DISTIBUTION CENTRES: WELCOME TO THE DANGER ZONE

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THE DISTRIBUTOR:

- A distributor, broker or agent is a type of supplier requiring evaluation and approval like any other supplier though they are merely a conduit between the actual supplier and the manufacturing company.

- Auditing and approval of a supplier does not replace the need to audit and approve the distributor, NOR does the audit and approval of a distributor, broker or agent replace the need to approve the manufacturer/supplier of the starting material.

DISTRIBUTORS ARE MERELY PART OF THE PEDIGREE:

- **Basic Premises Based on the WHO, IPEC and GDPs:**
  1. Excipient Users obliged to know complete supply chain.
  2. Distributors are therefore an extension of the supplier.
  3. Distributors include all parties involved in trade and distribution, (re)processors, (re)packagers, transport and warehousing companies, forwarding agents, brokers, traders, and suppliers other than the original manufacturer
  4. Excipient Makers, Users, and Distributors need to cooperate to make this work

EXACTLY WHAT DOES COOPERATION IMPLY:

- The Quality Agreement between original supplier and the customer must include the possibility of a distributor being used as an intermediary.
- In that case, an agreement must include requirements for periodic checks of the distributor to be performed not only by the supplier but by the customer as well and the distributor must be signatory to this agreement.
- The Quality Agreement must contain specific clauses as to how the good are to be received. Whether repackaging is permitted, along with specifics on how the distributor's FIFO system will operate.

ROLE OF THE SUPPLIER:

- **Raw Material Supplier:**
  1. Follow IPEC GMP and GDP, and provide COAs according to IPEC COA Guideline
  2. If a distributor is used, confirm on request, that the material was shipped to the distributor by alerting the customer of the date and time of the transfer.
  3. Periodically audit distributors used for adequate GDPs and contamination control using the IPEC GDP Guideline as the basis
  4. Conduct mock recalls to assure procedures utilized by the distributor are capable of performing during a real-life situation.

ROLE OF THE DISTRIBUTOR:

- Comply with IPEC GDP and other appropriate regulations as stipulated by the supplier and customer.
- Provide to the Customer, on request, chain of custody documentation (e.g. bills of transfer with financial data redacted)
- Provide appropriate COA with each shipment
- Conduct mock recalls to assure procedures
- If a holding tank is used can only contain shipments from the same manufacturer's site or terminal
- Have an effective change management program with customer notification
- Be able to demonstrate the secure separation of materials to prevent any accidental or intentional cross contamination.

ROLE OF THE CUSTOMER:

- Bears the final responsibility for all excipients used
- Audits or uses a qualified third party to audit all suppliers and distributors
- **On a periodic basis verifies the chain of custody**
- Performs appropriate testing once the materials are received to ensure identity. (Unfortunately this does not ensure against mixing of grades of an identical material.)

ONUS ON THE CUSTOMER:

- Must demonstrate that the material has gone through the expected distribution channel
  1. Need to track that other parties weren't involved in the transfer, holding or storage of materials for any extensive period of time that cannot be accounted for.
- Original manufacturer's and distributor's shipping papers (BOL minus pricing info) should be received and checked by user.
  1. Need to ensure that the documentation has not been altered in any manner.
- Periodic Site audits of manufacturers and distributors to verify paper trail
  1. Need to follow the paper trail exactly as it is recorded in the supplier and distributor documentation. Any variability is suspicious.
- Can be done by user or a qualified third party audit.
  1. Being a special kind of audit, it requires an investigative approach not normally exercised by audit teams. Tends to be more of a forensic nature.

THE CHINESE DISTRIBUTOR MARKET:

Sourced from an article originally published in MED TECH INTELLIGENCE 2017.

- The supply network in China is often multi-tiered and managed by large or mid-sized distributors that generate relatively high margins. Sub-companies of sub-companies.
- China's government has recognized the need to consolidate the fragmented market and to improve supply chain transparency.
- In December 2016, China's State Council issued the "Two-Invoice System" policy in hopes to eliminate sub-distributors and other intermediaries from the supply chain. (Primarily Medical Devices)
- In the long term, existing large and medium-sized distributors are expected to dominate the market under the new Two-Invoice System, while smaller, domestic distributors and sub-distributors will be forced to exit.

