



ISIA / USAHA Meeting

October 2016



International Serum Industry Association

- **International Association of serum producers, suppliers and customers, founded in 2006**
- **Members supply more than 90% of all animal serum used globally**
- **Members are also major suppliers of all animal derived products**
 - **Protein, Antibodies, Enzymes, etc.**
- **Expanded mandate includes all animal derived products**
- **Currently 56 members**
 - All major suppliers
 - Several large end-user companies





Members

REGULAR MEMBERS

ABATTOIR BASICS COMPANY
FOR RESEARCH THAT'S AS SIMPLE AS ABC

Access Biologicals LLC

Allevamento BLOOD

AmCell BIOSCIENCES

ANIMAL TECHNOLOGIES, INC.
A BIOLOGICAL RAW MATERIALS RESOURCE

ATLANTA biologicals

ATLAS BIOLOGICALS

abs AUCKLAND BioSciences

AusGeneX

AXENIA BIOLOGIX

BioARRA

Biocell LABORATORIES

BI Biological Industries
Culture of Excellence

biomin biotecnologia s/a

biosul

biowest THE SERUM SPECIALIST

Boval Boval BioSolutions, LLC

Bioproducts

CBP CALIFORNIA BIOLOGICALS

CENTRAL BIOMEDIA INC

CORNING

ExCell Bio

GE Healthcare

GEMINI BIO-PRODUCTS

gibco by Thermo Fisher Scientific

HEMOSTAT

JRScientific Inc. advantage inside

LSP LIFE SCIENCE PRODUCTION

MINHAI BIO

MILLIDORE SIGMA

MOREGATE BIOTECH AUSTRALIA AND NEW ZEALAND

NEWMAN BIOTECH AUSTRALIA

NICHIREI BIOSCIENCES INC.

nucleus Biologics

Proliant BIOLOGICALS
The Art of Serum. The Science of Protein.

River City Biologicals, Inc.

River City Biologicals, Inc. Brazil

RMBIO Rocky Mountain Biologicals, Inc.

SeraTec LLC

SERUM SOURCE INTERNATIONAL

SERUM TECHNOLOGIES

STEMCELL TECHNOLOGIES

tcs

VWR Sera-digm LIFE SCIENCE

VACCA BIOLOGICS LLC

WISENT BIOPRODUCTS

ASSOCIATE MEMBERS

BD

IDEXX LABORATORIES

Johnson & Johnson

LGC

KERRY

SILVER FERN FARMS

vrrrd

VSc[®] Viral Science



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** - Work to educate stakeholders on the scientific foundation of the safe use of serum and animal derived products.





Product Characterization

- Standardization of definitions
 - Minimize customer confusion
- Standardization of testing
 - USP collaboration
 - Chapters <1024> and <90>
 - Fetal bovine serum standard
- **Traceability program**
- **Fingerprinting of origin**
- **Gamma Irradiation task force**



Why the program works!

- Independent Audit
- 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 ?
- Certification not available for purchase



Scope of Traceability

- **What happened to the product every step of the way from the abattoir to the customer**
 - Not just Origin
 - Paperwork for exportation
 - What kind of serum is it ?
 - Blending of serum types and origins
 - Serum alternatives
 - Treatment of serum
 - Compliance with ISIA established definitions, QC tests, Country of origin, certificate of analysis
- **Certification is granted for maximum of three years**
 - No historic claims



Traceability Certified Companies

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

70% of companies that have been members for more than 2 years are certified or in the certification process



Status

- Increasing awareness and acceptance of program
 - Australian government
 - Chinese government
- Ongoing effort to keep current through program revisions
- Testing methods under investigation as addition to the program



Geographic Origin

There have been hints!



- In 1997 we became aware that strontium isotopes might provide an indication of geography of origin.....
- In 2013 we became aware that water isotopes were being used to determine geographic origin for other materials

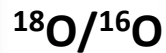
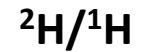
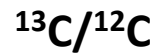


Isotopic Testing

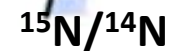
- In 2014 we heard a presentation that
 - Explained the heavy isotope technology
 - Showed that the technology was valid
 - Including beef in the USA!!
- We designed a pilot study to investigate heavy isotopes with samples from known geographic origin
- We also identified another testing method using trace elements and set up another another pilot study



Why are we interested?

