

CVM Evaluation of Drug Manufacturing

What Is Behind That Label?

22ND ANNUAL U.S. FISH & WILDLIFE SERVICE
AQUACULTURE DRUG APPROVAL COORDINATION WORKSHOP
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Why is there a CMC section?

To assure that the drug sold to the public will have quality attributes similar to those of the drug demonstrated to be safe and effective

To assure that the drug consistently meets appropriate quality standards

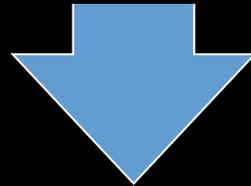
To assure that the drug you are using is the drug described on the label



Drug used in clinical studies
Safe and effective



CMC helps maintain the connection in quality
between the drug used in clinical studies and the
marketed drug



Drug marketed to consumers
Commercial product

Clinical Batches

Safety and effectiveness studies

Pilot Batches

CMC information

Engineering Batches

Scale-up from pilot to commercial

Process Validation Batches

Implementation of commercial manufacturing processes

Commercial Batches

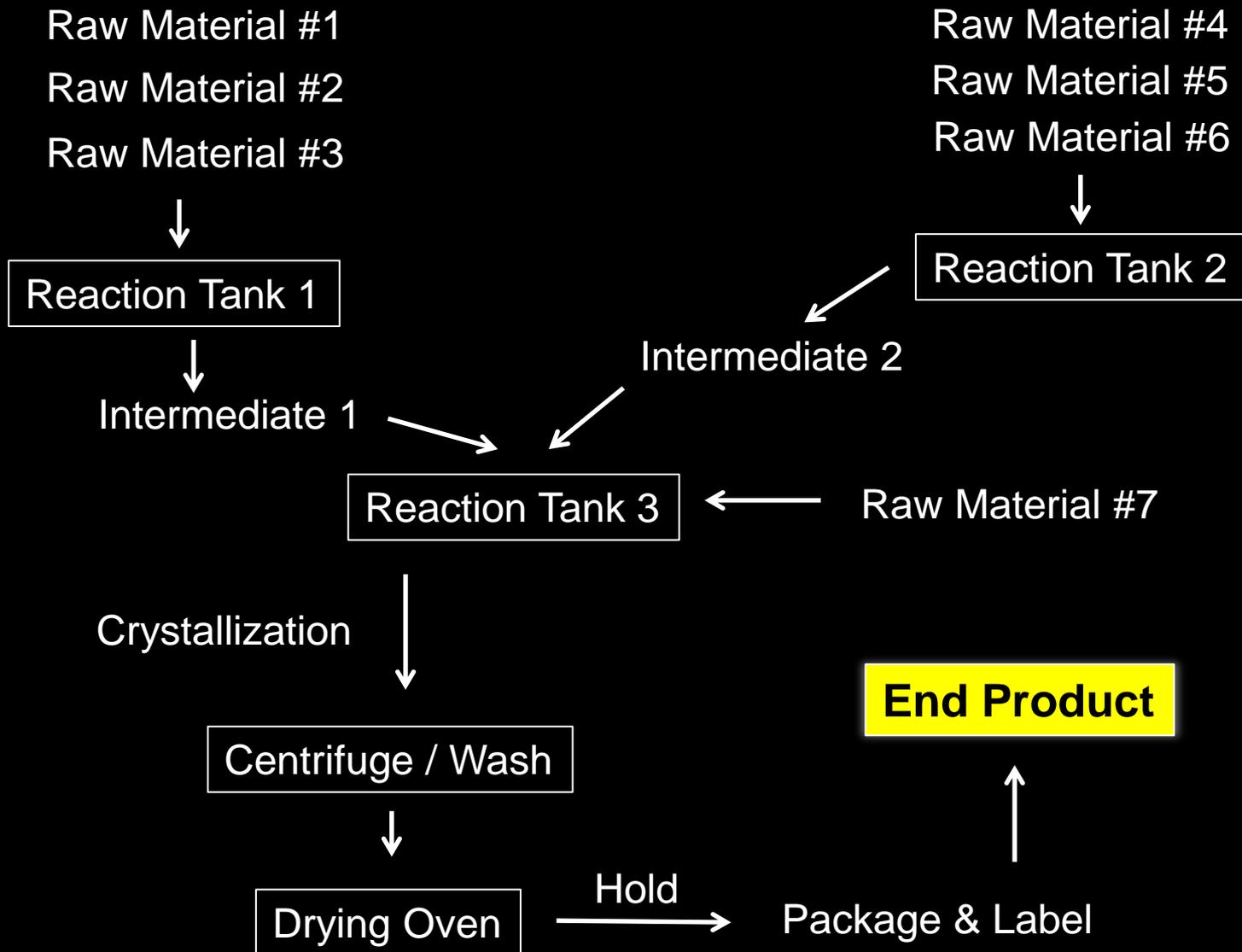
Product marketed to consumers

Batches at each stage should be made using the same or similar processes and raw materials

The formulation and manufacturing processes (including manufacturing sites, raw material suppliers, test procedures, etc.) should be the same for pivotal clinical batches, pilot batches submitted in the CMC technical section, and commercial batches.

Manufacturing changes need to be supported by CMC data, and in cases where manufacturing data are insufficient to support comparability, by clinical bridging studies.

Testing the End-Product is Critical



End Product

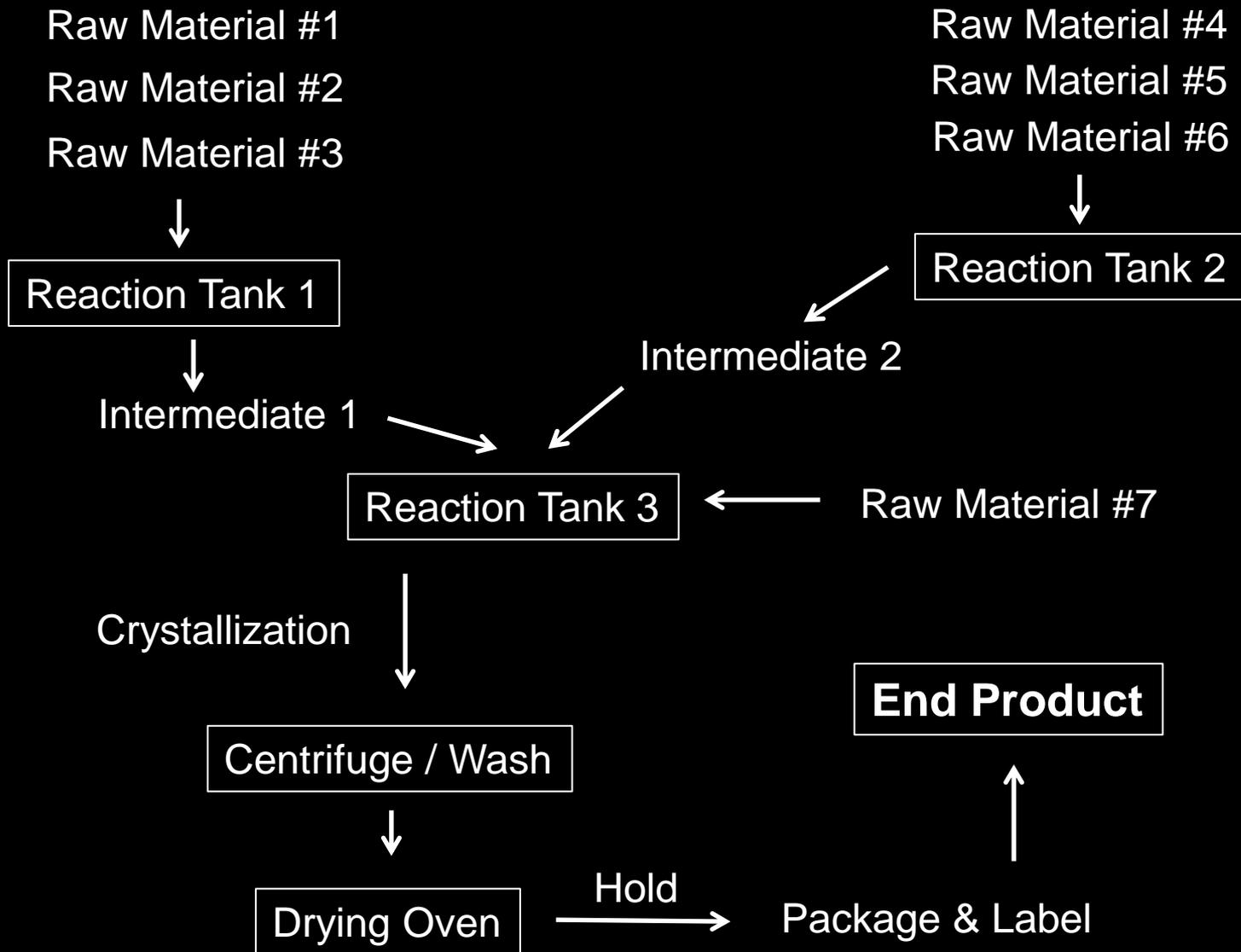
“Release tests”: A set of tests conducted on the end-product as a final check on the batch before the batch can be “released” for sale.

