THE ISIA JOURNEY

May 2018

CONTEXT: THE SERUM INDUSTRY IN 2006

The use of animal derived material for cell culture dates back over 70 years. The Salk Polio Vaccine was one of the first products mass-produced using cell culture techniques. This vaccine was made possible by the cell culture research of John Franklin Enders, Thomas Huckle Weller, and Frederick Chapman Robbins, who were awarded the Nobel Prize for Physiology in 1954 for their discovery of a method of growing the Polio virus in monkey kidney cell cultures.

The requirement for animal derived material as supplements for cell culture has grown into a complex and multi-million dollar industry, stretching across the globe. The complexity of the serum industry has previously been described by Leland Foster, the founder of the International Serum Industry Association (ISIA)[1]. Prior to the inception of the ISIA in 2006, the industry was best characterized by

- The central role of member companies in the advancement of life science research and the ever-increasing number of serum-based biopharmaceutical products in development and in production
- The global scope of supply and consumption
- The relatively small market size in contrast to the industries it supports
- The frequent intersections with many regulatory agencies and regulations; from import/export to quality control of medicinal products and diagnostic tests
- The disparate costs of raw material based on country of origin, resulting in substantial retail price differentials
- The product complexity requiring extensive customer education to counter years of accumulated misinformation
- The relatively large number of suppliers

This brief outline provides some background to the serious challenges which were faced by the animal serum supply industry. These problems could not be resolved by individual companies acting independently.

As with all small markets, there was a large amount of interaction between the major companies involved in the supply chain. It became clear that a trade association of global serum suppliers was necessary. Almost every other industry had a trade association. This was a successful model and needed to be replicated by the serum industry.

BEGINNINGS

The idea of such an association had been spoken about for some time by a number of key players. Following initial discussions between Dr. Leland Foster of Hyclone and Mr. Ole Nielsen of BioWest and with support and encouragement from others it was decided to convene a

meeting of interested parties. Dr. Rosemary Versteegen (retired InVitrogen/Gibco executive) agreed to facilitate the discussion.

The purpose of the initial meeting was to explore the possibility of such an association and to determine the willingness of suppliers to take on the challenges of ensuring its long-term success. A number of suppliers were approached with the idea. With considerable cajoling of some would-be participants, most of those contacted agreed to attend an inaugural meeting which was held in 2006 at a suburban Denver hotel and sponsored by HyClone, Sigma, and Life Technologies, three of the largest global serum suppliers at that time.

At this meeting, Leland Foster made the decision that HyClone would actively participate in the formation of the Association only if Moregate (Ms. Elizabeth Meixner, specifically) would agree to become part of the organizing group. Having received that commitment, Foster proceeded to press for the organization along with others.

The consensus of the attendees of this first meeting was that such an organization would be very useful. In a subsequent meeting, the organization was formalized and continues to this day. Key to the successful launching of the organization was hiring a well-qualified, knowledgeable executive to drive the daily business. Dr. Rosemary Versteegen became the first (and only-to-date) chief executive officer.

The name selected for the association was The International Serum Industry Association (ISIA)

CREATING A FOUNDATION

The immediate task, aside from the business of organization and funding, was to identify the founding principles which needed to be central in all plans and deliberations going forward. These are presented here without regard to priority.

- To harmonize common terms and definitions allowing the creation of an industry-wide glossary which would allow shared definitions of terms and language among suppliers, customers and regulators. This included selection and identification of common, quality-control testing protocols with agreed units of measurement.
- To unite all the members in support of the association as the common, authoritative voice for the industry in order to earn the respect and confidence of all industry constituents especially regulatory agencies.
- To establish self-policing of the membership by the acceptance of and adherence to a strict code of ethical conduct. Of most concern with ethical business practices were: (a) traceability – geographic origins stated in the certifications and on product labels must be correct and (b) product integrity – the material must indeed be the product identified in those certifications and on their labels.
- To proactively support global education by providing educational materials and accepting opportunities to participate in public forums to promote honest scholarship and to dispel long-held misunderstandings.
- To encourage regulatory agencies worldwide to take a more reasoned, science-based, globally-harmonized approach to import/export rules and quality control of medicinal

products. This global harmonization of import/export requirements agreed among national governments and their agencies would help address the geographically-based serum price differences and ameliorate the most compelling incentive for fraudulent practices – money.

