ADRIANA E. MANZI, PhD

Managing Director / Technical Consulting Group

adriana@athelnbiomed.com

US Cell: 858-405-4584

Decisive life science leader with nearly 30 years of experience in R&D of biologics, including biosimilars and cell therapies. Successful track record building and managing global, market-competitive, technical organizations supporting multiple therapeutic areas, customer audiences, products and services. Expert on the structural characterization of complex biologics using physico-chemical methods (i.e. NMR, MS, HPLC, CE, and hyphenated techniques). Expert on glycosylation analysis and glycobiology. CMC expert with extensive experience on due diligence, technical strategic and operational planning, troubleshooting and problem solving.

PROFESSIONAL EXPERIENCE

ATHELN, INC. (Southern CA based with Global reach) **Feb 2010 - Present**

Founder, President and Managing Director

Principal Consultant - Biologics CMC / Analytics / Glycobiology / Technical Strategic Planning

Atheln is an innovative biopharma Consulting and Contract Development Organization, specializing in the creation of product development and commercial strategies. Commercial and technical disciplines are integrated to maximize product value.

Atheln has a highly interactive network of consultants, in the US and Europe, in the areas of new product planning; biologics cell line, upstream and downstream process development; analytical development; CMC; non-clinical studies, Pharm/Tox, PK/PD; regulatory strategy; clinical; quality & compliance; project management; domestic and international sales & marketing; business development; and licensing. Atheln's hands-on style ensures effective planning, execution and management of deliverables.

Examples of past and present projects include:

- Responsible for all technical aspects of building a biosimilar portfolio fit to a EU client interest and capabilities including the evaluation of 56 potential candidate molecules. Designed the analytical comparability packages.
- Writing CMC Section for US filing of two monoclonal antibodies, one of them biosimilar
- Conducted analytical package due diligence in Asia for a biologic product to be licensed for the US market
- Review an unfavorable EMA feedback on the glycosylation analysis of a recombinant drug substance, designed remediation experiments and addressed the regulatory concerns
- Global technical due diligence for licensing three biotherapeutic products, focusing on the analytical package
- Evaluation of a recombinant protein comparability after process scale up (mammalian expression)
- Review and optimization of many physicochemical analytical methods and their validation packages for all stages of product development

- Led Analytical Development efforts, wrote CMC section of IND and continues to advice on a novel chimeric antibody-like molecule (fusion protein) for the treatment of angiogenesis-related diseases that successfully completed Phase I clinical trials and is now on Phase 2 for its use in wet AMD. This included the evaluation of the impact of carbohydrate changes on the in vivo biological activity.
- Conducted and provided resolution to several OOS investigations
- Leader development team for a novel oncolytic virus platform
- CMC advisor for a nanoparticle delivery technology platform
- CMC advisor for the development of an engineered FGF-1 expressed in bacteria and targeted to corneal dystrophies
- CMC advisor for the Cystinosis Research Foundation for the development of a new delivery technology and a cell therapy suited for the treatment of this orphan metabolic disorder
- Head of QA for a virtual company conducting Phase 2 clinical studies in wet AMD for a fusion protein with a novel MOA
- Member Scientific Advisory Board for a Global Biologics CMO/CRO organization. Role: Analytical technologies
- Led technical team, including CMC, non-clinical, clinical, and regulatory disciplines, in the preparation of a strategy and a FIH to Phase 2 development plan for one API in three forms of administration for four indications.
- Evaluated LCM (Life Cycle Management) technical opportunities for immunoglobulin products
- Advised on all CMC topics and prepared CMC Section of IND for a humanized IgG1 kappa immunoglobulin for treatment of PNH expressed in mammalian cells
- CMC advisor and lead of technical team (non-clinical, clinical, regulatory disciplines) for a synthetic glycolipid immunotherapy for solid tumors
- Prepared CMC section of pre-IND briefing package for an allogeneic human platelet-derived topical ophthalmic solution for dry eye
- CMC due diligence of an oncology cell therapy approach on Phase 3 clinical development in support of investment group
- CMC due diligence in Europe for a allogeneic cell therapy to be licensed for the US market
- CMC due diligence for a nanoparticle delivery technology platform in support of lead investor
- Technical due diligence on a new equipment for evaluation of protein aggregation in support of investment group
- Reviewing CMC section of a biologic BLA
- Design of a CMC strategy for a new type of monoclonal antibody-like platform
- CMC lead investigator for a University technology transfer group assessing a 10-year development program of a biologic for multiple therapeutics indications which license had been canceled
- Led GAP analysis team (CMC, biology, non-clinical, clinical, regulatory) for the development plan of a novel, first-in-class, small molecule therapeutics targeting cancer stem cells (CSCs) in the central nervous system (CNS)
- Led the team (CMC, non-clinical) conducting GAP analysis and writing a SBIR application for the development plan of small molecule thyrotropin (thy) receptor (thyr) agonist for thyroid cancer
- Designed Quality Systems for two virtual companies in the ophthalmic area, one virtual company in the stem cell area and three virtual companies dedicated to small molecule oncology products
- Advisor to two biologics CMOs with operations ranging from process development and Phase I clinical production to commercial production