Release tests should evaluate characteristics critical to the safety and effectiveness of the product, e.g., potency, impurities, solubility, drug release rate, microbiological contamination, adventitious agents, etc.

The tests and acceptance criteria (what constitutes pass/fail) should be proposed, justified, and supported by data in the drug application. For example:

- What test method is used to measure potency of the product?
- Does the complex nature of the product (e.g., crude tissue) mean that chemical tests alone are insufficient to measure potency and that biological activity should be measured?
- Is the potency method capable of accurately measuring potency in the presence of impurities and degradants?

Manufacturing Process



Manufacturing Process

Testing the end-product is necessary
but by itself is insufficient

- Relying on end-product testing is an ineffective and inefficient way to control product quality
- A manufacturer that understands and continuously reevaluates their manufacturing process is better equipped to maintain or improve product quality and consistency
- When a problem arises, manufacturers that understand their process can conduct systematic investigations into what caused the problem and determine how to fix it

What assumptions are you making if you rely solely on end-product testing?

Assumption: Your sampling procedures are adequate to catch all problems.

Reality: Sample size is limited - How many units or containers in a batch can you sacrifice to testing?

Assumption: Your test methods are sensitive enough to catch all problems.

Reality: Test methods have limits in their detection capabilities – combined with sampling limitations, how badly would something need to go wrong before you can detect it?

Assumption: You have anticipated all manufacturing problems and have developed a test to detect each of them.

“...as we know, there are known knowns; there are things we know we know. We also know there are known unknowns; that is to say we know there are some things we do not know. But there are also unknown unknowns – the ones we don't know we don't know...”

Donald Rumsfeld, Secretary of State
February 2012, Pentagon Briefing

Reality: The limited set of tests performed on the end-product are a critical final check, but alone cannot anticipate, prevent, or detect all possible problems that can and will happen during the manufacturing process over the commercial life of the product.

“Inspection does not improve the quality, nor guarantee quality. Inspection is too late.

The quality, good or bad, is already in the product.

As Harold F. Dodge said, ‘You can not inspect quality into a product.’”

W. Edwards Deming

Manufacturing processes change...

- Raw material suppliers
- Manufacturing sites
- Manufacturing processes
- Manufacturing equipment
- Packaging
- Specifications
- Testing procedures

...but product quality should be constant
(or improve with experience and understanding)



“There is nothing
permanent except change.”

