements and negotiated prices of the FSS contract. Many current FSS contract holders have a BPA in place for one or more of their products as it is a simple and valuable tool for manufacturers to increase sales by offering an additional discount to eligible entities for FSS contract purchases.

However, effective May 16, 2011, the Federal Acquisition Regulation (FAR) council issued an interim rule which greatly increased the competition requirements for multiple award Indefinite Delivery, Indefinite Quantity (IDIQ) contracts, the category to which a BPA belongs. Under this interim rule, all multiple award IDIQ contracts awarded on or after May 16, 2011 will be subject to the following requirements:

1. Fair notice of the intent to make a purchase, to include a description of the work to be performed and the basis on which the selection will be made, must be provided to all multiple award contract holders who offer such products or services.<sup>1</sup>
2. All contractors must be given a “fair” opportunity to make an offer and all offers must be “fairly” evaluated.

More specifically, all pharmaceutical and medical equipment orders over the Micro-Purchase Threshold of \$3,000 which are placed under a BPA that was awarded on or after May 16, 2011 will have to be competitively bid by the contracting officer, which means that all BPA holders will have to be fairly considered before the purchase is made. Further, for orders which exceed the

<sup>1</sup> <http://www.gpo.gov/fdsys/pkg/FR-2011-03-16/pdf/2011-5553.pdf>

Simplified Acquisition Threshold (SAT) of \$150,000, the contracting officer will be required to submit a Request for Quotation (RFQ) through the government’s e-Buy system, consider all submitted quotes prior to placing an order and document his or her compliance with the new process. In other words, the days of the incentive-based BPA are over. At first glance, the new requirements appear quite cumbersome, however, it should be noted that for purchases under \$150,000, the interim rule states that contracting officers must only document that all BPA holders have been given a “fair opportunity” for consideration. The definition of a fair opportunity is not explicitly stated, which should allow for some leniency on purchases under the \$150k threshold. On the other hand, the requirements for purchases over the SAT are quite stringent and will be a heavy burden for the contracting officer. Needless to say, it will be very interesting to see how these new requirements affect both the Federal agencies and the FSS contract holders in the near future. Additionally, manufacturers will need to exhibit an increased level of patience as the contracting officers implement the changes and navigate the pitfalls that will surely be encountered.

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## Clinical Quality Management Systems – Regulatory Agency Emphasis

By: Billy Grimme, CIS Project Manager

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.<sup>1</sup>

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.”<sup>2</sup> 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.”<sup>3</sup>

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:<sup>2, 3, and 4</sup>

- 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:<sup>2</sup>

- 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.

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

- 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.


  
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## Biotech Startups and the role of Regulatory Compliance

By: Rick Moore, Sr. Associate and Abram Balloga, Associate

Even with the recession stutter in funding availability, biotechnology (biotech) growth over the past five years has outperformed other sectors in the life sciences. The NVCA (National Venture Capital Association) launched a website feature highlighting venture-backed companies nationwide. According to one “NVCA Spotlight”, approximately 1,900 life science companies received venture capital funding for a total of \$41.2 billion in the last five years.<sup>9</sup> During those five years, the states of California, Massachusetts, and Pennsylvania posted the greatest number of venture-backed life science companies. Due in part to these investments, the growth outlook for biotech over the next five years looks to be outstanding, growing at an average annual rate of 9.1% to become a \$136 billion industry by 2015.<sup>6</sup>

The U.S. government has also provided assistance to biotechs, often included in broader attempts to stimulate growth and ingenuity. Backing sentiment with coin, on January 31st President Obama announced the launching of Startup America, a program that aims tax credits and \$2 billion in federal matching funds toward incubating American entrepreneurship. This stimulus invests in human capital and the future value of creativity - let's keep the ball rolling, let's innovate. Startup America is chaired by Steve Case, co-founder of AOL, and will work closely with the Council on Jobs and Competitiveness led by General Electric CEO Jeff Immelt, and operates under the Small Business Administration. This program is only the latest of brightening forecasts for hungry biotech startups who found themselves heavily fund rationed during the recession. Other sources of financial aid available to startups include:

- The Orphan Drug Program, Charging for Investigational New Drugs
- Prescription Drug User Fee Act Waivers and Reductions for Small Business
- Unsolicited Grant Applications seeking FDA support
- Solicited Grant Applications – FDA grant programs
- Grants and Funding Opportunities at the NIH (National Institutes of Health)<sup>7</sup>

Although wallets continue to open for start-ups, there are other forces adding to biotech momentum. The funding portion of this trend is actually, although an enabler, not causation to growth. Rather, it is the prospect of market opportunity that attracts money, at least from private sources. Many factors apply; however, we will narrow the discussion to three – 1) the pharmaceutical patent cliff 2) changing demographics, and 3) the role of regulatory compliance.

