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TROUBLESHOOTING:
MEDIA IN THE IVF LABORATORY

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Vitrolife

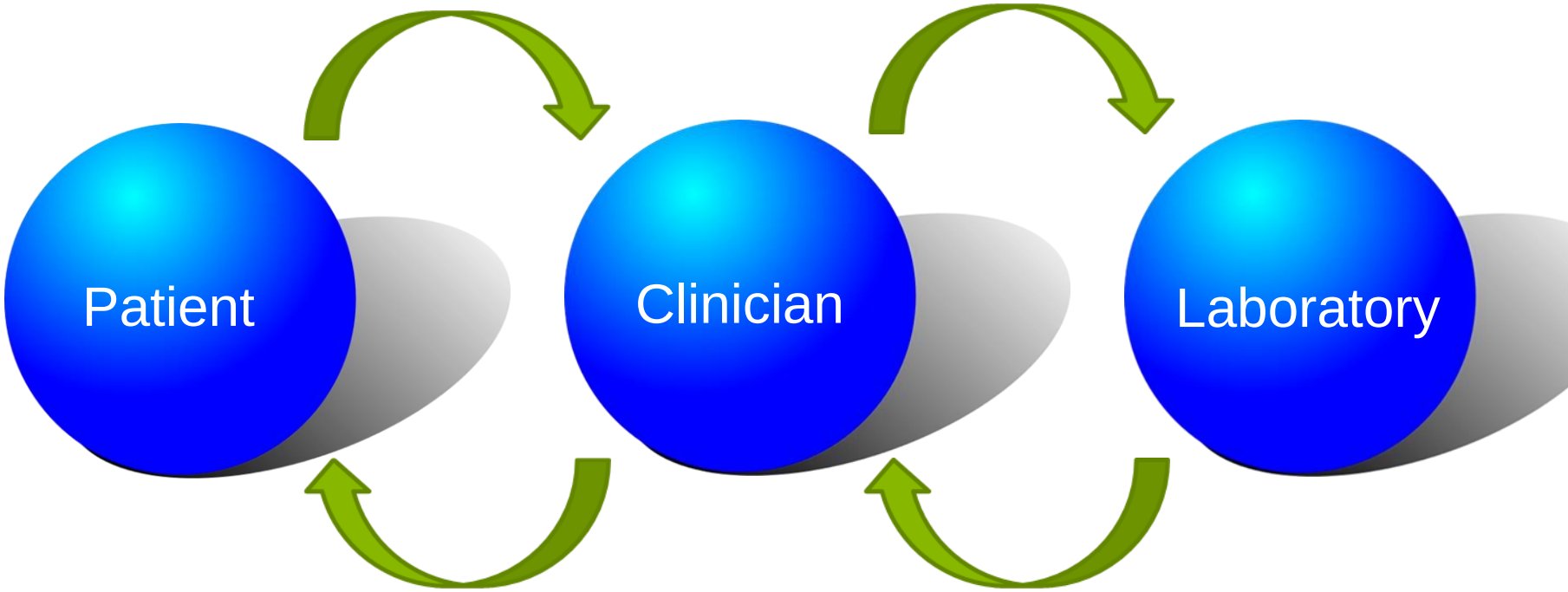
DISCLOSURES

- Vitrolife employee
- Vitrolife is a international manufacturer and distributor of ART medical devices, including (not limited to) culture media, disposable plastic and glass devices, lasers and time-lapse imaging and incubation systems.