Heraclitus

A Drug's Commercial Life

1999:
Drug
batches
are made
for clinical
studies



2005:
CVM
approves
the drug for
marketing



2006:
First commercial
batches are
manufactured and
sold to the public



Clinical
studies
demonstrate
that the drug
is safe and
effective



2008:
Drug product
manufacturing
moved from
New Jersey to
Missouri

2010:
Product
expiry
extended
from 12 to
24 months

2013:
Changed
supplier of
container-
closure

2016:
Active
ingredient
manufacturing
moved from
UK to China



2011
Modified the
manufacturing
process to
improve
efficiency

2015:
HPLC method
replaces
microbiological
method to
assay drug

Summary:

17 years ago, safety and effectiveness studies were performed using a drug product made in New Jersey and the active ingredient made in the United Kingdom.



Today, the drug product is made in a different facility using different procedures and is marketed in a different container, and the active ingredient is made by a different company at a new site.

- What changes, if any, happened to the impurity profile?

- Does the new assay method accurately measure the drug?

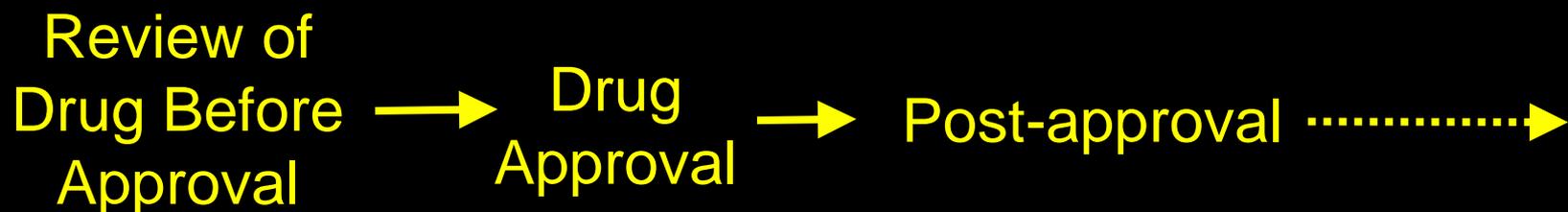
- Is the product stable in the new container-closure system throughout the labeled shelf life?

- Are new suppliers providing raw materials of comparable quality?

- Are meaningful controls and checks being made throughout the manufacturing process at the new sites?



The drug sponsor must report CMC changes to CVM for as long as it owns and markets the product



**CVM reviews CMC changes
and
stability data from on-going studies**

Reporting Post-Approval Changes to CVM

Potential adverse impact of change

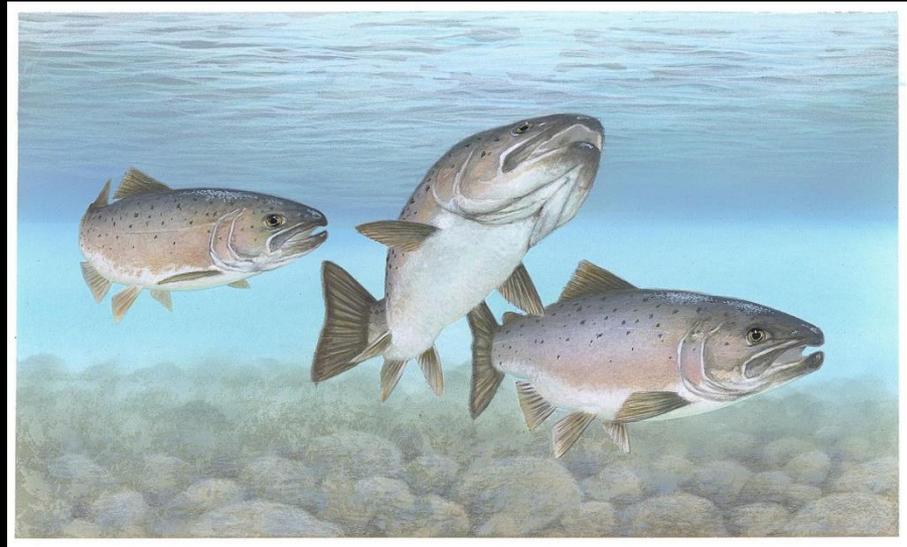
High



Low

- **Prior Approval Supplement**
- **Supplement – Changes Being Effected in 30 days**
- **Supplement – Changes Being Effected**
- **Minor Changes & Stability Report**

Clinical studies show the test article is safe and effective.