CREATION

At a subsequent meeting in Boston, Massachusetts later in 2006, the framework of the organization was laid down. The first documents were created.

1. By-Laws for the organization
2. Budget
3. Dues philosophy

This was finalized during the first annual meeting in Pasadena, California in late 2006. The Board of Directors was elected and Leland Foster was elected as first Chairman of the Board of Directors. Rosie Versteegen was employed as the first Chief Executive Officer. The first membership dues were determined.

THE REGULATORY WORLD BEFORE 2006

In the late 1980s the world and the industry were stunned by an outbreak of Bovine Spongiform Encephalitis (BSE). As a result, several pieces of regulation that impacted the import and use of serum were enacted across the world. In particular, the European Community (EC) enacted first, the Balai Directive (Council Directive 92/65/EEC) in 1992 and subsequently, in 2002, Regulation (EC) No 1774/2002, which laid down health rules concerning animal by-products not intended for human consumption. The ambiguity caused by the latter resulted in different interpretations by member states and even individual Border Inspection Posts within a single country. As a result, the importation of serum into the EU was strictly forbidden. Fortunately, the UK, through the intervention of DEFRA (UK Department of Environment, Food and Rural Affairs), was enabled to become the gateway to Europe for the importation of this very critical material.

JUMPING IN HEAD FIRST (2006-2009)

Soon after its founding, the ISIA began an intense outreach to a wide spectrum of groups, and a communication network was created from scratch. Today's version in shown below.

Over time, the ISIA began to be included in meetings and even asked for input and assistance in forging new regulatory guidelines.

As a result, progress was made by the newly formed ISIA Regulatory Team in Europe, to include the following:

- ISIA collaborated with DEFRA to publish guidelines on DEFRA letterhead on how to import animal sera into the UK.
- The 2007 Foot and Mouth Disease outbreak in the UK, which resulted in a finished product hold, was resolved in three days using ISIA wording.
- EC523/2008 was published, allowing legal importation of Category 1 material from NZ, USA and Australia. Category 1 serum is so called if the animal it was sourced from may have residual chemicals present, including growth hormone.
- EC Directive 1069/2009 “laying down health rules as regards animal by-products and derived products not intended for human consumption” was published.

The ISIA also began work on other principle driven activities:

- Beginning in Europe, close ties were forged with regulatory authorities worldwide
- Definitions of serum types and countries of origin were published.
- The first Traceability Policy was developed and approved by the Board. An audit checklist was created, and Animal Technologies became the first Traceability-Certified member.
- A white paper on Standardization of Quality Control was published.
- After a tentative start, the ISIA developed an excellent relationship with the United States Pharmacopeia (USP) to develop the current guidelines on Fetal Bovine Serum (FBS) and serum, eventually resulting in USP <1024>, <90> and the release of the USP FBS standard.

SPREADING WINGS (2010-2013)

After five years of operation, the ISIA regular membership had doubled. In addition, the category of Associate Membership was opened up to end users of the products, with the result that nine associate member companies were added. The resources available from ISIA and the influence of the Association were being increasingly recognized.

The ISIA continued its outreach and involvement in the following:

- EU Directive 142/2011 implementing Regulation (EC) No 1069/2009 "laying down health rules as regards animal by-products and derived products not intended for human consumption" was published.
- After extensive discussion with member states, the ISIA guidance to the above was published.
- CE marking clarification to members was published.
- Successful input was provided to European Medicines Agency (EMA) concerning guidance on use of serum and trypsin[2,3].
- First serum-related publication was published by ISIA, Siegel and Foster[4.]

GROUNDING IN SCIENCE (2013-2017)

The ISIA showed it was *the* balanced source of information on education for serum quality, testing and use. There was a growing awareness by the industry, customers and regulatory bodies on the need for new testing methods. During this period:

- The ISIA published or assisted in the publication of five additional scientific papers on serum issues[5,6,7,8].
- The ISIA also published four Gamma Irradiation scientific papers [9,10,11,12], with two more to follow in 2018.
- Traceability Certification continued to expand with 23 major companies certified and more in process.
- A pilot study for the Determination of Country of Origin by stable isotopes analysis was performed. As a result, a partnership with Oritain Global Ltd. was begun and the use of trace elements was pioneered. More than 500 samples from a wide variety of geographies were sourced from traceability certified ISIA member companies to establish an industry-wide global database. A publication is in preparation.
- ISIA collaborated with members to further develop a rationale for the determination of animal age in serum using IgG and GGT analyses[13].