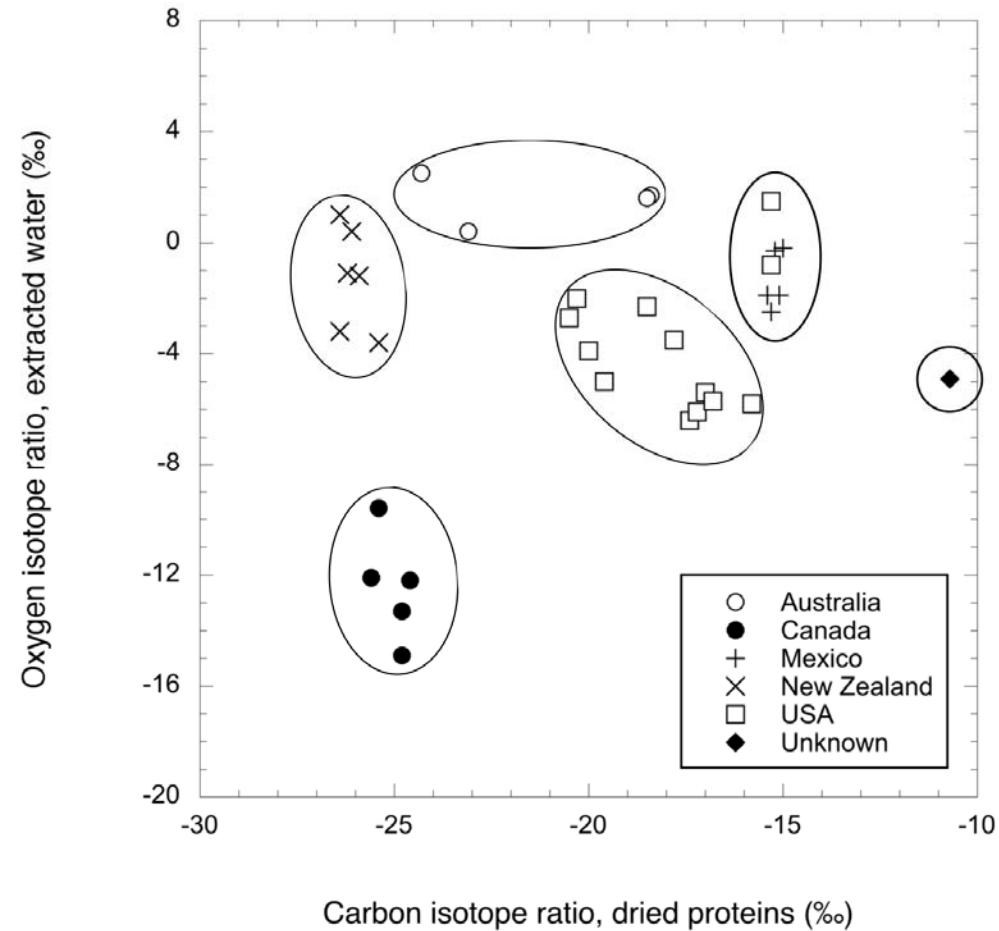


The application of stable isotope and trace element analysis in forensic investigations can distinguish materials that are chemically identical.