The CMC technical section helps ensure the commercial product is also.

Are regulatory standards for the
manufacture of aquaculture drugs
too stringent?

Is it important for aquaculture drugs
to be made under
Current Good Manufacturing Practices?
(cGMPs)

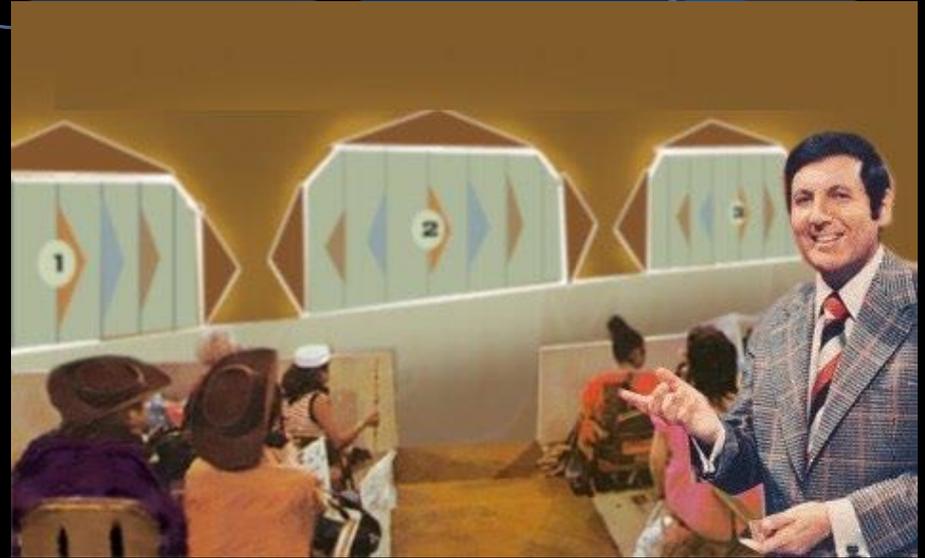
Let's Make a Deal!

(Aquaculture Drugs Edition)



Let's Make A Deal!

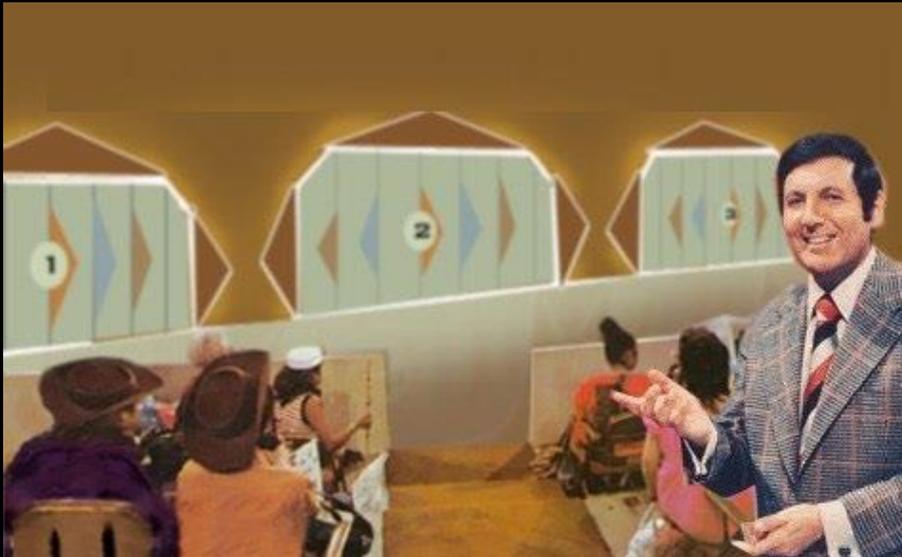
(Original Version)



Contestant must choose one of three closed doors without knowing what's behind them
...and gets whatever is behind the chosen door.
A new car? A TV? A gag prize?