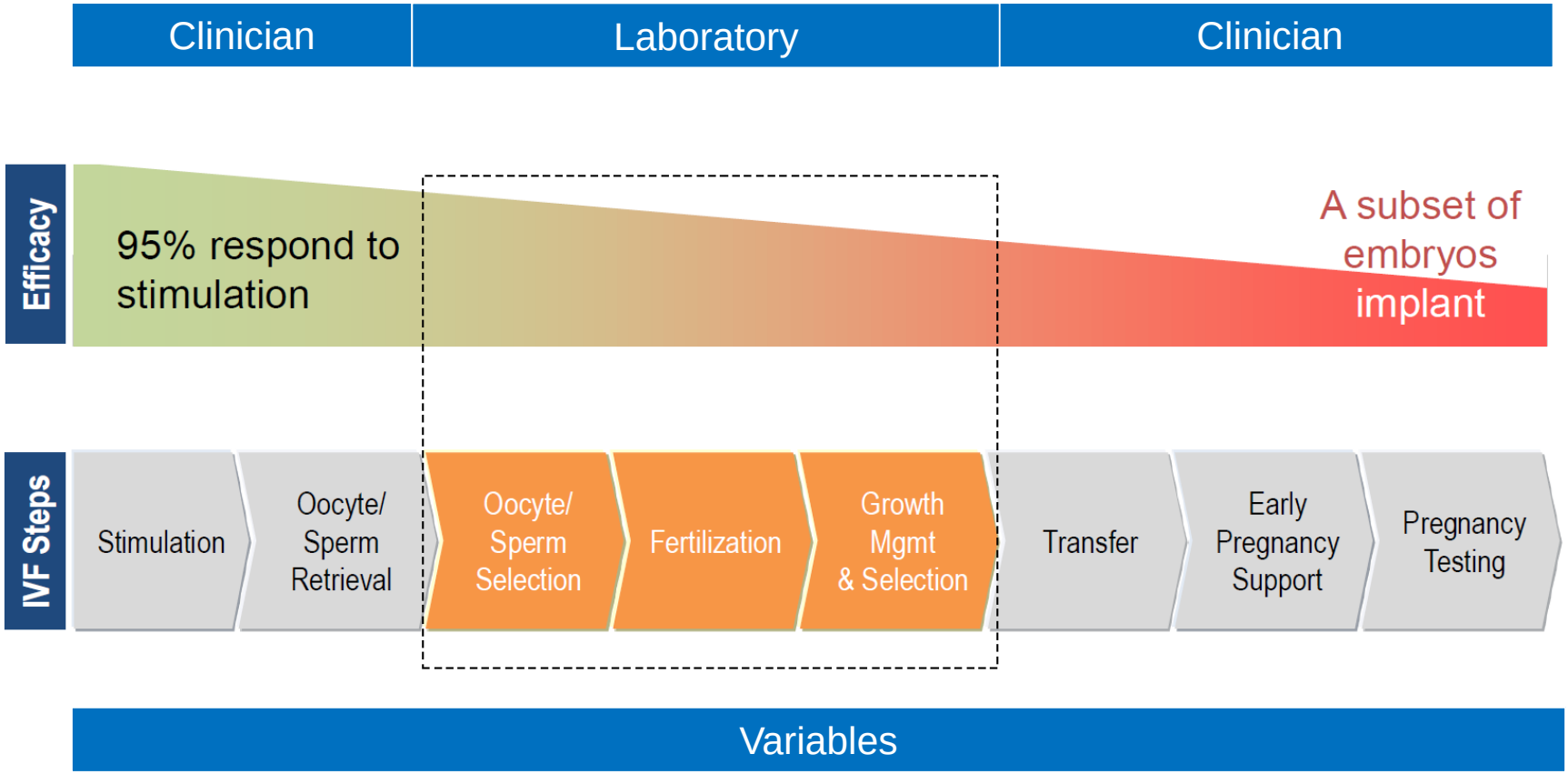
AGENDA

- Background
- Manufactures Responsibilities
- Troubleshooting Basics
- Conclusions

STAKE HOLDERS IN IVF
CHAIN OF CUSTODY
BLAME CHAIN



VARIABLES



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Montag, M. ESHRE Symposium 2016 (Reproduced with permission of author)

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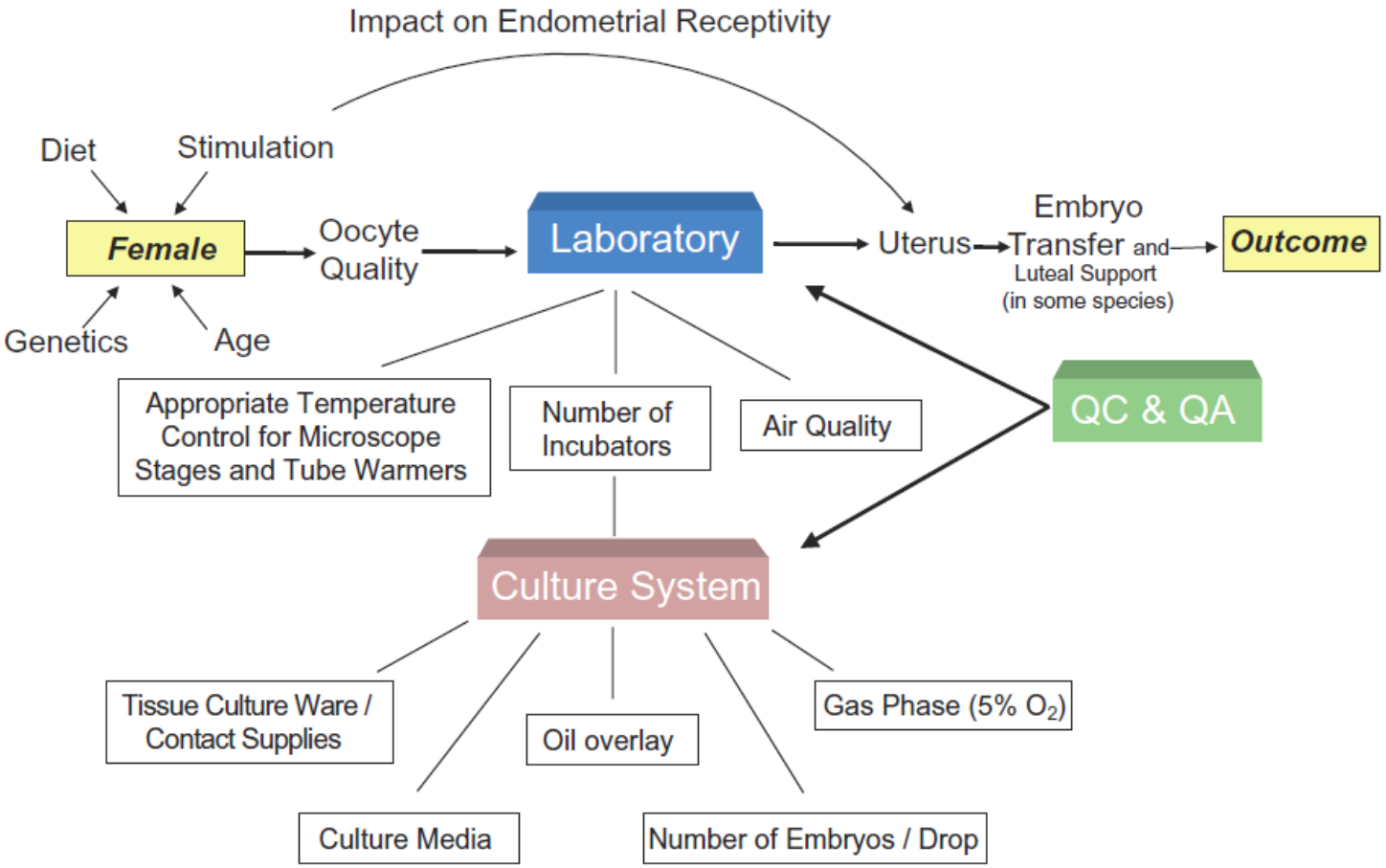
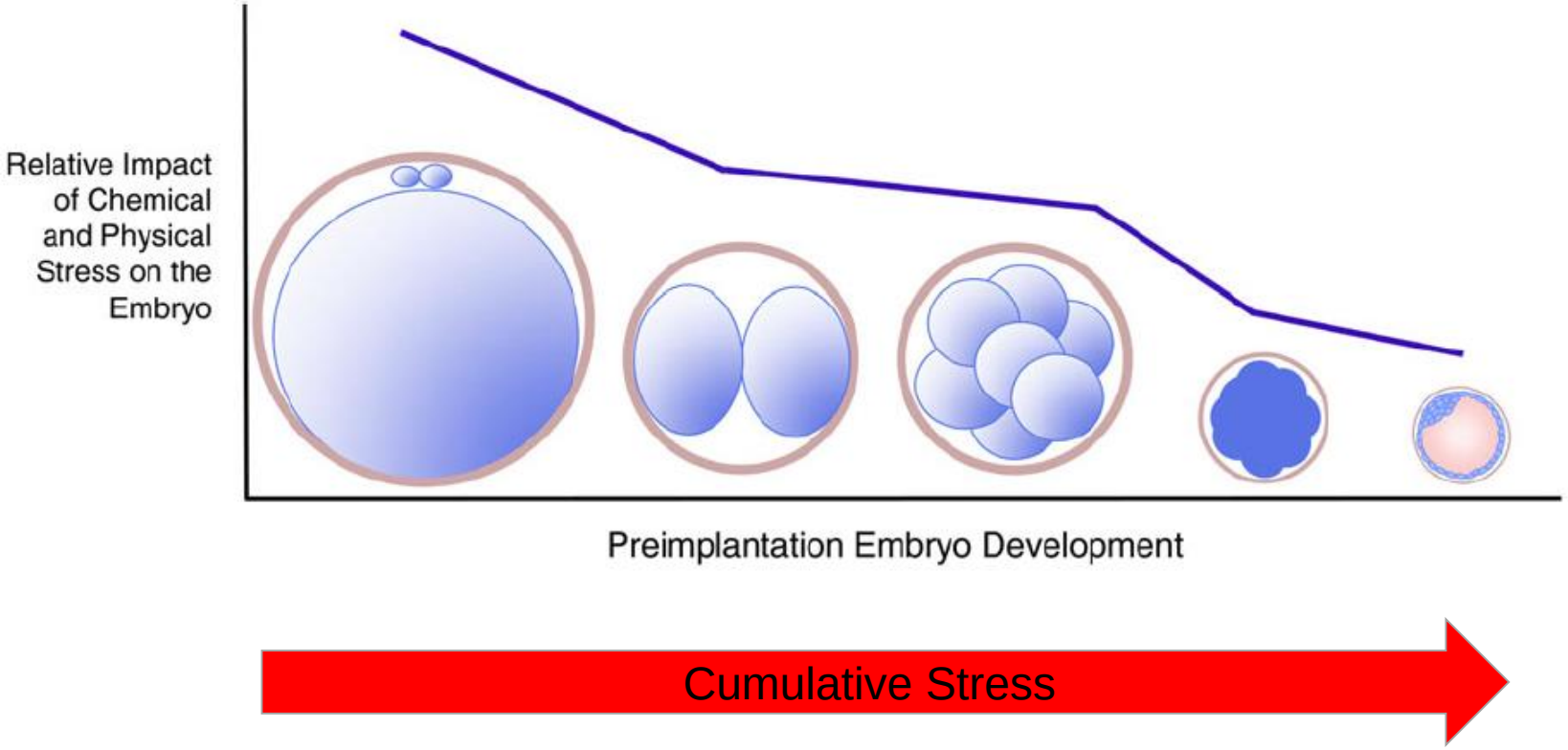
REALITY