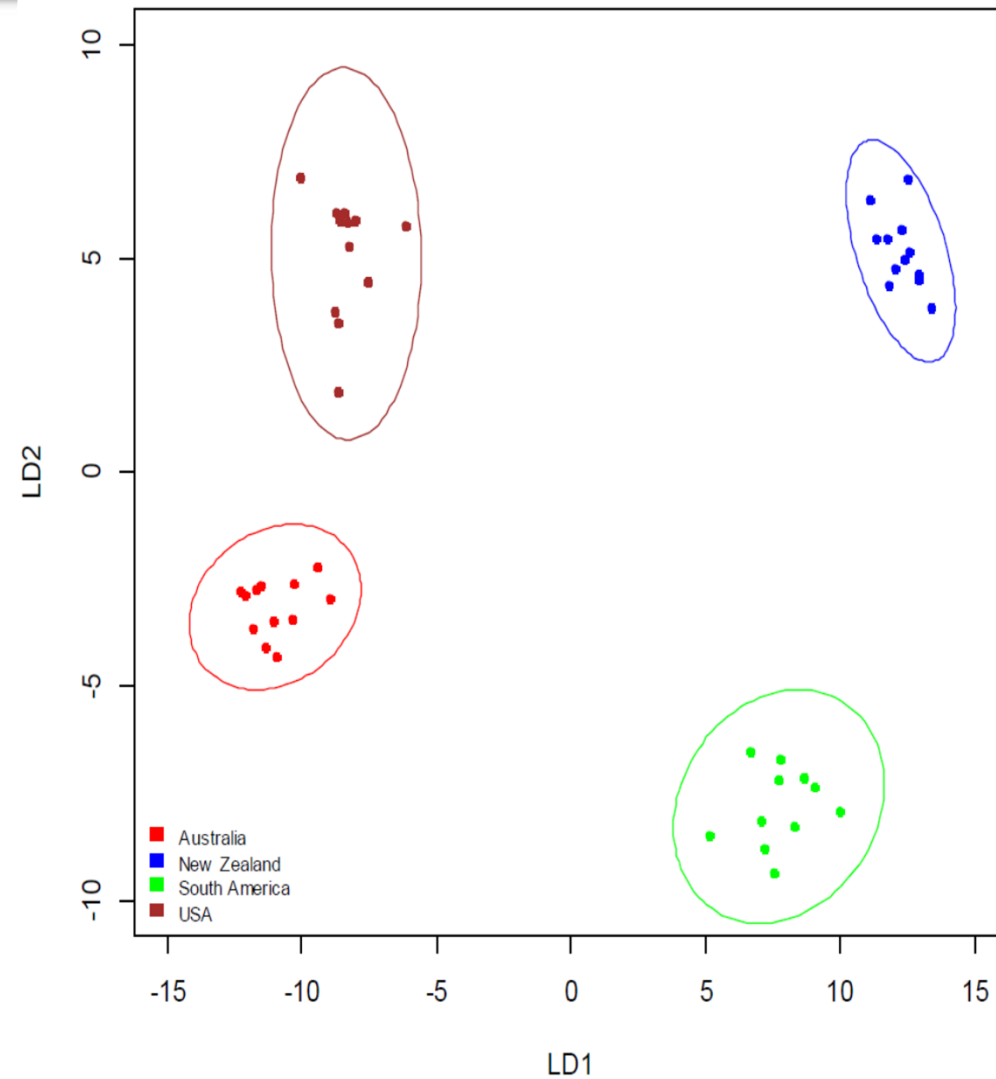


Pilot Study Stable Isotopes





Pilot Study Trace Elements





Current Comparison

- Further analysis confirms better resolution using trace elements
- Current results give 99% certainty for geographies tested with 150 samples tested so far
- We are working to define an industry data base and develop a program to identify geographic origin





Current Status

- After considerable investigation and discussion
 - We are in the process of finalizing an agreement to develop an industry wide trace element data base
- We are also monitoring for other technologies to determine origin and age of source
 - Antibody based methods



Future of Traceability

- Combination of testing and paperwork audit will strengthen the program
 - Continued focus by ISIA
- Increased focus from customers and regulators will also strengthen the program





Gamma Irradiation Task Force





Gamma Irradiation Task Force

- A proposal was made at the USAHA meeting in October 2015 to allow FBS irradiated outside the USA to be imported
- USDA and USAHA both knew there was a need to understand this subject better
- ISIA volunteered to work on this project
 - Project approved at the 2015 ISIA Annual Meeting
- Several months spent recruiting experts
 - First meeting held in January 2016



What is the concern?