Aquaculture Drugs Edition

- You need to buy an antibiotic to treat the fish at your aquaculture facility
- You have 3 manufacturers to choose from
- Behind Labels 1, 2, and 3 are the different manufacturers, each making the same antibiotic



Which Label
Do You Pick?

Additional Information!

Each manufacturer has subjected their drug to the same set of release tests, and according to their test reports, all three drugs pass all tests!

Label #1

Certificate of Analysis

Test 1: Passed
Test 2: Passed
Test 3: Passed
Test 4: Passed
Test 5: Passed
Test 6: Passed

Label #2

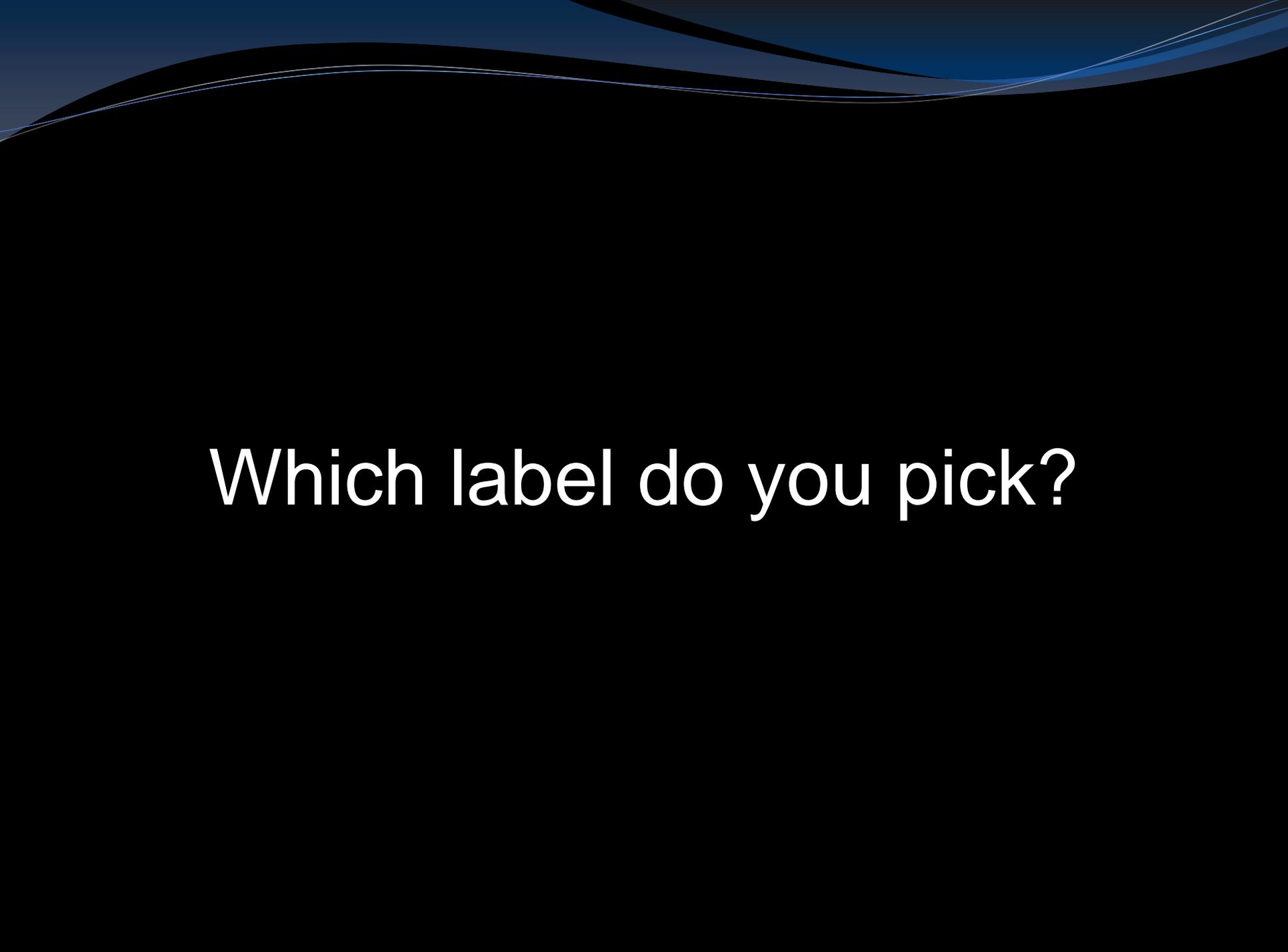
Certificate of Analysis

Test 1: Passed
Test 2: Passed
Test 3: Passed
Test 4: Passed
Test 5: Passed
Test 6: Passed

Label #3

Certificate of Analysis

Test 1: Passed
Test 2: Passed
Test 3: Passed
Test 4: Passed
Test 5: Passed
Test 6: Passed



Which label do you pick?

What's Behind Label #1?



Manufacturer behind Label #1:

- Maintenance and sanitation at facility is poor
- Effectiveness of equipment cleaning is never verified, and no records are kept of when equipment is cleaned or calibrated
- Procedures are modified by employees based on their personal experience (e.g., written on Post-It Notes next to work station)
- Key manufacturing parameters (e.g., how long to mix ingredients) are based on employee intuition and not supported by objective data.
- Successful conduct of manufacturing relies on the experience of a few knowledgeable individuals, and procedures are not clearly documented.
- Test methods are assumed to be accurate, but not verified
- Customer complaints are not recorded or followed up
- Due to inadequate production records and lack of systematic investigations, attempts to determine the causes of quality issues fail, or are addressed by trial-and-error corrective attempts, or default to blaming employees instead of the system
- Employees run away or hide facility records when third party auditors arrive

What's Behind Label #2?



Manufacturer behind Label #2:

- Facility has adequate lighting, ventilation, plumbing, and sanitation