THE DISTRIBUTION LAYER:

- The Distributor layer in China is extremely fragmented with over 13,000 distributors, most of whom only supply a local market. The three largest distributors, Sinopharm, Shanghai Pharmaceuticals and China Resources only account for 20% of the market. With a landscape of multiple channels, layering of distributors and multiple handoffs before reaching the final destination, the potential for error is exponentially increased at each exchange.

VISIBILITY OF THE DISTRIBUTOR SUPPLY CHAIN:

How Does One Audit this Chain When:

- Uncovering the beginning to end supply chain visibility is a major challenge in China.
- Visibility often disappears once suppliers hand off to their immediate distributors.
- It is essential that Distributors have an IT system that adheres to Good Supply Practices (GSP) but this is not always the case.
- But the fact that these IT systems are not integrated throughout all the layers of distributors means that the actual flow and volume cannot be traced.

From ATKEARNEY 2017-04-25

DISTRIBUTORS MUST NEVER:

- Automatically replace material from another supplier
- Upgrade Material
- Label non-GMP material as compendia grade based on testing
- Mix generic products in with original products.

ISSUES WITH DISTRIBUTORS:

- Capacity and Inventory Planning

  1. Specifically this has to deal with conflict of interest. As distributors are not normally bound to the particular customer of the supplier, their intent is to move product in and out as quickly as possible in order to generate profit. Therefore, it may often be a case of first come, first serve and even though the quality agreement between customer and supplier may assert a frequency and quantity of shipment, that may not always be met.

REPACKAGING:

- If a starting material has been repackaged or relabeled and not supplied in the original actual manufacturer packaging, the repackaging operation must be fully compliant with the PIC/S Guide to GMP – Part II, Section 17
- If repackaging is performed, it must be agreed to by all parties in the Quality Agreement and assurances of transfer error are dealt with accordingly.
- It is unacceptable for results from a starting material manufacturer's Certificate of Analysis to be transcribed from the original to another supplier's letter head.
- If goods are received in which the original seals of bottles have been broken, then it cannot be assumed that the contents have not been tampered with.

ISSUES WITH DISTRIBUTORS:

- Counterfeit Goods Are Usually a Final Product Concern But Now Entering All Phases of the Product Development Chain:
  1. Example Corning Conical Tubes
  2. Pharmaceutical raw materials manufacturers are negatively affected by counterfeiting. As a result, medicine surveillance services and fake - identification technologies such as mass spectrometry (MS), infra-red (FTIR) spectroscopy, nuclear magnetic resonance (NMR) spectroscopy, Raman spectroscopy, and gas chromatography-mass spectrometry (GC-MS) are gaining prominence (from SpendEdge Report)
  3. In late 2013, Chinese authorities reported detaining 1,300 suspected counterfeiters and confiscating $362 million worth of fake drugs and raw materials. (2019 HealthResearchFunding.org)

REPORT FROM CORPWATCH 2018-12-06:

- “Pharmaceutical ingredients can pass through three or four trading companies, none of which check their quality. The ultimate manufacturer may not realize the ingredients came from an uncertified chemical company.”
- "It is unrealistic for us to certify all factories that make intermediates and regulate them like medicine products," said Ms. Yan, the Chinese Drug Agency official. “But if companies make active ingredients, a more refined product, then they must be regulated by drug authorities,” she said.
- "Under-regulated manufacturers are increasingly becoming the source of A.P.I.'s used in the production of counterfeit medicine," R. John Theriault, former head of Pfizer's global security
- "We have never investigated a chemical company," said Ms. Yan, deputy director of policy and regulation at the State Food and Drug Administration. "We don't have jurisdiction."