Gardner and Lane, 2003)

IMPACT OF STRESS



Wale and Gardner, 2016

MANUFACTURERS

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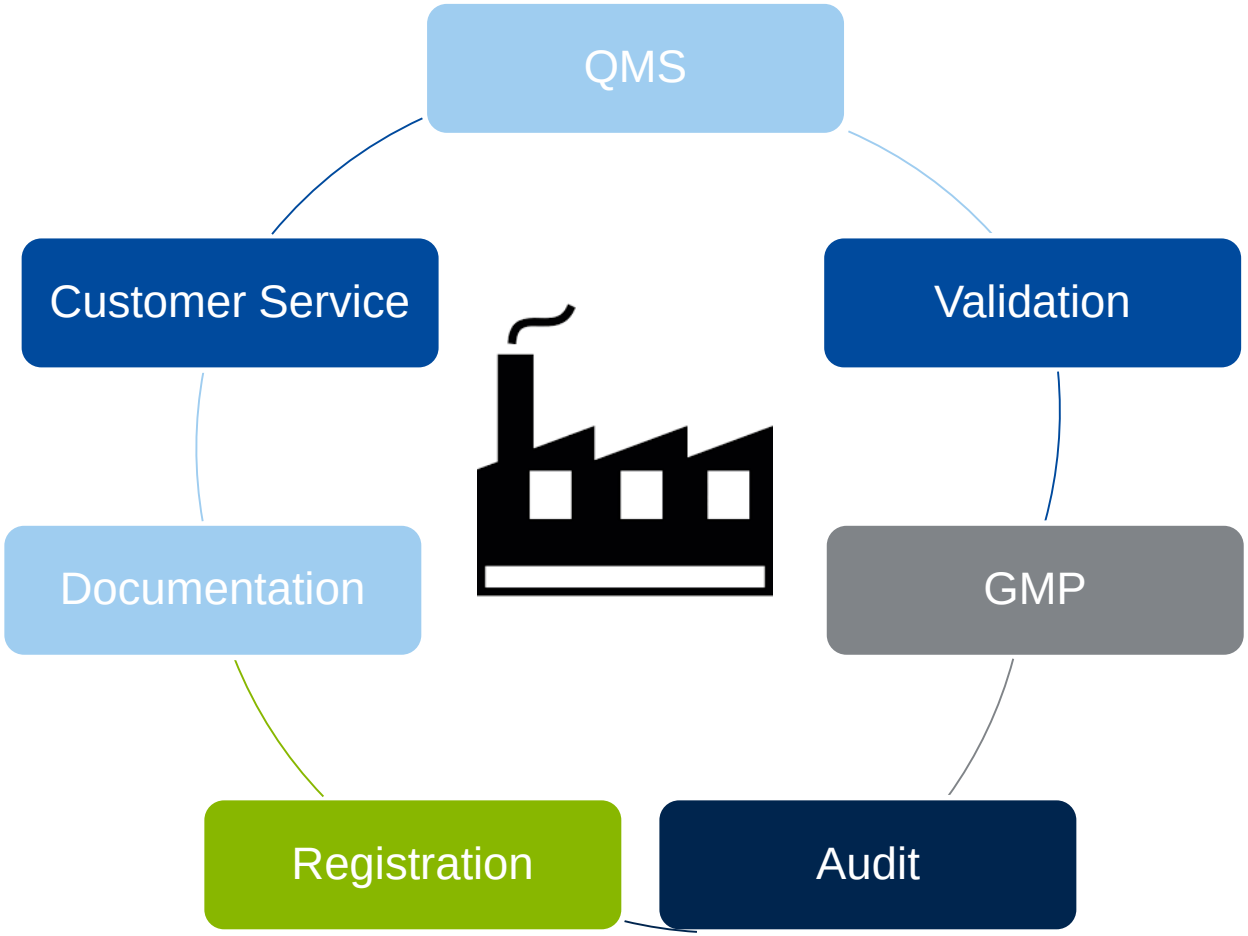
MANUFACTURERS