TODAY

From its beginnings in 2006, ISIA has become a strong voice for the industry Our growth continues both in members (Figure 1) and meeting attendees (Figure 2). The governance of the Association is strong and stable at both the Board (Figure 3) and Officer level (figure4). Our global reach continues to expand as shown by our meeting locations (Figure 5). We look forward to continued success in our quest to ensure the long-term continuation and success of serum and animal derived products for the global life science industry.

Figure 1: ISIA Membership Growth

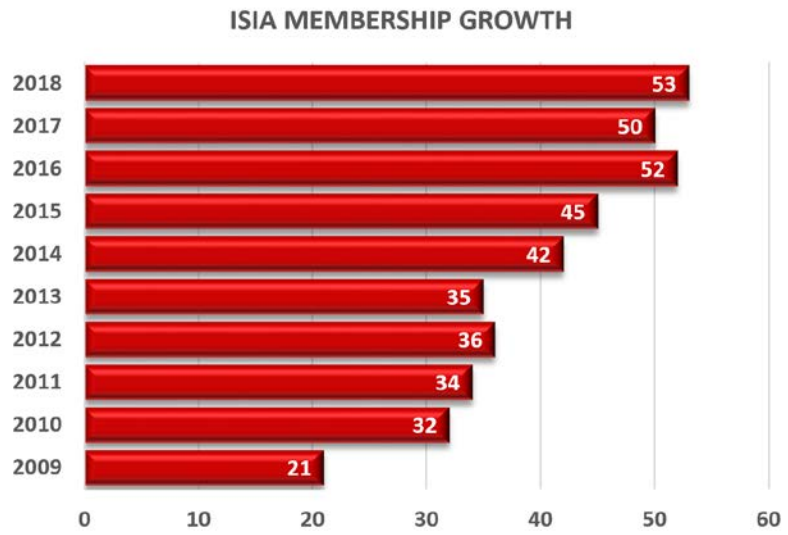

Figure 2. ISIA meeting Attendance

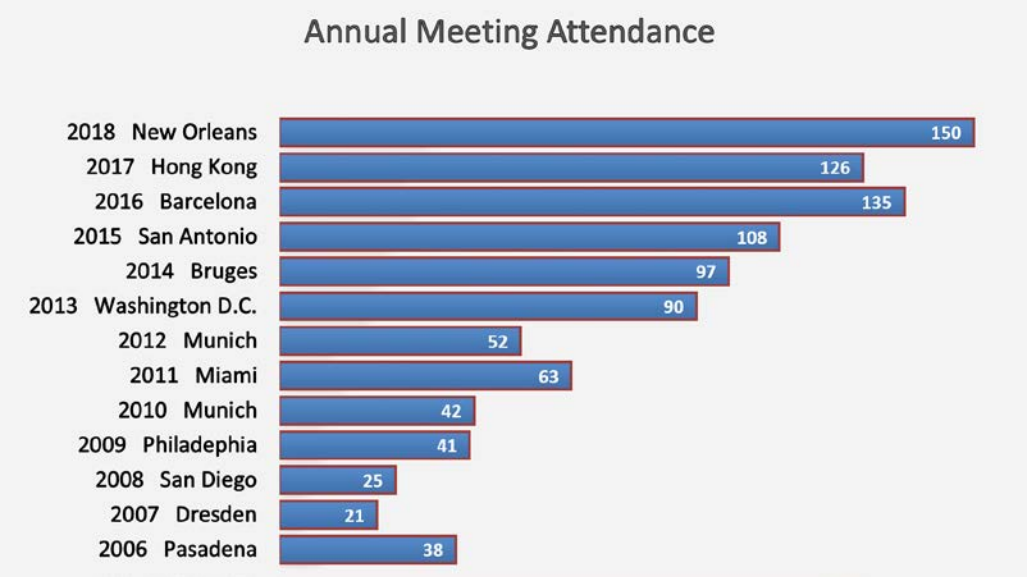

Figure 3. Board Chairs since founding

2006-2008	Leland Foster, HyClone
2008-2010	Elizabeth Meixner, Moregate Biotech
2010-2012	Steve Doelger, Sigma
2012-2014	George (Skip) Wrape, Animal Technologies
2014 -2016	Jim Crean, ThermoFisher Scientific
2016 - present	Jenny Murray, Life Science Production

