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GDP for APIs New Regulations

The Shift to Monitoring BioPharma Product Quality Throughout Their Lifecycle

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GDP for APIs New Regulations – The Shift to Monitoring BioPharma Product Quality Throughout Their Lifecycle

For years, pharmaceutical manufacturers have talked about the «last mile». With mail order pharmacies, direct to pharmacy / patient channels, and things like orphan drug clinical trials – the «last mile» can be complex – yet largely unregulated.

The other end of the pharmaceutical supply chain, the inbound supply of ingredients, has received more solid guidance from regulators. In 2000, major markets including the EU and US supported the ICH Q7 initiative, by publishing their own guidelines specifically for GMP for APIs. Although GMP guides have included some elements on storage and distribution; the only GDP focused guide was the WHO Guide on GTDP for Pharmaceutical Starting Materials – until recently.

2015/2014 were big years for APIs:

- **2015:** EU Commission's Guideline on GDPs for APIs was published, being the first regulatory binding document on distribution for APIs, not just GMP
- **2015:** Europe, ICH, PIC/S and Health Canada have / or were in the process of writing guidance specifically for drug substances
- **2015:** Brazil and Israel were approved as EU GMP import countries, deemed equivalent to standards of European API manufacturers. They joined Australia, Japan, Switzerland and USA
- **2014:** the EU overhauled GMP Guide Annex 18 to provide 47 pages specifically on APIs

Mark Paxton, CEO of Rx360, the international consortium for safe supply of medicines, said «concern has been growing across all regulatory authorities in all regions about the ability to assure the quality of drugs and their components as they move in international commerce. Thus, collaboration (between regulatory agencies) has increased out of necessity. Implementation of the EU's Falsified Medicines Directive in 2012 has been a catalyst for much of this collaboration.» The US Drug Supply Chain Security Act (DSCSA) of 2013 is the other major overarching guidance.

Timeline of Guidelines for GMP and GDPs of APIs

Guideline	Effective Date
ICH Q7 GMPs for APIs	November 2000
FDA Q7A GMP for APIs	August 2001
WHO GDP for starting materials	2003
EU's Falsified Medicines Directive	2011
US Drug Supply Chain Security Act (DSCSA)	2013
Health Canada GMPs for APIs	November 2013
EU GMP Annex 18 APIs Revision	August 2014
Brazil RDC Resolution #69	December 2014
EU GDP for APIs	March 2015
EU GMP for Excipients	March 2015
ICH Q7 Q&A GMP for APIs (updated post EU Annex 2015 updates)	June 2015
PIC/S GMP, PE 009-12 APIs	October 2015

The references section at the end of this paper includes links to each guidance listed in this table.

Why now?

Gone are the days of focusing on the high-value supply chain from point of manufacture to wholesaler. It's clear regulators, industry groups and the manufacturers themselves want to see better control of the full lifecycle of medicines – from inception to consumption.

There have been too many incidences of people being harmed from lack of quality GMP production of drug substances and quality control in sourcing APIs. The famous Heparin case in 2008 linked 81 deaths and 785 serious

adverse events to the adulterated raw ingredients exported from China. Paxton of Rx360 says «If the global heparin issue in 2008 did anything, it made all of us much more aware that manufacturers need to better understand how starting materials are manufactured. This means not simply knowing vendors of API and excipients, but their suppliers too. In addition, manufacturers need to get ahead of the GDP curve by working closely with their downstream partners to ensure they understand GDP requirements. Often, these partners will not fully understand their obligations. For example, what does it mean to validate a temperature-controlled environment? Simply having a thermostat is absolutely not acceptable.»

From the pharmaceutical manufacturer's business point of view; to prove their products are safe to be consumed to customers and patients, they need the data to show quality control through the entire lifecycle of a product. Today, with a large percentage of medicines requiring temperature control, that evidence is often temperature data. But pharmaceutical supply chains are not simply from point A to B – not any more. In the globalized world of pharmaceutical supply chains, medicines touch many hands, airports, depots, trucks, a pharmacy, then patient.

A practice called Stability Budget is helping pharmaceutical manufacturers combine temperature data across all those hands, or legs of a supply chain, to ultimately provide the evidence that the sensitive product has been safeguarded along the entire supply chain and the patient therefore knows they are using a safe product. To create and manage stability budgets, it's almost imperative to use a central database or platform for all temperature, product and shipment data.

