Supply Chain of 503b Pharmacies

Setting the Stage

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Comments from MHRA

"MHRA continues to note concerted efforts to falsely obtain stock by some parties from suppliers, and has undertaken targeted inspections of supply chain integrity, resulting in cases of regulatory and enforcement action."

MHRA Blog May 8, 2019

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Comments from MHRA

"Further emerging trends have been observed by MHRA around criminal attempts to sell falsified and stolen stock into legitimate supply chain by a variety of methods. This creates the prospect of patients being supplied with substandard medicines, by way of gaps in the qualification process of suppliers."

MHRA Blog May 8, 2019

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Falsification of Companies

Companies form based upon a mirror image of the legitimate firm. The emails are hyphenated or gmails. The webpages appear to be authentic. Licenses are falsified.

Companies sell and then transfer their license to a new owner, which then delivers falsified drug substances.

The EU is powerless to verify these changes.

MHRA Blog May 8, 2019

Back in the USA

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Requirements in FDA's Guidance Document

APIs - Assay and ID as per 21CFR211 on qualification of supplier; subsequently, use only the supplier CoA

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Excipients – Qualification of Supplier followed by supplier CoA

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Label Submission – Names of raw materials should be listed on FDA's Substance Registration system

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Requirements in FDA's Guidance Document

The FDA Guidance Document allows the acceptance of the Supplier CoA as long as the following requirements have been met:

1. **Perform a paper review of the supplier's SOPs**
2. **Confirm the supplier's test results**
3. **Confirm that ingredients meet USP/NF, if possible**
4. **One ID test on each incoming lot**
5. **Specifications conform to ICH Q6a**

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Requirements in FDA's Guidance Document

Additional Points:

Each container must be inspected to verify appropriate labeling recognizes the contents

The package integrity must be evaluated prior to use

Requirements in FDA's Guidance Document

Additional Points:

ICH Q6 allows skip lot testing, including microbiology

Pharmacy must determine proper testing of APIs and excipients so that it meets their final product specification requirements

And Away We Go

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Issues

Known Problems

1. Not every container of a product shipment may contain what is stated on label. (Salt vs KCl, Glycerin vs DEG)
2. Pharmacy must verify that the raw materials are listed under an approved NDA/NDC
3. Pharmacy purchases cheaper chemicals and fills quantities into "approved API container"
4. Industry purchases APIs and Excipients that reference older version of USP

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Issues

Known Problems

1. **Supplier has not registered all manufacturing facilities with FDA, thus supplying chemicals from a non-registered facility.**
2. **Drug Listings are not an approval by FDA for the product. Firm listing the drug product is responsible to ensure compliance.**

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Excuses

1. Testing takes too much time as customer needs product tomorrow -
2. Testing is too expensive – my patients wont pay the cost
3. We didn't select the right test specifications, because these were easier
4. We forgot
5. The lab didn't do the test
6. We forgot to list that test on the chain of custody
7. The lab cant do that test
8. The sample got lost in the mail/transport