- Expert witness in a case related to production of a recombinant protein in bacteria
- Global market analysis of technical capabilities of fill & finish operations and manufacturers of state-of-the-art analytical technologies
- Conducted many GAP analyses of product development and manufacturing compliance in preparation for filing, licensing and acquisition
- Conducted international audits of several biologics CMOs / Contract Laboratories

MANZI & ASSOCIATES (San Diego, CA) **Jun 2006 – Feb 2010**

President & Principal Consultant

Provided technical consulting services for research and development of biologics, including all aspects of CMC, for all stages of development.

Accomplishments included:

- Acted as VP Product Development for virtual company up to successful IND filing and phase 1 clinical trial for an autologous therapeutic dendritic cell vaccine for refractory prostate cancer
- Built the Quality System for two virtual companies, including writing SOPs, batch records, specifications, etc.
- CMC management for production of a fusion protein in BHK cells
- Revision of the CMC section of a BLA for a transgenic protein
- Revision of a CMC section of the IND of two gene therapy products – expressed in E. coli
- Qualification of five CMOs and auditing of over 10 other sites in the US and EU
- Quality aspects of the manufacturing of stem cells treatments
- Advice on analytical methods development and validation for FDA compliance covering diverse recombinant and fusion proteins and cell therapies
- Writing of seven CMC sections
- Set up of specifications for five drug substances and drug products
- Design of four stability studies for recombinant proteins
- Design of comparability studies for a recombinant protein and a gene therapy after process changes
- International due diligence for recombinant and transgenic proteins, including risk analyses for planned EMEA and FDA filings
- Supported a regulatory group with CMC advice in formulation development of a malaria vaccine, new formulations for biosimilar low molecular weight heparins and antibiotics

BAXTER HEALTHCARE CORPORATION (San Diego, CA / Round Lake, IL) **1998 - 2006**

Senior Director - Corporate Tech Resources / Member, Leadership Team *2004 – 2006*

Senior Director, Research – Corporate Tech Resources *2003 – 2004*

Technical Director *2001 – 2003*

Acted as a global consultant to all Baxter divisions and business units.

Responsibilities / Accomplishments included:

- Chemistry of small molecules and biomolecules, including support of life cycle management (Factor VIII, plasma derived and recombinant, Advate®) and new developments (Factor VIIa) of Baxter's coagulation products, testing of polysaccharide vaccines, modernization of testing related

to polysaccharides used in renal dialysis and solving an investigation related to their recall in Europe due to anaphylactic reactions (icodextrin/Extraneal®) and development of an analytical platform for LMWH (low molecular weight heparins).

- Technical strategic planning for Baxter biosciences, renal, medication delivery, and cell therapies businesses, including support of discussions with regulatory authorities and preparation of CMC sections for submissions.
- Analytical consulting and problem solving spun to all US (AK, CA, FL, IL, NC, NJ, Puerto Rico) and European Baxter large manufacturing sites as well as the plants in Singapore, Mexico and Colombia and smaller support operations distributed Worlwide.
- Major accomplishments included: Solving technical problems at manufacturing sites of raw material suppliers that impacted Baxter products. One such endeavor resulted in $75 M savings to Baxter and received a Corporate Award in 2006.
- Successfully designed and executed the CMC for two biopharmaceutical programs with development plans spanning 10 years. Led the analytical function for key programs such as Epoietin Omega (15 team members; >2M/year budget). These projects included extensive comparability studies of recombinant glycoproteins, including a biosimilar product.
- Built a team dedicated to state-of-the-art analysis of biomolecules new to Baxter addressing the growing biopharmaceutical business. The Biotechnology Analytics team was designed based on a gap analysis and long-term strategic planning spanning the areas of biochemistry, bioseparations, bioanalytical support of PK/TK studies, mass spectrometry and NMR (60% members with PhD, 20% MS and 20% BS degrees). The instrument park included: twelve regular, micro and Nano HPLC systems with UV-Vis, radioactive, fluorescence, RI, MALLS, and ELSD detectors; three CE units with UV and fluorescence detection, one linked to MS; three MS systems (LCQ, TSQ and LTQ), peptide sequencer; pressure cycler; two NMR spectrometers at 400 and 600 MHz including cryoprobe and MAS probe as well as robotics for sample preparation and analysis. All activities were conducted in compliance with GLP and cGMP practices.
- Built a team dedicated to the analysis of PK samples by chromatography and LC-MS. These were all small molecule API from approved products that were reformulated for optimized sustained delivery. Work included the development and validation of analytical methods as well as transferring them to different global testing sites.
- Deployed biotechnology analytics capabilities across Baxter divisions worldwide making significant contributions supporting due diligence efforts, setting-up the methods required for the analytical comparability of recombinant glycoproteins, analysis of complex polysaccharides for the renal and vaccines markets, supporting the optimization of cell-culture processes, developing and validating specific stability-indicating analytical methods for biomolecules, supporting preclinical studies in a variety of animal models as well as clinical studies, performing metabonomics by NMR and setting up PAT (process analytical technologies) for biologics. These efforts were rewarded with a Corporate Award in 2004.