Temperature Control Challenges

But what about before a product reaches final dosage manufacturing? What type of quality control is happening during the inbound supply chain and sourcing of raw ingredients? Warehouses, analytical labs, manufacturing sites, cleanrooms and depots are all part of the drug substances supply chain; and all require environmental control. For example, stability chambers and labs require complete control of temperatures, to push and pull the environment to add stress, or forced degradation, to the API to establish the stability of a molecule.

«Manufacturers need to get ahead of the GDP curve by working closely with their downstream partners to ensure they understand GDP requirements. Often, these partners will not fully understand their obligations. For example, what does it mean to validate a temperature-controlled environment? Simply having a thermostat is absolutely not acceptable», says Mark Paxton, CEO of Rx360.

One of the biggest challenges for APIs is the lack of any stability data, which requires tighter temperature control until the stability limits are understood. In the pack-out process, temperatures can vary considerably for very low temp applications, dry-ice or LN2. APIs can change form as well, they may be manufactured and stored in dry ice conditions, but shipped in liquid nitrogen at -196 °C. Managing these different temperature control requirements is complex. Pharma needs shipping systems and data loggers that can handle all temperature extremes for an entire API supply chain, ideally into final dosage manufacturing to ensure the same types of data sources and ability to statistically compare the data over time.

For example, the API Rifampicin, its bulk raw material (BP/Ph.Eur.) must be stored and transported under nitrogen in an airtight container, protected from light at temperature of ≤ +25 °C. On the other hand, the «API Indinavir is highly hygroscopic at relative humidity above 60%. In the presence of moisture and/or elevated temperatures, the API undergoes conversion to an amorphous material or to a hydrate crystal form and to the formation of degradation products i.e. lactone and several unidentified impurities occur.» 12 Temperatures should be continuously monitored to maintain ≤ 33% at +25 °C or degradation will occur.

Bottom-Line Regulatory Expectations

Basically any company procuring, importing, supplying, manufacturing or exporting active substances is required to follow the new EU GDP for APIs guidelines10 Core principles of these guidelines include:

- **You need a QMS** – «2.1 Distributors of active substances should develop and maintain a quality system setting out responsibilities, processes and risk management principles». The QMS should include records are contemporaneous; deviations from SOPs are documented; CAPAs are undertaken to correct and prevent deviations; and changes that may affect storage and distribution of active substances are evaluated.

Today the pressure is on API suppliers to perform long-term stability studies for their products, and provide more clear temperature requirements stated on the label of each shipment of APIs.

- **You need Quality Agreements** – «6.12. Where storage or transportation of active substances is contracted out, the distributor should ensure that the contract acceptor knows and follows the appropriate storage and transport conditions. There must be a written contract between the contract giver and contract acceptor, which clearly establishes the duties of each party. The contract acceptor should not subcontract any of the work entrusted to him under the contract without the contract giver's written authorization.»

- **One QP responsible** – «3.1 The distributor should designate a person at each location where distribution activities are performed who should have defined authority and responsibility for ensuring that a quality system is implemented and maintained … The one personnel should be trained on the requirements of GDP for active substances.»

- **Accurate, compliant archiving of records, and long-term records of sale** – «4.9 Records should ensure the traceability of the origin and destination of products so all suppliers can be identified.»

- **Effective temperature monitoring** – «5.1 Monitoring devices that are necessary to guarantee the quality attributes of active substances should be calibrated according an approved schedule against certified traceable standards».

- **Prove temperature control in your facilities** – «6.4 Active substances subject to specific storage measures, e.g. narcotics and products requiring a specific storage temperature or humidity, should be immediately identified and stored in accordance with written instructions and with relevant legislative provisions».

Dear API Supplier: Where is your QMS?

As described above, today's APIs have strict temperature monitoring, analytic testing and quality control requirements. The additional requirements are creating a learning curve for many API suppliers. But that hasn't stopped pharmaceutical manufacturers from putting pressure on suppliers since the 2015 GDP API regulations.

Today pharma wants API manufacturers and distributors to provide proof of quality control. Most shipments contain little QC information accompanying the delivery of drug substances to the pharmaceutical company. However, when a massive bulk quantity of a common API can be used for up to five years manufactured into final dosage – how can pharma guarantee its shelf life? Today the pressure is on API suppliers to perform long-term stability studies for their products, and provide more clear temperature requirements stated on the label of each bulk shipment of APIs.

The EC 2014 update to GMP for API makes it clear, «The (API) manufacturer shall monitor the stability of the active substance through stability studies». The regulatory guidance goes further to say «The (API) manufacturer shall issue certificates of analysis for each batch of active substance upon the request of competent authorities, distributors and/or manufacturers of medicinal products supplied directly or indirectly with the active substance.» 8 Question is – why doesn't this QC information make it to the shipping label or purchasing documents?