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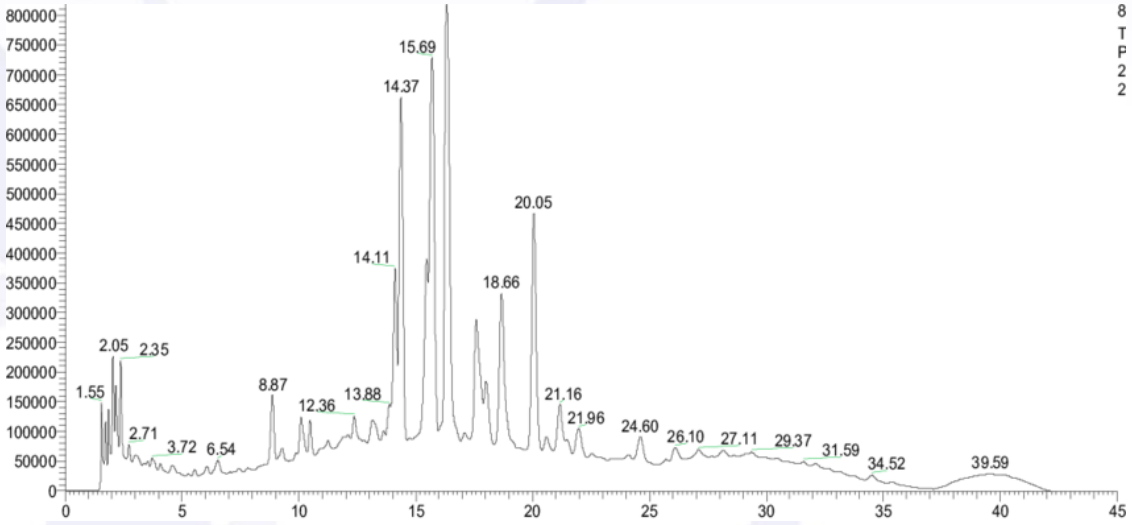
Opportunities for Failure

1. Testing Glycerin ID test (DEG?)
2. Assay results where the API tests higher than the USP standard (More pure than USP PRS)
3. No testing for impurities during processing



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Requirements in FDA's Guidance Document

Additional Points:

Non-sterile ingredients, including water, used in sterile products, must be tested for microbial and endotoxins

Sterile water can be obtained and not tested, with proper CoA for its intended use

Sterile Water for Injection vs Sterile Water for Irrigation

Requirements in FDA's Guidance Document

Additional Points:

Retest not needed if stored under label claim and used within expiry date

Retest and internal expiry dating required if stored for post expiry date and in conditions outside of label claim

Issue: Storage of ingredients under refrigeration losing water

Requirements in FDA's Guidance Document

Additional Points:

Pharmacy must develop Supplier Quality Agreement and include such systems in the QMS

a. List testing prior to release to 503b Pharmacy

b. Testing records, including spectra and chromatograms with CoAs

c. Change notice commitment

d. Supply chain management if the supplier is not the original manufacturer

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Requirements in FDA's Guidance Document

Additional Points:

No testing required:

a. **Purchase listed raw material**
b. **Each label examined for verification**
c. **No recalls have occurred**
d. **Package integrity has been verified**
e. **Not repackaged**

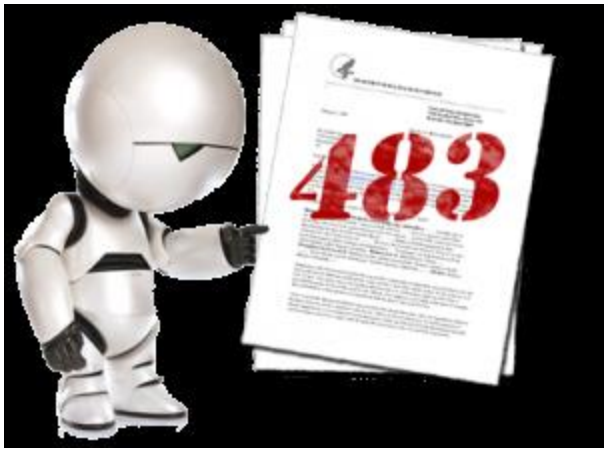
Requirements in FDA's Guidance Document

Issues:

41% of drug recalls are from drug repackagers over last 5 years

27% or 1002 Recalls are from 2 drug repackagers –

a. **Cross contamination**
b. **Label mix-ups**



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Group Questions

1. With known issues, what risks to patients exist with the current plan/program?
2. With limited testing and high costs of manufacturing compounded products, what additional cost cutting opportunities can be achieved?
3. With the ability to provide more personalized medicine through Outsourcing Facilities, what additional benefits can be obtained by streamlining supply chain?
4. What information should be required of upstream and down stream of the raw material to the final product by each group connected to the raw material or finished goods – raw material manufacturer, repackager, relabeler, further processing, 503B pharmacy, end user? Include EPA and OSHA requirements.

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