Figure 4: Officers since founding

Year	CEO	Treasurer	Secretary
2006	Rosemary Versteegen	Stephen Judd, Gemini	Karen Blaine, Mediatech
2007	Rosemary Versteegen	Stephen Judd, Gemini	Karen Blaine, Mediatech
2008	Rosemary Versteegen	Stephen Judd, Gemini	Jenny Murray, APS
2009	Rosemary Versteegen	Stephen Judd, Gemini	Jenny Murray, APS
2010	Rosemary Versteegen	Stephen Judd, Gemini	Jenny Murray, APS
2011	Rosemary Versteegen	Stephen Judd, Axenia	Jenny Murray, APS
2012	Rosemary Versteegen	Stephen Judd, Axenia	Jenny Murray, APS
2013	Rosemary Versteegen	Stephen Judd, Axenia	Jenny Murray, APS
2014	Rosemary Versteegen	Stephen Judd, Axenia	Jock Elliott, Moregate Biotech
2015	Rosemary Versteegen	Stephen Judd, Axenia	Jock Elliott, Moregate Biotech
2016	Rosemary Versteegen	Stephen Judd, Axenia	Jock Elliott, Moregate Biotech
2017	Rosemary Versteegen	Stephen Judd, Axenia	Jock Elliott, Moregate Biotech
2018	Rosemary Versteegen	Stephen Judd, Axenia	Jock Elliott, Moregate Biotech

Figure 5: Annual meeting History

Year	Location	Country
2006	Pasadena, CA	USA
2007	Dresden	Germany
2008	San Diego, CA	USA
2009	Philadelphia, PA	USA
2010	Munich	Germany
2011	Miami, FL	USA
2012	Munich	Germany
2013	Washington, DC	USA
2014	Bruges	Belgium
2015	San Antonio, TX	USA
2016	Barcelona	Spain
2017	Hong Kong	People's Republic of China

2018	New Orleans, LA	USA

REFERENCES:

1. Foster, Leland : ISIA: The Rationale, ISIA website/member center
2. Guideline on the use of bovine serum in the manufacture of human biological medicinal products EMA/CHMP/BWP/457920/2012
3. Guideline on the use of porcine trypsin used in the manufacture of human biological medicinal products EMA/CHMP/BWP/814397/2011
4. Siegel, William and Foster, Leland Foster: Fetal Bovine Serum: The Impact of Geography Fall 2013, BioProcessing Journal
5. Versteegen, Rosemary: Serum: What, Where, & When Spring 2016, BioProcessing Journal Vol.15/No.1
6. Siegel, William: Fetal Bovine Serum: Risk Management Spring 2016, BioProcessing Journal Vol.15/No.1
7. Versteegen, Rosemary Serum: A Better Characterized Biological July/August 2017, American Pharmaceutical Review July/August 2017
8. Gamma Irradiation of Animal Serum: An Introduction
9. Versteegen, Rosemary, Plavsic, Mark, Nims, Raymond, Klostermann, Robert and Hemmerich, Karl: Gamma Irradiation of Animal Serum: An Introduction Summer 2016 BioProcessing Journal [Vol.15/No.2]
10. Plavsic, Mark, Nims, Raymond, Wintgens, Marc and Versteegen, Rosemary: Gamma Irradiation of Animal Serum: Validation of Efficacy for Pathogen Reduction and Assessment of Impacts on Serum Performance Summer 2016 BioProcessing Journal [Vol.15/No.2]
11. Croonenborghs, Bart, Pratt, Andy, Bone, Lorraine and Senescu Mara: Gamma Irradiation of Frozen Animal Serum: Dose Mapping for Irradiation Process Validation Fall 2016 BioProcessing Journal [Vol.15/No. 3]
12. Brown, Sue, Croonenborghs, Bart, Head, Kevin, Senescu Mara, Nims, Raymond, Plavsic, Mark, and Versteegen, Rosemary: Gamma Irradiation of Animal Serum:Maintaining the Cold Chain Throughout the Process 2017 BioProcessing Journal Open Access article
13. Cheever, Michelle, Master, Alyssa and Versteegen, Rosemary: A Method for Differentiating Fetal Bovine Serum form Newborn Calf Serum 2017 BioProcessing Journal Open Access article