Recently at the IQPC Cool Chain conference in Frankfurt January 2016, several small API manufacturers from Europe joined a discussion on GDP for APIs. Their intent was clear and evident they wanted to understand the new EU GDP for API regulatory requirements better and asked questions of the pharmaceutical companies to understand their needs. From some API suppliers, education is key. For API suppliers in further regions in Asia, well, that's a whole other story.

Dear Pharma Manufacturer: What Are You Doing to Ensure Quality Ingredients?

Who's responsible for ensuring your APIs are quality controlled from inception? What about on the way to your facility – is that the responsibility of your 3PL or specialty courier handling temperature controlled vats of biological APIs? How involved in the process do you get as a pharma manufacturer beyond basic GMP qualification of API vendors?

Rx360 has commented, «previously, unless there was a potential for degradation, manufacturers did rely on their couriers' processes and procedures to handle their acquired API and excipients. However, with the increased thermal sensitivities of many materials, assumptions can no longer be tolerated. Moreover, due to the unacceptable risk associated with diversion, manufacturers are requiring – as are the medicines regulatory authorities – documented accountability; both to ensure the materials are in fact what they purport to be, and to ensure they

have been properly and securely handled. This is an area where implementation is just beginning, but assuredly is expanding at an increasing rate.»

Note to Drug Manufacturer: Manage the API procurement process in a more controlled manner. These new regulations are prescriptive, but not descriptive. Like any partnership, communication is key. Clearly set out Quality Agreements and contracts detailing who is responsible for each leg in the supply chain, who's monitoring the regulated produced – who overall is responsible for appropriate transport conditions?

Beyond the mandatory Quality Agreements, what else can pharma do to ensure quality control of their drug substances?

- Choose the right supply chain partner and shipping solution. However, some pharma practitioners say there are not many options for bulk shipping systems.
- Ask your courier or 3PL if they perform lane qualifications, have they qualified lanes that you will be using?
- Ship by sea for low value API. But caution, the reefer needs to be full to ensure complete circulate and effective temperature control.
- Can API suppliers send smaller quantities? Why not sell at bulk prices, and offer pharma fees to hold stock and ship as needed? Is a «consumption model» a future scenario for this niche industry?

Stability Budget – a Solution for a Drug's Lifecycle?

A stability budget is a methodology that assigns each leg of a product lifecycle or supply chain, a certain amount of stability data. So instead of shipping strict +2 °C..+8 °C with no variables or allowances; rather you allow each leg of the supply chain some lenience to use a small part of a stability budget – thus reducing temperature alarms, QA investigations and wasted resources.

However, drug substances and APIs have little stability data available. Therefore they wouldn't be factored into a stability budget. But when do drug substances become a finished product? Is there a gray area when stability of a «product» starts and stops?

So called «warm times» occur during fill finish. According to FDA Drug Security Act and EU GMP Annex 15 – any and all GMP environments must be quality controlled, which most often means temperature monitoring of cleanrooms and biological processing rooms.

Do these «warm times» slip under the purview of Quality Assurance groups? With increasing regulatory pressure for monitoring from ingredients through manufacturing to patient – these «warm times» will surely become underscrutiny as well. Question is – who's going to connect the dots through the lifecycle, create and use a stability budget to guarantee to patients downstream that their medicine is safe to be consumed?

Bottom line? Overall, regulators are looking for pharma to map their entire supply chains from the sourcing of integrediants through R&D and manufacturing supply chains. Don't leave any stoned unturned, so to speak.

Conclusion

Standards across drug substances manufacturers can vary around the world. But today, there is clear guidance from not just a couple major markets, but several global standards agencies that API manufacturers must bring their facilities, methods, processes, systems and controls into compliance with GDP and GMP standards, or pharmaceutical manufacturers won't do business with them.

Every step in the drug's lifecycle must be quality controlled, monitored and documented. Where is the proof that the drug substances have maintained required temperature specifications, or that transport conditions have been met? Regulators are asking for this evidence now.

One of the newest guidance documents, EU GDPs for APIs, reflects those already published since November 2013 for finished product. Some might say, what really is new? Yet, the fact that the EU, other major market

regulators and international standards bodies have recognized the need for guidance tracking back to the ingredients of medicinal products, clearly demonstrates that the pharmaceutical manufacturer, and their suppliers, are now not only ethically, but legally required to monitor the quality of medicines throughout their full lifecycle – from inception to consumption.

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