TRACEABILITY:

- the supply chain for each starting material procured through a distributor, broker or agent should be traceable to the actual manufacturer of the starting material. All receipts, transfers, bills of lading must be obtainable and original.
- Where supply is through a distributor, broker or agent, the actual manufacturer/producer of the starting material should be included in the starting material specification (refer to PIC/S Guide to GMP, Clause 4.14) and included in the supplier approval process.

HENCE THE IDENTITY TEST:

Reliance on the identity test is one of the only means by which we can have any reassurance that materials have not been tampered with and is the reason that regulatory agencies are insisting for excipients that each bottle in a lot be separately tested but…

1. If an analytical grade product is mixed into a pharmaceutical grade material it will not be identified by the test.

2. As sampling is normally taken from the top of a container, any foreign material may be missed if it was packed at the bottom.

3. Tampering of liquids can often be performed without any evidence of breaking the original seals.

IDENTIFY RELIABLE DISTRIBUTORS:

Customers and Suppliers should work together to find a suitable distributor that is identified in their Quality Agreement. Possible means are through recognition programs or search agencies.

- **VAWD**, the **V**erified - **A**ccredited **W**holesale **D**istributors Program
  1. It was established in 2004 to help safeguard against the threat of counterfeit drugs.
  2. This program was developed and is administered by the National Association of Boards of Pharmacy and offers an objective, third-party audit system.
- **Pacific Bridge Medical**
  1. A contracted agency that has intimate industry knowledge and extensive on-the-ground presence to identify and qualify the best distributors in Asia.
  2. Conduct screenings of potential distributors to evaluate whether they are a suitable and competent.
  3. Client list based on 30 years of experience in Asia.

IN CONCLUSION:

- As we've seen over the past few days, maintenance and security of the supply chain is critical to the success of any manufacturer but the impetus to secure that supply chain is with the manufacturer themselves. The only way they can secure the supply chain is through an intensive and reliable auditing procedure that does not rely on others to provide information to satisfy the requirement of the regulatory agencies that the manufacturer exhibits control at all time. The only way that control can be demonstrated is by being an active participant in every phase of the transfers and holding facilities of the supply chain. Yes, this places a higher demand on the ability to audit and to be more precise, the ability to audit properly. In far to many instances, audits are seen as a necessary pain and not treated with the respect they deserve.

