Who is ISIA

• International association of serum and animal derived product sourcers, producers, suppliers and
  • customers, founded in 2006
    – Currently xx members
    – Members are also major suppliers of many other animal derived products
      • Proteins, Antibodies, Enzymes, etc.

• Members supply more than 90% of all animal serum used globally
• More than 80% of all materials used in healthcare applications are certified
  – No human material or food applications
ISIA Mission

• ETHICS - ISIA shall establish, promote and assure compliance with uncompromised standards of excellence and ethics in the business practices of the global animal serum and animal derived products supply industry.

• SAFETY AND SAFE USE - Primary focus will be on safety and safe use of serum and animal derived products through proper origin traceability, truth in labeling, and appropriate standardization and oversight.

• EDUCATION – ISIA will work to educate stakeholders on the scientific foundation of the safe use of serum and animal derived products.
So how can the industry help our customers improve their management of the risks associated with serum and other animal derived materials?
• Current Critical Programs
  – Traceability
  – Origin testing
  – Age Testing
  – Gamma Irradiation
Traceability

An important risk mitigation program
How the Program works!

- Rigorous Independent Third Party Audit
  - Performed by an ISIA approved/trained auditor
  - To an ISIA approved audit plan
  - Using a detailed ISIA audit protocol

- Modelled after ISO audits
  - Non-conformances are dealt with similarly
    - Similar to ISO 22005
Why the program works!

- Covers all aspects of what happened to the product every step of the way from the abattoir to the customer
- Covers all transactions in the company – Not just those for a specific customer
- Focuses on each handoff – What came in at what price? – What went out at what price?
- Would have found the product adulteration/misrepresentation discovered in 2013
Traceability

• Certification is not available for purchase
  • A company has to meet all the requirements
    • Ordering and shipment audits for distributors

• Certification is granted for three years
  – No historic claims
  – We can’t fix the past!
Traceability Certified Companies

- Abattoir Basics Company
- Animal Technologies Inc.
- Atlas Biologicals
- Axenia Biologix
- BioArra
- Biomin Biotechnologia
- By Productos S.A. de C.V.
- Central Biomedica Inc
- GE Healthcare
- Gibco Thermo Fisher
- Scientific
- Life Science Production
- Moregate Biotech
- Newman Biotech Australia
- Proliant Health & Biologicals
- River City Biologicals
- Rocky Mountain Biologicals
- TCS Group
- VWR/Seradigm
- SeraTec LLC
- Serum Technologies
- Vacca
- Others in progress
Status

- More than 85% of material used in bio-processing applications is certified.
- Increased focus from customers and regulators will strengthen the program.
- Ongoing effort to keep current and strengthened through program revisions— Not yet mandatory
- New testing methods under investigation as an addition to the program.
Origin Testing
An important risk mitigation program
Serum Countries of Origin

- North America: 34%
- Central America: 2%
- South America: 36%
- Asia: 0%
- Pacific: 20%
- Europe: 6%
- Africa: 3%
Serum Sourcing

• South American material is widely used in research outside of the USA

• Manufacturing and Industry prefer serum from certain geographies based on disease prevalence and rigorous infrastructure
  – FMD, BSE, other infectious agents
  – Robust infrastructure
  – Rigorous regulatory implementation

• NZ, Australia, and USA are currently preferred sources for pharmaceutical manufacturing
Why are we interested?

We are looking for a technology that can distinguish materials that seem to be identical.
Geographic Origin

• In 2014 we became aware that stable isotopes might provide an indication of geography of origin...........
  – Hamburger meat
Pilot Study - Stable Isotopes

USA and Mexico Overlap
Trace Element Analysis

- The mix of trace elements found in soil are unique to a location
- 33 trace elements are analyzed for each sample
- Statistical analysis of the results can identify geography
7 Countries can be identified to date

Canada and Central America removed for clarity

350 + samples
The USA, Mexico and Brazil

- All geographic pools have unique fingerprints
- Samples from Central America are sparse in numbers so far but indicate closer similarity to Mexico
- Brazil remains very distinct
Blending can be Detected

- Blending is more readily detected between origins of distinct fingerprints
- Economically motivated levels of blending can be identified
Other Reasons for this Approach

• It is relatively rapid and quantifiable (and not too expensive)
• ISIA is ensuring that the database is developed using samples from certified companies from known geographies
• Based on our agreement, there will be ONE industry database
  • Accurate results and minimized potential for error
• Since our inception, ISIA has been very much against mixing of materials from different geographic origins.
  – This methodology can detect mixtures
• We will not disclose which of the 33 trace elements give rise to the result for each geography.
Interpretation of Results

• A decision limit based on a 99% confidence interval of the reference data is used to define whether the result is considered consistent (pass) with the database or inconsistent (fail) with the database.