MANUFACTURERS

- Good Manufacturing Practice for medical devices
  - FDA Code of Federal Regulations; Title 21, Part 820

> "to govern the methods used in and the facilities and controls used for the design, manufacture, packaging, labeling, storage, installations, and servicing for all finished medical devices intended for human use".

- ISO 13485:2008 Medical devices – Quality Management Systems – Requirements for regulatory purposes
- ISO 9001:2008 Quality Management Systems – Requirements
- CAN/CSA 13485:2008

DOCUMENTATION
QUALITY MANAGEMENT

- Receiving records
- Personnel training
- Purchasing/Distribution
- Manufacturing record
- QC/MEA
- Certificate of Analysis
- Customer Service

CERTIFICATE OF ANALYSIS

G-TL™

REF	CONTENT	LOT	EXPIRY DATE
10145	1x30 mL	506667	2017-10-20

INDICATION FOR USE
Medium for culture of embryos from fertilisation to the blastosyst stage.
Caution: Federal (US) law restricts this device to sale by or on the order of a physician or practitioner trained in its use.

DESCRIPTION
Bicarbonate buffered medium containing hyaluronan and human serum albumin.

APPLICATION
For use after equilibration at 37°C and 6% CO_2.

RAW MATERIALS
The raw materials were tested and evaluated by stringent quality control procedures.

COMPOSITION

Alanine	Alanyl-glutamine	Arginine	Asparagine
Aspartate	Calcium chloride	Calcium pantothenate	Cystine
EDTA	Gentamicin	Glucose	Glutamate
Glycine	Histidine	Human serum albumin*	Hyaluronan
Isoleucine	Leucine	Lysine	Magnesium sulphate
Methionine	Phenylalanine	Potassium chloride	Proline
Pyridoxine	Riboflavin	Serine	Sodium bicarbonate
Sodium chloride	Sodium citrate	Sodium dihydrogen phosphate	Sodium hydroxide
Sodium lactate	Sodium pyruvate	Taurine	Thiamine
Threonine	Tryptophan	Tyrosine	Valine
Water for injection (WFI)			

*Pharmaceutical infusion-grade for medical use, free from HBV, HCV and HIV.

PRODUCT PROPERTIES	SPECIFICATION	RESULT
pH (at +37°C and 6 % CO_2 atmosphere)	7.30±0.10	7.32
Osmolality [mOsm/kg]	270±5	270
Sterility Assurance Level (sterile filtration)	1E-3	1E-3
Bacterial endotoxins (LAL assay) [IU or EU/mL]	<0.25	<0.25
Mouse embryo assay (1-cell)[% expanded blastocyst within 96h]	>=80	>=80
Mouse embryo assay (1-cell)[blastocyst cell number within 96h]	No statistical difference [1]	PASS

[1] Mean cell number of the test group is statistically compared to the control group. The mean of the test group must not be statistically different (P>0.05) to the control to constitute a Pass.

2017-06-30
Camilla Johansson
Quality Control Manager

MANUFACTURERS
DEVIATIONS

FDA CFR Title 21, Part 820.198 sub-part M:

- Each manufacturer shall maintain complaint files.
- Each manufacturer shall establish and maintain procedures for receiving, reviewing, and evaluating complaints by a formally designated unit. Such procedures shall ensure that:
  - (1) All complaints are processed in a uniform and timely manner;
  - (2) Oral complaints are documented upon receipt; and
  - (3) Complaints are evaluated to determine whether the complaint represents an event which is required to be reported to FDA.

MANUFACTURERS
OBLIGATIONS

Media Manufacturing must:

- Comply with 510(k)
- Comply with GMP
- Comply with QMS
  - Requires detail documentation
  - Changes/Deviations reported (internally/externally)
  - Reregistration as required per FDA