- Equipment is routinely checked to ensure proper operation, and cleaning procedures are shown to be effective
- Incoming components, containers, and closures are quarantined until their quality for use has been verified
- Procedures are clearly written, and personnel are properly trained
- Accuracy of test methods are verified
- Manufacturing process is supported with data, and key manufacturing steps are monitored with in-process controls
- Productions records document what, when, who, how, and where
- Shelf life and product quality are monitored by on-going stability studies
- A quality control unit reviews procedures, records, and test results
- Customer complaints are documented and addressed
- Investigations into quality issues determine root causes and result in successful corrective actions

From which manufacturer do you want to buy your antibiotic?

Which manufacturer do you think is capable of consistently selling you a safe and effective product, batch after batch, year after year?

Which of Manufacturer #2's practices do you think are NOT important?

- Facility has adequate lighting, ventilation, plumbing, and sanitation
- Equipment is routinely checked to ensure proper operation, and cleaning procedures are shown to be effective
- Incoming components, containers, and closures are quarantined until their quality for use has been verified
- Procedures are clearly written, and personnel are properly trained
- Accuracy of test methods are verified
- Manufacturing process is supported with data, and key manufacturing steps are monitored with in-process controls
- Productions records document what, when, who, how, and where
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The practices used by Manufacturer #2 are typical of what is legally required for pharmaceutical dosage forms:

Current Good Manufacturing Practices
(cGMPs)

21 Code of Federal Regulations (CFR) 211

Current Good Manufacturing Practices

	Type A Medicated Articles	Type B and C Medicated Feeds	API	Pharmaceutical Dosage Forms
GMPs	21 CFR 226	21 CFR 225	ICH Q7A	21 CFR 211