- Many customers, suppliers and others do not fully understand gamma irradiation
 - “Suppliers are secretive”
 - “There don’t seem to be any rules about how the process is validated”
 - “Gamma kills all viruses”
 - “All the big suppliers have their own irradiation facilities”
- ISIA recommends Gamma Irradiation as THE method of choice for post manufacturing treatment of serum



Task Force Participants

Participant	Affiliation	Representing
Sue Brown	TCS Biosciences	Supplier
Bart Croonenborghs	Sterigenics	Irradiator
James Dunster	Moregate BioTech	Supplier
Debbie Elms	Thermofisher Scientific	Supplier
Randy Fitzgerald	Proliant	Supplier
Greg Hansen	GE Healthcare/HyClone	Supplier
Karl Hemmerich	Ageless Processing Technologies	End-users
Huw Hughes	Zoetis	End-users
Robert J. Klostermann	Merial	End-users
Ray Nims	RMC Pharmaceutical Solutions	End-users
Mark Plavsic	Torque	End-users
Andy Pratt	GE Healthcare	End User
Mara Senescu	STERIS	Irradiator
Pierre Leonard	GSK	End User
Martell Winters	Nelson labs	End User
Marc Wintgens	Excellencia	End user

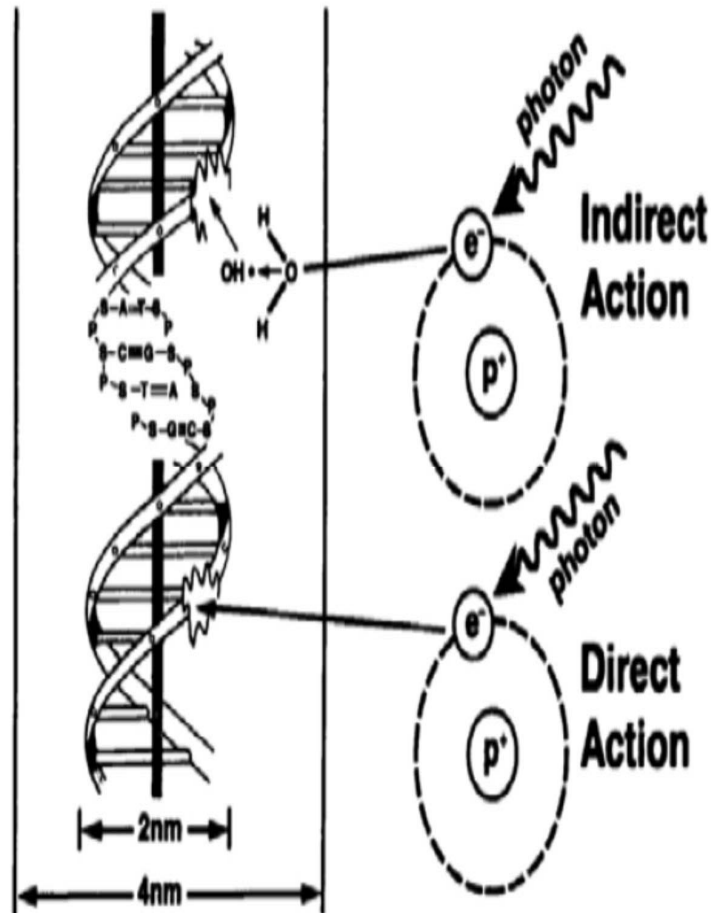


Approach

- It was agreed that
 - We would not wait until this was perfect or totally complete to begin publishing
 - Or it might never happen.....
 - The task would be broken up into several parts
 - These parts would stand alone and be published as ready
 - FDA requested that this be freely available!
 - We might turn this work into a standard eventually



Mechanism of Action



Ambient temperature
No scavengers
Aqueous solutions
Oxygenated

Low temperature
Scavengers
Low Oxygen



Areas of Focus

- The task is currently broken into 6 parts with different experts taking the lead

FOCUS	LEAD	STATUS
Introduction to Gamma Irradiation and Serum	RJV and Karl Hemmerich	Published
Effect of Gamma Irradiation on viruses	Mark Plavsic and Ray Nims	Punlished
Dose mapping and validation	Andy Pratt and Bart Croonenborghs	Final editing
Effect of gamma irradiation on polymers	Karl Hemmerich	Almost final
Product Maintenance through the process	Sue Brown and Mara Senescu	Outline complete
What does all this mean	TBD	Waiting for solid drafts of first 5