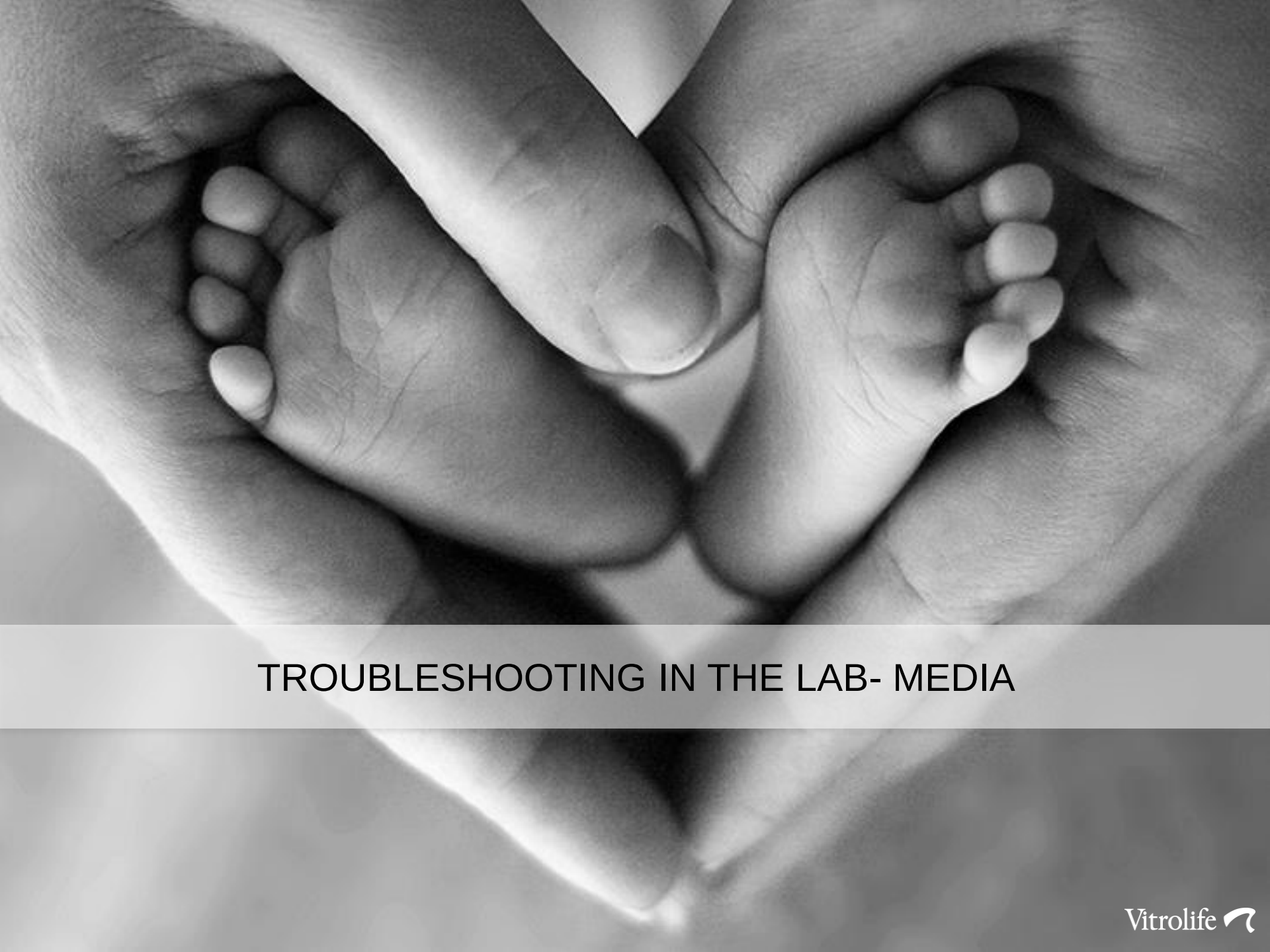
    (Significant technology or safety modifications- See FDA)

MANUFACTURERS

The root cause of *most* culture media complaints are not related to the media itself.

Generally there are other factors that caused the observations

- Transport
- Handling
- Disposables



TROUBLESHOOTING IN THE LAB- MEDIA

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TROUBLESHOOTING

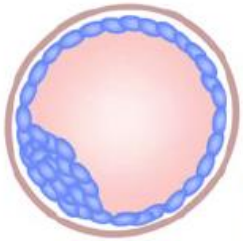
FACTORS

QC and QA:
- Identify possible toxins in the laboratory
- Maintain/improve efficacy

Oxygen concentration:
- Reduce to <10%
- Include antioxidants in media

Tissue Culture Ware:
- Emission of VOCs
- Appropriate QC to avoid embryo toxicity

Albumin:
- Blood-derived albumin may contain phthalates
- Role for recombinant albumin for safety and standardization



Static Culture:
- Leads to changes in medium composition
- Creation of unstirred layers
- Toxin build-up

Number & type of Incubators:
- Effects on pH and temperature stability

Number of Embryos & Drop Volume:
- Impacts efficacy of embryo derived factors

Oil overlay:
- Reduce shifts in pH & provide greater temperature stability

Isolettes:
- Maintain constant pH & temperature stability
- Provides barrier to VOCs

Pipetting:
- Minimize number of manipulations
- Use of the slowest speed with gentle pipetting action

Air quality:
- Monitor frequently
- Off-gas plastic ware if required
- Use of appropriate filtration