• A detailed publication on this work is in development
Current Status

• Agreement finalized with
• We are adding 550 more samples from 8 major geographies to strengthen the trace element data base for bovine serum and plasma
• After validation, other certified company data will be included to form ONE industry database
• Data base will be fit for purpose by year end
  • Secret Shopper program begun
Additional Testing

• We are also monitoring for other technologies to determine origin and age of source
  • Biomarkers
Age of Animal

• **Fetal Bovine Serum (FBS)** is obtained from the blood of fetuses of healthy, pre-partum bovine dams that have been deemed fit for human consumption through ante- and/or post-mortem veterinary inspection. It is collected in abattoirs inspected by the competent authority in the country of origin. There are no deletions or additions (including preservatives) allowed.

• **Newborn Bovine Calf Serum (NBCS)** is the liquid fraction of clotted blood derived from healthy, slaughtered bovine calves aged less than 20 days, deemed fit for human consumption through ante- and/or post- mortem inspection. It is collected in abattoirs inspected by the competent authority of the country of origin. There are no deletions or additions (including preservatives) allowed.
Age of Animal

- ISIA has been actively supporting an effort by a member company to identify other markers
- Low IgG has long been recognized as a possible marker for FBS
  - Protein A stripped FBS is commercially available
- Until now there as been no firm specification for IgG
- Analysis of a 29 component vet panel has demonstrated that such a marker exists
  - Pooled samples of FBS and NCBS from certified companies
NCBS/FBS Comparison

NBCS < FBS for gamma glutamyl transferase (GGT), IgG, total bilirubin, and globulin
Age of Animal

• Focus on GGT
  – All results comparable except for those run on the Siemens Dimension Expand
  – Multiple runs give consistent results

• GGT is an excellent and robust marker for the presence of NCBS
NBCS diluted in FBS

\[ R^2 = 0.9994 \]

% NBCS to FBS (N=3)

GGT in IU/L

- Observed GGT
- Predicted GGT
- Observed FBS GGT Max

7 IU/L
NBCS in FBS mixing results

%NBCS Determination in FBS from GGT

- Predicted GGT from Data
- Observed FBS GGT Max

% NBCS (N=32) to FBS (N=39)

GGT IU/L

0% 5% 10% 15% 20% 25% 30% 35% 40% 45% 50% 55% 60% 65% 70% 75% 80% 85% 90% 95% 100% 105% 110% 115% 120%

7 IU/L

50 GGT

11.02%
Age of Animal

- Mixing experiments show that calculated results correspond closely with actual measurements.
- Reported GGT values over 10 IU/L in FBS would strongly suggest that the source of the material should be questioned.
- Specifications for IgG
  - less than 300 micrograms/ml
  - less than 10 IU/ml

will be recommended for FBS by ISIA
Age of Animal

• A detailed publication has been submitted based on the results discussed
• Even if we know where serum comes from, and what the source was, there are still concerns around the presence of adventitious agents

• So how else can we mitigate risk?
Gamma Irradiation

An important risk mitigation program
Gamma Irradiation

• This program was undertaken in response to a proposal made to this committee in 2015
• An expert committee was convened comprising users, irradiators, and suppliers
• USDA has been kept apprised of all activities
  – Risk Assessment
ISIA has always recommended Gamma Irradiation as THE method of choice for post manufacturing treatment of serum

- HTST, UV either cause loss of biological activity or are not economically viable
- Traditional heat inactivation is inconsistent and can negatively impact biological activity
- Nano Filtration cannot be used at scale
What is the concern?

- Many customers, suppliers, regulators, and others do not fully understand gamma irradiation.

  - “Suppliers are secretive”
  - “There don’t seem to be any rules or regulations about how the process is validated”
  - “Gamma kills all viruses”
  - “All the big suppliers have their own irradiation facilities”
The task is currently broken into 6 parts with different experts taking the lead.

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<td>Introduction to Gamma Irradiation and Serum</td>
<td>RJV and Karl Hemmerich</td>
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<td>Effect of Gamma Irradiation on viruses</td>
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Publication

All articles are being published in BioProcessing Journal in Open Access and can be found on the ISIA website!
Conclusions

- ISIA continues to work to improve the characterization of FBS and related products

- Key programs are active in
  - Traceability
  - Geographic origin
  - Age testing
  - Risk mitigation
Conclusions

• ISIA will continue to publicize all findings to customers and global regulators
  – OIE

• ISIA will fully implement Ethics and Non-compliance Policies against non-compliant members and non-members alike

• An educated purchaser (supplier or customer) is our best solution
  – If it looks to good to be true it probably is!
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You are invited to attend our 13th Annual Meeting April 25 & 26, 2018 in New Orleans, USA

Find registration information on our website soon! www.serumindustry.org
Thank You!

Find out more at

www.serumindustry.org