Main Points in Introduction

- Why is post-manufacturing treatment required
- What kinds of treatment methods are available
- Why Gamma irradiation is the method of choice
- How Gamma Irradiation works
- What types of equipment are used
- What regulations are involved in the use of Gamma Irradiation





Main Points in Effect on Viruses

- Validation of the efficacy of gamma irradiation for viral inactivation
 - Conducting virus inactivation studies
- Efficacy of Gamma Radiation for Pathogen Reduction in Serum
 - Inactivation of viruses
 - Inactivation of mycoplasma
- Assessment of Serum Performance following Gamma Irradiation





Main Points in Dose Mapping/ Validation

- Dosimeters have temperature dependent response that is not well characterized
 - What steps are needed to deal with this.
- Dosimeter positions should be on the filled parts of the sterile barrier system
 - not outside the cryotainer during modelling



Slide 27

RV1

Rosemary Versteegen, 5/11/2016

RV [2]1

I am not an expert on gamma irradiation dosimetry systems, but I do know that some technologies have different capabilities than others.

It could be interesting to note that consideration must be given for the selection of the dosimetry system, for example - alanine dosimetry systems versus radiochromic dosimetry systems versus poly-methylmethacrylate (Harwell Red dosimeters) as well as the capability of the gamma irradiation facility QC laboratory to use the various dosimetry methods. I think that the alanine dosimetry system seems to be the current favorite, but I am not familiar with performance of this dosimeter under the conditions of dry ice packed serum.

Rosemary Versteegen, 5/11/2016



Main Points in Dose Mapping/ Validation

- Assessment must be made about effects on dose delivery arising from
 - Serum moving around in irradiation container
 - Partially filled irradiation containers
 - Various quantities of dry ice due to time in process
 - Other product in the irradiator
- PQ Dose map is unique to irradiator and packaging/loading pattern



Slide 28

RV2

Rosemary Versteegen, 5/11/2016

RV [2]2

I am not an expert on gamma irradiation dosimetry systems, but I do know that some technologies have different capabilities than others.

It could be interesting to note that consideration must be given for the selection of the dosimetry system, for example - alanine dosimetry systems versus radiochromic dosimetry systems versus poly-methylmethacrylate (Harwell Red dosimeters) as well as the capability of the gamma irradiation facility QC laboratory to use the various dosimetry methods. I think that the alanine dosimetry system seems to be the current favorite, but I am not familiar with performance of this dosimeter under the conditions of dry ice packed serum.

Rosemary Versteegen, 5/11/2016



Effect on Polymers

- Effect on biological activity
 - Nucleic acids
 - Proteins
- Effect on packaging and hence biological activity
 - Leaching





Cold Chain Management

- Why is temperature control so important?
 - Low temperature favors the direct mechanism of energetic photon interaction with pathogen nucleic acids leading to inactivation
 - At ambient temperature the indirect mechanism involving radiolysis of water to form oxygen radicals can cause damage to serum components adversely impacting performance





Cold Chain Monitoring

- Customers are becoming more concerned about management and proof of cold chain maintenance
- Temperature monitors can be included in shipment to and from gamma facility
 - During the gamma irradiation process, temperature monitors likely will need to be removed.
- During removal and return of serum to vehicle, proof of temperature control will not be available
 - There will be 'gaps' in temperature traceability.





Things to Consider

- Vendor Capabilities and Capacity
- Cold chain management
 - Freezer space
 - Dry Ice
- Dosage specifications
 - Balance between virus reduction and biological activity





Customer Education

- Serum suppliers must rely on on 3rd parties
 - Transport Carriers, gamma irradiation plant staff
- It takes a TEAM - Serum suppliers are not in control of the full process
 - Delays / issues can and do arise in this part of the supply chain
- Careful coordination with irradiators can result in seamless, accurate irradiation of serum



Publication

All articles will
be published in
BioProcessing
Journal in open
access





Thank You!