Speaking on the first factor mentioned above, some of this growth is attributable to the needs and wants of global pharmaceuticals. With depleting pipelines and approaching patent expirations, pharmas intend to pad product portfolios, sell in new market places, and diversify:

*Indeed, there is no escaping that 20, even 30 years ago there was an abundance of drugs in the pipeline that upped the valuation of pharmaceutical companies and their share prices: everything was upbeat and there was plenty of innovation and constant demand. In the last five years, however, all of this has been significantly reduced due to the cost of R&D and bringing out new drugs, getting approval from the FDA and registering in different markets. Nowadays, it's far more difficult for pharmaceutical companies to continue to produce blockbuster drugs, which is unquestionably having an impact on their current valuations (viii).*

One opportunity that pharmaceuticals jostle for is a budding biotech startup. Given the magnitude and scope of the industry growth, as well as science driven similarities between the two businesses, pharma has been buying heavily into young biotechs. So heavily in fact that Big Pharma became the major force behind an 85% increase in 2009 biotech funding.<sup>4</sup> In these acquisitions, joint ventures, and partnerships, pharma brings to the table operational funds as well as powerful branding, marketing, and distribution tools that the small biotechs cannot provide on their own. Recent examples of this include Sanofi-Aventis snatching up Genzyme as well as partnering with Glenmark Pharmaceuticals in a \$663 million development pact. Seizing upon such diversification opportunities, and expanding into pharmerging markets, Big Pharma is banking that a drop of market share gained today will result in a torrent of revenue down the road.

The second market trend on the mind of biotech startups is the rapidly increasing customer base. For example, both the United States and China have aging populations, and this demographic shift inevitably increases demand for healthcare. Both societies are living longer, and proportionally, their populations are increasingly over the age of fifty, a milestone after which healthcare increases in priority and expenditure. China, even more so than the U.S., will face this issue. Although baby boomers comprise a significant generation, the population control efforts of China – most notably the two child per family limit – has pronounced this gradient for the Chinese.

Given the macro state of life science companies today, and how future trends will affect biotech, market conditions are ripe for growth, and opportunistic monies are betting on startups – “According to a July 2010 PricewaterhouseCoopers report, venture capital investment in U.S. biotech during the first half of 2010 increased 49 percent compared with the previous year, with \$7.7 billion invested and a 23 percent increase in the number of deals.”<sup>5</sup>

Although the funding trend regained its energy since August of 2008, the typical biotech start-up lifecycle is brittle and more often than not, a short lived exercise. Many obstacles threaten their success, and limited budget. One of the greatest challenges for a group determinedly focused on R&D is the regulatory environment. It is often difficult to prioritize resources for compliance with the whirlwind of other problems associated with kicking off a business.

Start ups worry first and foremost about running out of capital before generating revenue – or at minimum, in lieu of revenue, value adding intellectual property that increases future cash flow potential and thus their valuation and fund raising ability. This being the case, FDA approval is the Everest that most biotechs fail to summit. Often they become mired in retrials or additional study requirements where budgets bleed out followed shortly by reserves. Some must surrender to bankruptcy without knowing whether approval would have eventually been granted. Therefore it is critically important for these startups to remain squeaky clean throughout trials, otherwise they will bog down and prematurely exhaust their capital.

Clinical trials often cost as much as one billion dollars and require around 9 years to complete. If a company fails a

regulatory hurdle in the U.S., much time and money must be invested in correcting the error, and avoiding both of those instances is key to survival. The sentiments of ACSH’s Dr. Gilbert Ross are equally shared by firms and investors:

*Drug development has slowed because of regulatory concerns. Pharmaceutical companies and researchers are facing tighter governmental guidelines, and when faced with that kind of uncertainty, you can’t blame them for withdrawing from drug development instead of being proactive and taking chances.<sup>12</sup>*

Common regulatory concerns for an emerging company include:

1. Documentation – appropriate policies, procedures (SOPs) developed, implemented, aligned with training programs
2. Vendor compliance – vendor oversight management of Clinical Research Organizations, Investigators, Sites, Technology providers
3. Clinical Quality Management System (QMS)- processes, procedures, tools and technologies
4. Corrective and Preventive Action (CAPA) Programs – identification of non-compliance, corrective actions and preventive actions
5. Independent examination of trial-related activities and documents

Benefits to better compliance management:

1. Address compliance concerns by developing high-quality, user-friendly policies, SOPs and streamline business processes
2. Outsourcing clinical trials and other R&D activities has proven to be a cost-effective approach, if managed properly
3. A clinical QMS can track overall processes and help monitor quality and reduce costs
4. Appropriate CAPA programs can lead to improved subject protections and data integrity
5. Inspection readiness programs identify key issues/concerns prior to an agency audit; prepare for FDA meetings with an understanding of Good Clinical Practice (GCP) fundamentals, including compliance and monitoring responsibilities

6. Training programs can address audit findings and other compliance-related issues

deals that would have otherwise been a “win win” for pharma and biotech.

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9. Analysis of current training approach and needs, develop training strategy, incorporate SOPs into training modules and deliver training to clinical R&D/GCP audience

For the foreseeable future, biotech startups will sprout wherever funding can be found. Some will flourish and some will stumble over, among other obstacles, the stringent regulatory environment. A poor compliance record or non-existent compliance program may reduce the value of the firm being acquired or in some cases derail the deal. Pharma is quickly realizing the costs of non-compliance through expensive litigation, damage to the brand, and negative publicity. For a pharmaceutical sizing up potential joint venture or acquisition targets, exposure to past or future non-compliance liability is certainly to be avoided. At the end of the day, non-compliance may sour prospective

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## FDA, EMA, TGA Collaboration

By: Yasmeen Muhammad, CIS Senior Consultant

The United States Food and Drug Administration (FDA) is required by law to conduct regular inspections of manufacturing companies. Because pharmaceutical production and quality control are very important functions, regular cGMP inspections are to be conducted in full compliance with cGMP standards and requirements. With the pharma industry expanding into international markets, the amount of inspections needing to be conducted has increased causing the FDA and other regulatory agencies to fall behind schedule. This calls for a need to have global inspection standards for ensuring the safety, efficacy and quality of the drug products being manufactured.

Recently, the FDA announced that they will be working with the European Medicines Agency (EMA) and the Australian Therapeutic Goods Administration (TGA) to finalize a joint Good Manufacturing Practice (GMP) inspection program for the inspection of sites manufacturing active pharmaceutical ingredients (API). The collaboration is based on a pilot initiative, started in December 2008, which aimed to coordinate inspections of manufacturing sites of importance to more than one of the agencies. The goal of the pilot initiative was to:

- Avoid duplicate inspections of the same API manufacturer
- Utilize the resources for inspections of other API manufacturers
- Increase the number of API manufacturer inspections

With the success of the pilot initiative, the agencies have decided to make the collaborative inspection program permanent.

The program utilizes a database called the “Master List.” Participating agencies enter the names of manufacturing sites of interest and any reports of recent inspections into the database. Other participating agencies can view the database and search for an overlap in sites of interest. If an overlap is found, the agency can request to do a joint inspection. In instances where an inspection has already taken place, the agency may request the report of the inspection performed and either cancel their own

inspection, postpone their inspection or tailor their inspection plan based on the results of the inspection report obtained. The program has allowed for more API sites to be monitored and inspected.

This is not the first time different regions have come together to aid in global harmonization of the pharma industry. Two major collaborations formed are the International Conference on Harmonization (ICH) and the International Organization for Standardization (ISO). ICH is comprised of experts from regulatory authorities and the pharma industry from Europe, Japan and the United States that discuss scientific and technical aspects of drug registration to harmonize and ensure that safe, effective and quality medicines are manufactured globally. ISO is an international standard setting body comprised of representatives from various national standard organizations in over 160 countries that set worldwide industry standards in areas such as quality, environmental controls, safety, reliability and efficiency.

Looking towards the future, the FDA and EMA have already started another collaborative pilot program earlier this year that will allow simultaneous evaluation of quality elements, known as Quality by Design (QbD), of applications that are submitted to both agencies concurrently. If the pilot program shows favourable results, it will be another positive step towards global harmonization in our pharma industry. The FDA, EMA and TGA all stand to benefit from the new collaborative inspection program. These agencies have set an example for other regions to follow in an effort to streamline their cGMP processes and stand out in the global pharma industry.

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