CMC review and cGMP
assessment have the same goal:
Drug quality

Current
Good
Manufacturing
Practices

Chemistry,
Manufacturing,
and Controls

CMC review and cGMP
assessment overlap but are not
the same

Examples of what field investigators do on a cGMP inspection:

- Interview personnel, observe operations, and audit documents to verify that the firm is following cGMPs
- Verify that the firm is following the procedures filed in the CMC technical section.
- Verify that manufacturing processes have been validated
- Trace production of individual batches through historical production records
- Assess whether the firm's Quality Control unit makes appropriate decisions about the production and release of batches
- Check equipment qualification, cleaning, and calibration logs
- Examine responses to customer complaints
- Evaluate whether change control procedures are in place
- Determine if investigations concerning quality issues and corrective actions are satisfactorily conducted

Examples of CMC technical section concerns:

- What is the manufacturing process, from start (raw materials) to finish (packaging and release)?
- Are critical manufacturing parameters identified and controlled to ensure consistency of the product?
- Is the quality of the materials used to make and package the drug controlled?
- Are test methods accurate and are the intended labs capable of performing them?
- Are product specifications justified with data?
- Are there data to show that the manufacturing procedures consistently produce a safe and effective drug?
- Do stability data support the label storage conditions and shelf life period?

CMC ≠ cGMP

- CVM Division of Manufacturing Technologies reviews the CMC technical section – which is not an evaluation of current Good Manufacturing Practices (cGMPs) – and will request inspections if needed
- cGMP compliance is assessed by inspections by investigators in the FDA Office of Regulatory Affairs – but FDA Centers are involved under certain circumstances
- District Offices (within the Office of Regulatory Affairs), CVM Division of Manufacturing Technologies, and/or Division of Compliance determine regulatory actions regarding inspections

What's Behind Label #3?



Manufacturer behind Door #3:

- Facility has adequate lighting, ventilation, plumbing, and sanitation
- Equipment is routinely checked to ensure proper operation, and cleaning procedures are shown to be effective
- Incoming components, containers, and closures are quarantined until their quality for use has been verified
- Procedures are clearly written, and personnel are properly trained
- Accuracy of test methods are verified
- Manufacturing process is supported with data, and key manufacturing steps are monitored with in-process controls
- Productions records document what, when, who, how, and where
- Shelf life and product quality are monitored by on-going stability studies
- A quality control unit reviews procedures, records, and test results
- Customer complaints are documented and addressed
- Investigations into quality issues determine root causes and result in successful corrective actions

Manufacturer #3 says they are doing the same practices as Manufacturer #2.

Manufacturer #3 can sell you the same antibiotic, but at a lower price.

From which manufacturer do you buy?

Additional Information:

An on-site inspection of Manufacturer #2 has confirmed that it is in fact operating as claimed.

Manufacturer #3's statements have not been independently verified.

From which manufacturer do you buy?

Are regulatory standards for the
manufacture of aquaculture drugs
too stringent?

Almost 400 fish dead after chemical mix-up at Texas State Aquarium

By Andreas Preuss, CNN

Updated 5:40 AM ET, Thu April 23, 2015



The Texas State Aquarium says a chemical mix-up is to blame for the most significant loss of marine life in its 25-year history.

(CNN) — A poisonous chemical used in film processing is being blamed for killing almost 400 fish at the Texas State Aquarium.

The chemical got into the Corpus Christi facility's fish tanks last week by mistake during a parasite treatment. The aquarium director says containers were mislabeled.

The aquarium thought it was using the drug trichlorfon, but instead an "isomer of hydroquinone resorcinol" was used, [according to test results](#).

The National Institutes of Health identifies hydroquinone as a common but toxic chemical that is used in film processing, as a stabilizer in paint and motor fuels, and in cosmetics.

Center for Veterinary Medicine Guidances for Industry

[http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/
GuidanceforIndustry/ucm042450.htm](http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm042450.htm)