Light:
- Minimize exposure

Wale and Gardner, 2016

TROUBLESHOOTING
ROOT CAUSE ANALYSIS

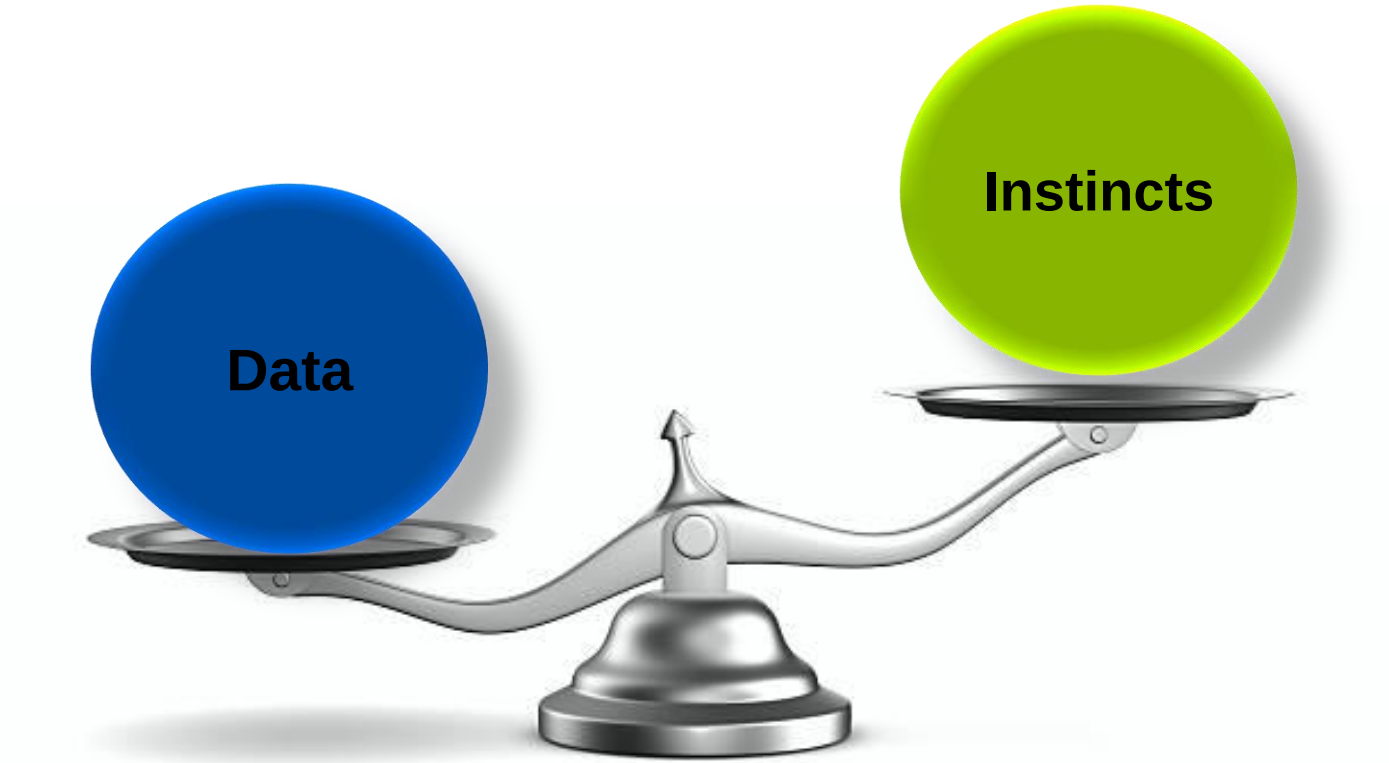
Methods for RCA:

- Brainstorming
- 5 “Why’s”
- Flowcharting
- Fishbone diagrams
- Affinity diagrams

Must be:
- Organized
- Thorough
- Logical

TROUBLESHOOTING

INVESTIGATION



TROUBLESHOOTING
IDENTIFYING THE PROBLEM

TROUBLESHOOTING

STRATEGY FOR RCA

TROUBLESHOOTING
INVESTIGATION

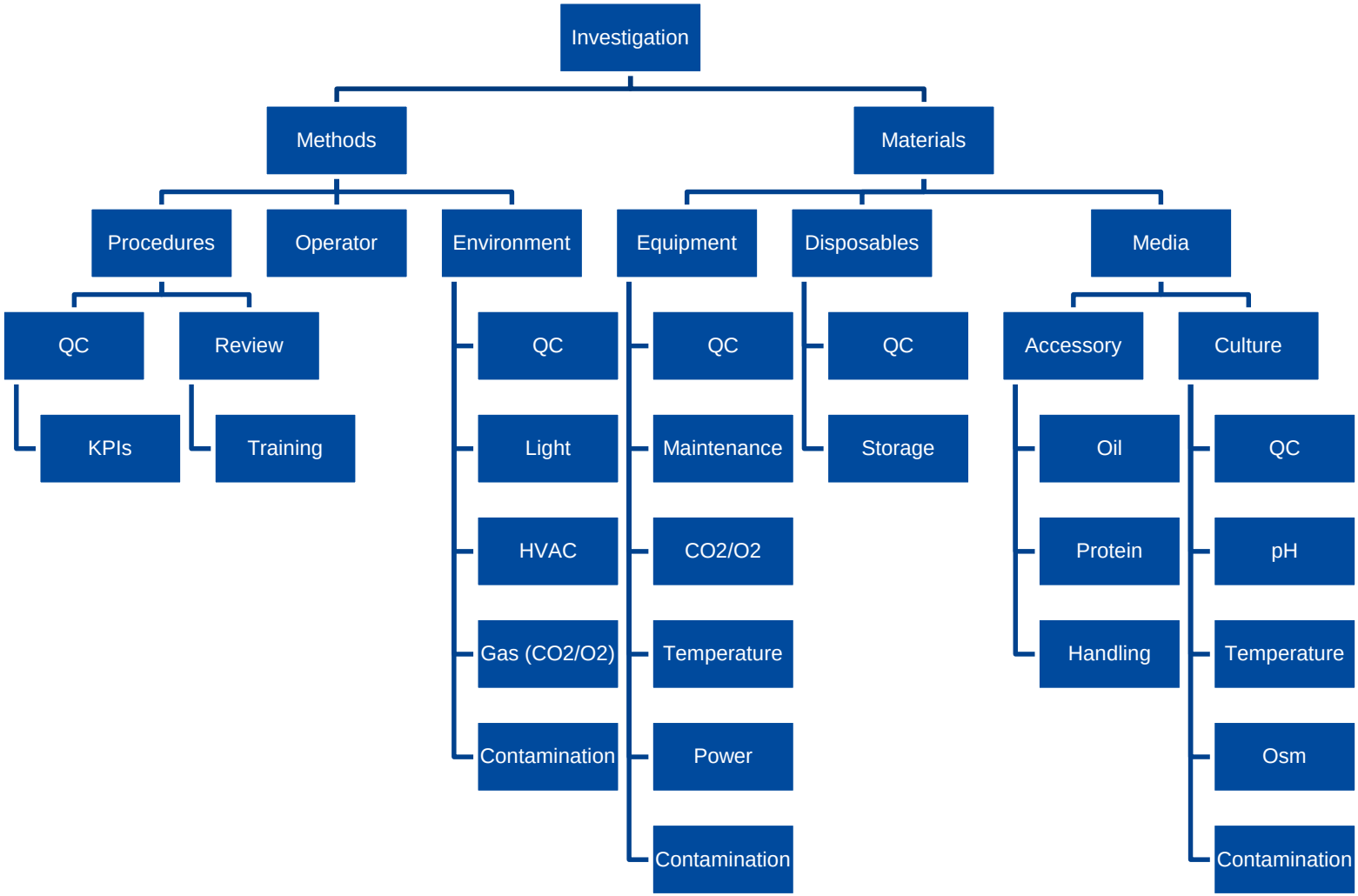
What's the Goal:

Identify *all* possible factors influencing the observations

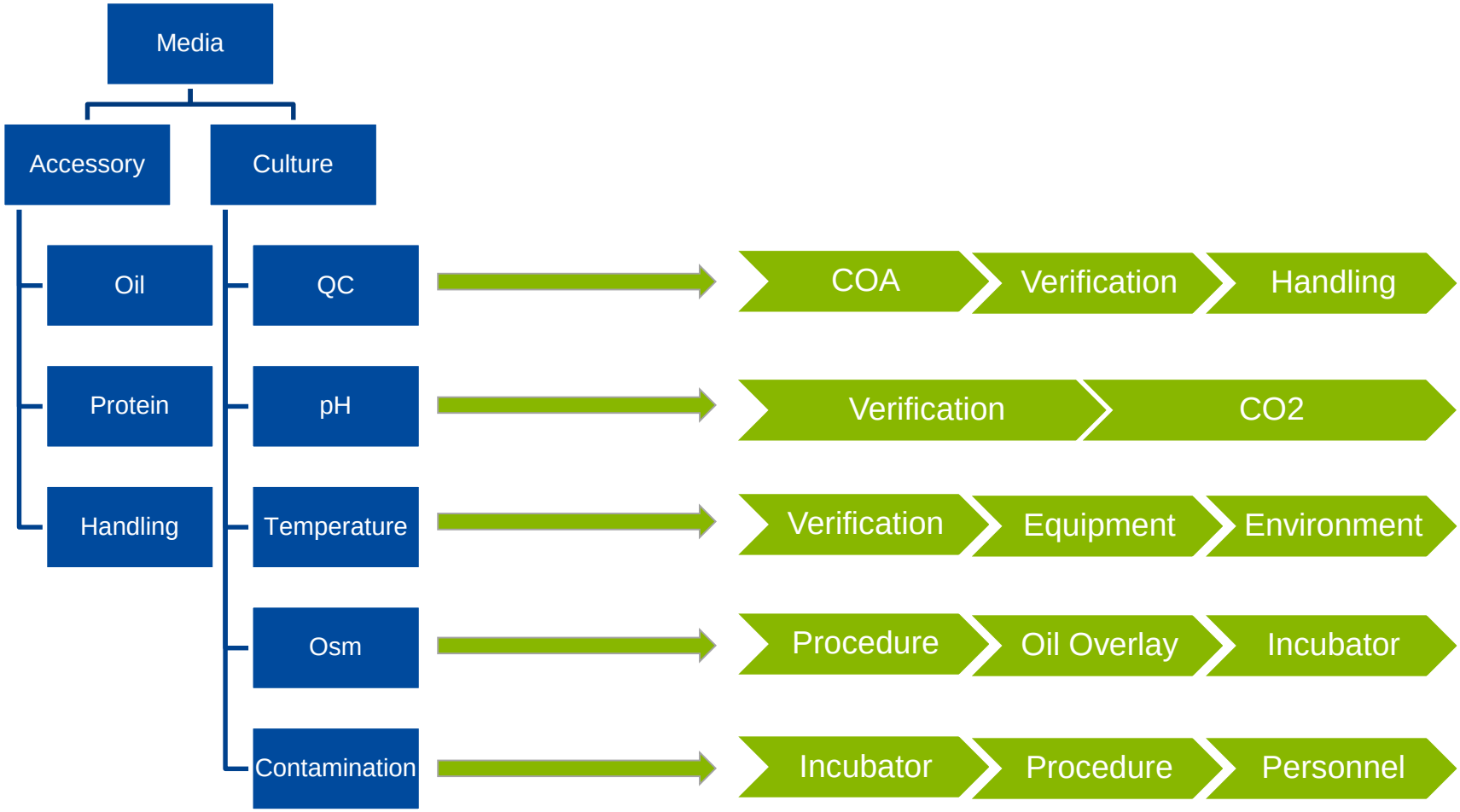
- What happened
- How it happened
- Why it happened…so that
- Actions for preventing reoccurrence are developed

TROUBLESHOOTING

INVESTIGATION



TROUBLESHOOTING
INVESTIGATION



TROUBLESHOOTING
INVESTIGATION

Staff

- Background
- Proficiency
- Observation
- Communication

Quality Management System

- KPIs
- Strategy
- Internal Notification
- External Notification

TROUBLESHOOTING
INVESTIGATION

QC Review

- Verify Control materials:
  - LOT #
  - REF #
- Verify methods:
  - Procedures
  - Equipment
  - Environment

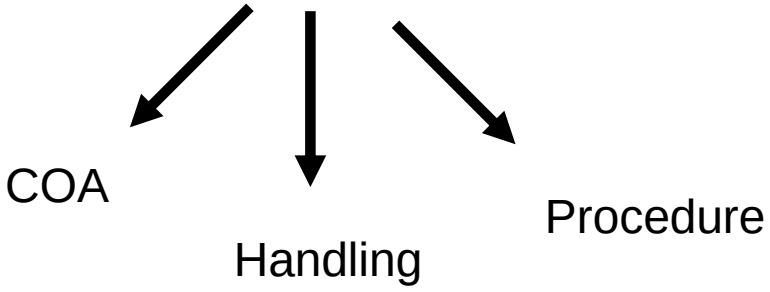
Activity:

- Matrix of data
  - all LOT# used
  - All personnel
  - Look for changes
  - Identify unique observations