SEMINAR SIX COMPLETED

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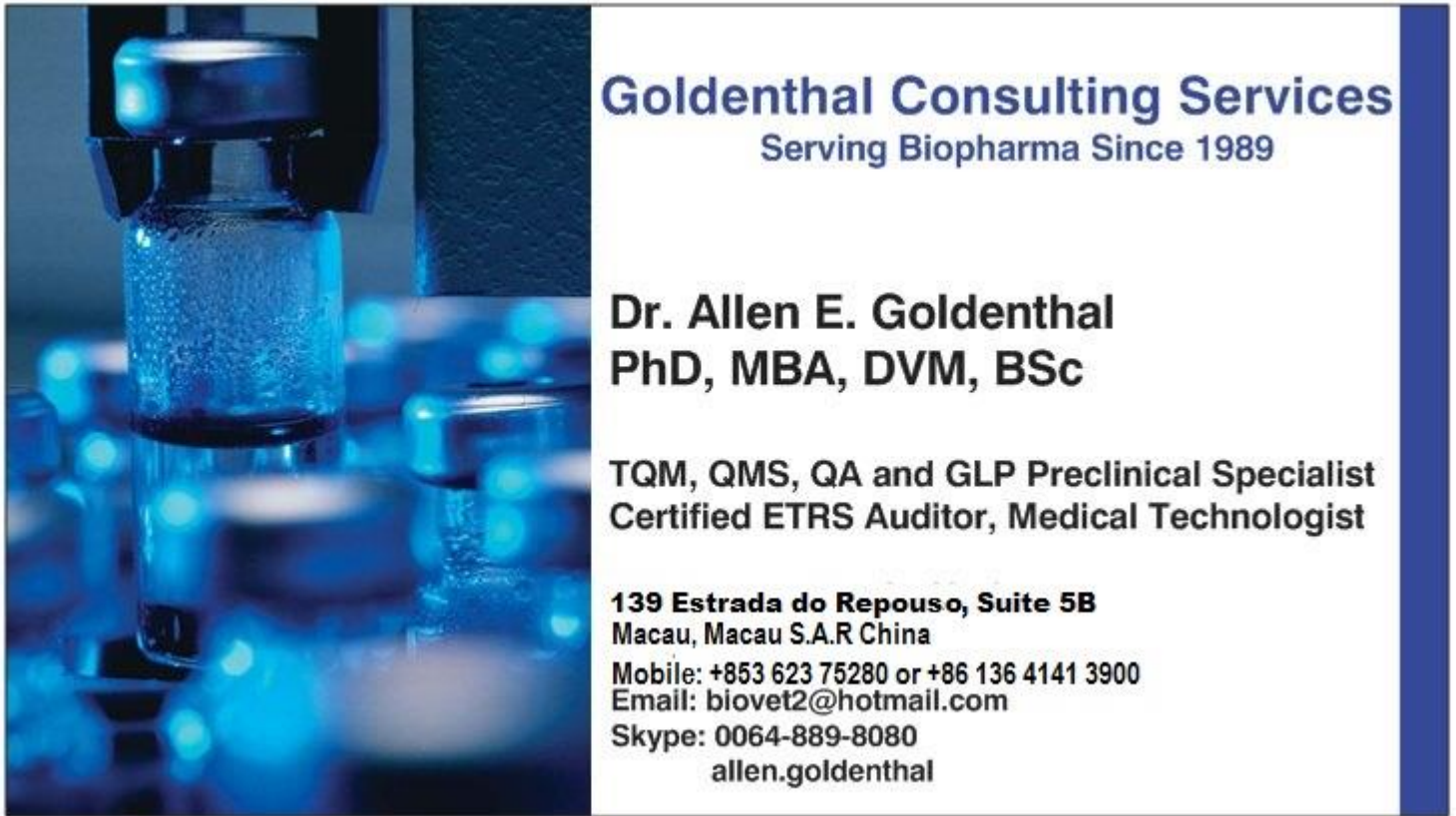

TIME FOR WORKSHOP #2:

PROBLEM 1: Your vaccine manufacturing facility performs none of its own animal testing. Everything is sent to a CRO with a fairly good reputation.

One of the release tests is a modified UP-DOWN LD50 type test in which animals receiving the highest titration dose intracebrally can have no more than two of the four mice die in that group to be passed.

All four mice in the high dose group die, the test is repeated and this time the result is as expected and the test is signed off as a pass. As the company auditor from the manufacturer, you are on-site and you uncover this information, not having any knowledge that the test failed the first time. You examine their investigation report and see that they concluded they could not find any fault with the performance of the initial test and therefore suspected the issue was most likely a subacute illness that afflicted the first group of mice from their SPF colony and therefore the test could be repeated.

Examining their argument, what do you conclude regarding the way in which this was managed and what concerns do you have regarding the CRO in general?

TIME FOR WORKSHOP #2:

PROBLEM 2: An FDA Warning Letter was recently issued to a contract testing lab that contained a clear warning:
in Warning Letter No. 12-NWJ-12, dated February 17, 2012, to Biochem Laboratories, Inc, the Director of the New Jersey District wrote the following:
"In your response, you state that you have informed your clients on the importance of validating the methods, but they have chosen not to validate the methods. In addition, you state that you will inform them again in writing. Your response, however, is inadequate because you do not provide your firm's planned corrective actions for this CGMP violation. You are responsible for ensuring that the test methods used by your firm are validated."

There are several issues here that need to be discussed. Superficially it sounds like the FDA is holding the contract lab responsible but who is ultimately responsible for method validation?

As the client vaccine manufacturer referred to in this letter, what are your thoughts on this issue as to ultimate responsibility and what are the positive/negative perspectives as an outcome of the FDA's consideration of this matter in their final statement?