NEXTRAN INC. (San Diego, CA) **1999 - 2001**

Technical Director *2000 - 2001*

Associate Director, Analytical Development/Quality Control *1999 - 2000*

Nextran, an affiliate of Baxter Healthcare Corporation, was at the forefront of xenotransplantation research. Nextran had a GMP farm to provide transgenic pig organs for human transplant. Research and development was under way to suppress the immune response to such transplants. Responsibilities included:

- Selected analytical platform and designed analytical methods development and validation protocols. Led a team of four scientists (M.S. and B.S. degrees) in protocol execution. The molecules being tested included:

- Oligosaccharides and the small molecule raw materials used in their manufacturing
- Polymers (PEGS) used as carriers of such oligosaccharides

- Prepared Drug Master Files
- Supported manufacturing, troubleshooting and solving problems for the cGMP production of recombinant enzymes in mammalian, yeast and bacterial cell culture and for the synthetic chemistry operation.
- Led the Quality Control Department of the cGMP facility: managed stability programs; set up specifications for raw materials and products; selected and audited contract laboratories; led in-house reference standard program, including design of qualification packages and CoAs.

CYTEL CORPORATION (San Diego, CA) **1998 - 1999**

Associate Director, Analytical Development

Cytel was a biotechnology company in the carbohydrate field that developed a technology for chemo-enzymatic synthesis of complex carbohydrates. This technology allowed for the first time the cost-effective commercial production of carbohydrate pharmaceuticals as well as others for the food and cosmetics industries.

- Optimized and modernized the analytical development department in preparation for NDA submission: hiring and training personnel (MS and BS degrees); equipment selection, purchasing and validation (i.e. HPLCs, detectors, LC-MS, preparative HPLC); establishing a program for the purification and testing of in-house reference standard candidates; writing departmental SOPs, etc.
- Built the analytical component of the CMC section for Cytel's leading drug candidate (a substituted octasaccharide) in a record eight months. This included the designed and supervision of the development of new methods for raw materials, key intermediates, bulk drug substance and final vialed product.
- Set up specifications for oligosaccharide products and raw materials
- Led the development and validation of analytical methods
- Designed stability studies and evaluated their results

UNIVERSITY OF CALIFORNIA SAN DIEGO **1986-1998**

***Department of Medicine* (San Diego, CA)**

Assistant Adjunct Professor, Medicine *1991 – 1998*
Director, Glycobiology Core Facility *1991 – 1998*
Visiting Scholar, Cancer Center *1986 – 1989*

Acted as Principal Investigator in projects studying complex carbohydrates of biological significance, collaborating with a multidisciplinary group of researchers (physicians, biologists, biochemists, etc.).

- Developed original approaches for the characterization of carbohydrates in biomolecules (glycoproteins, glycolipids, polysaccharides, glycosaminoglycans in heparin and LMWH, GPI-anchors, etc.) by physicochemical methods, including a variety of HPLC techniques, LC-ESI-MS and NMR.
- Developed a strategy for the parallel isolation of all classes of glycoconjugates from cells and tissues. Worked extensively with a variety of cell cultures and mammalian tissues (rat, mouse, human).
- Chemistry leader in 15 different research projects in parallel. Provided strategic planning for successful analytical results to those multidisciplinary projects.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.