TROUBLESHOOTING

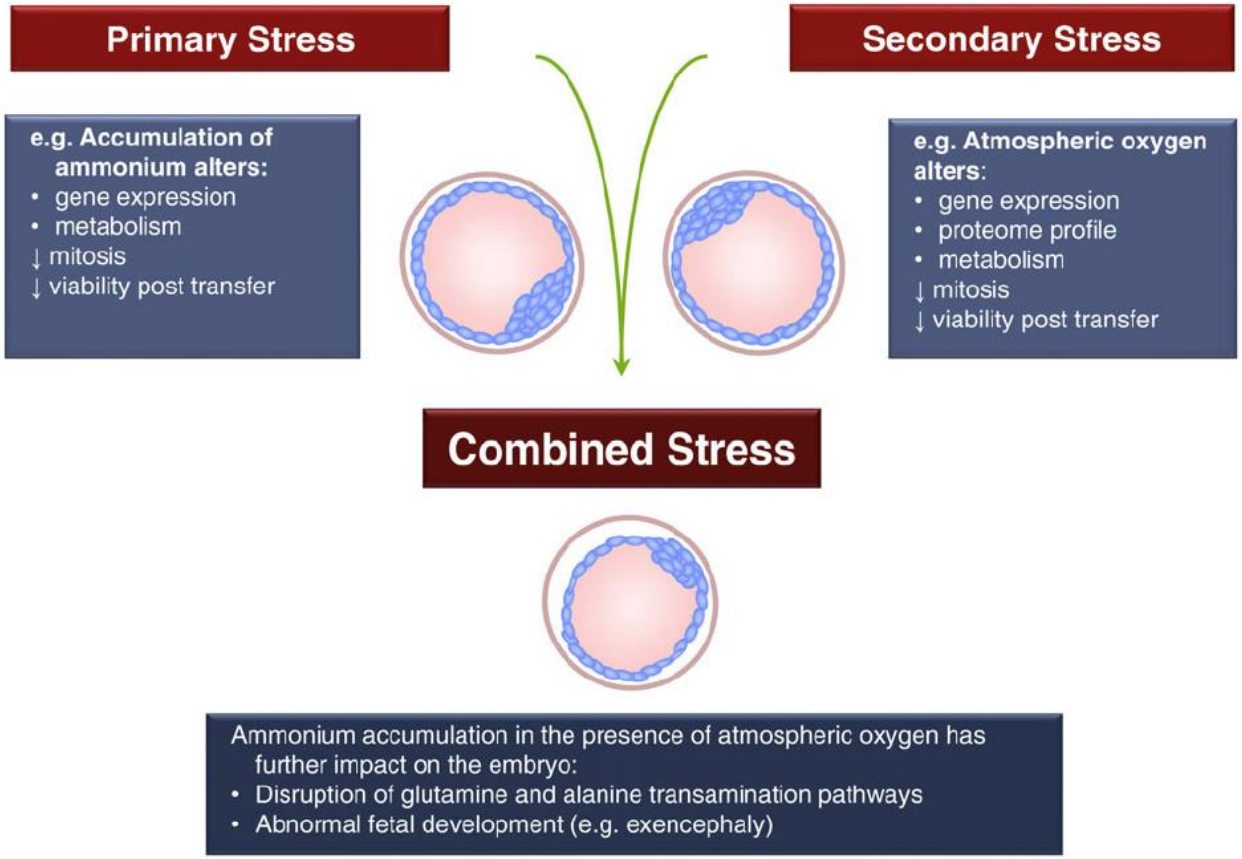
INVESTIGATION

Material	Dish Operator	C/O Operator	Incubator	Hyaluronidase	OVOIL	Protein	Dish	G-MOPS+	Results
RM #1	BG	ES	191	XXXXXX	ABABAA	12311	20180101	SSSSSS	Pass
RM #2	BG	ES	191	XXXXXX	ABABAA	12311	20180101	SSSSSS	Pass
RM #3	KD	ES	191	XXXXXX	ABABAA	12311	20180101	SSSSSS	Pass
RM #4	KD	ES	191	XXXXXX	ABABAA	12311	20180101	SSSSSS	Pass
FP #1	BG	ES	191	XXXXXX	ABABAA	12311	20180101	SSSSSS	Pass
FP #2	BG	ES	191	XXXXXX	ABABAA	12311	20180101	SSSSSS	Pass
FP #3	BG	ES	191	AAAAA	ABABAA	12311	20180101	SSSSSS	Fail
FP #4	BG	ES	191	AAAAA	ABABAA	12311	20180101	SSSSSS	Fail



TROUBLESHOOTING

ROOT CAUSE



Wale and Gardner, 2016

TROUBLESHOOTING
ROOT CAUSE

Smoking gun

- Media was contaminated
- Incubator humidity pans ran dry
- CO2 runs out
- Clinical deviations
- Sally was sick and was coughing in the incubator
- Construction in building

Lab Fairies

- It just went away!

TROUBLESHOOTING
ROOT CAUSE

Human error is never ~~commonly identified as~~ the root cause

Often there are other identifiable cause:

- Lack of training
- Procedure
- Neglect
- …

TROUBLESHOOTING

CAPA

Corrective Action: Action taken to immediately limit or correct the results of the identified problem. Risk mitigation?

- *Replace the contaminated media*

Preventative Action: Actions taken to ensure the problem isn't repeated.

- *Change procedure to prevent contamination from happening (add PPE or stop supplementing product off label)*

TROUBLESHOOTING
FOLLOW-UP

Internal

- Review of the issue following CAPA
- Evaluate the effect of the preventative actions
- Evaluate the effect of corrective actions eff
- Has it happened again?

External

- Contact clinical staff
- Contact manufacturers
- If it’s a determined to be a notifyable problem the manufacturer is obligated to perform investigation, including CAPA and regulatory notification, per FDA.

CONCLUSION

- Troubleshooting is a complex but critical activity
- Variation in results can impact clinical outcomes
- Many variable are in play, so troubleshooting needs to be organized
  - There can be more than one cause
- Manufacturers are:
  - Responsible for controlling their processes
  - Required to report customer observation and evaluate the severity
- The goal is to discover the root cause and follow up!
- Sometimes the initial suspected causes opens other doors!

REFERENCES

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- Wale, P.L., Gardner, D.K., 2016. The effects of chemical and physical factors on mammalian embryo culture and their importance for the practice of assisted human reproduction. Hum Repro Update, Vol.22, No.1 pp. 2–22, 2016.
- Elder K et al. (2015) Troubleshooting and Problem-Solving in the IVF Laboratory. Cambridge University Press.

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