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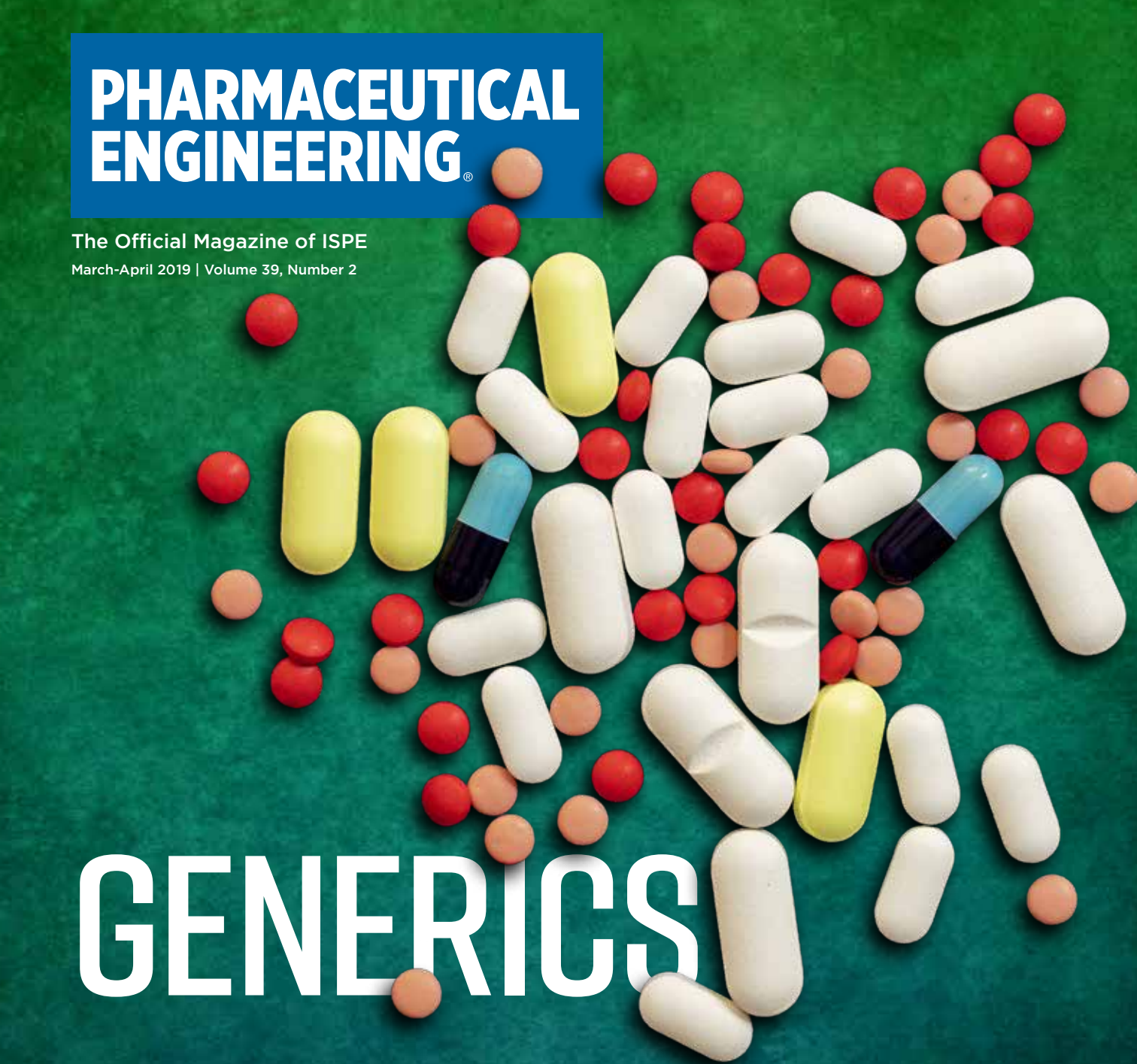

GENERICS

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GENERICS: INDUSTRY PERSPECTIVES FROM FOUR LOCALES

In recognition of the growth and importance of generics to the pharmaceutical market, *Pharmaceutical Engineering* takes a look at what's happening in four global markets: India, China, Japan, and the Philippines.

ON THE COVER This artwork symbolizes the many generics that are in growth mode in markets around the world.

FEATURES

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REPORTS FROM ISPE CONFERENCES

In this issue, PE provides coverage of multiple sessions from the 2018 ISPE Biopharmaceutical Manufacturing Conference, including a Women in Pharma® roundtable session (page 14), and coverage from the first ISPE Europe Aseptic Conference (page 46).

DEPARTMENTS

TECHNICAL

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Pharmaceutical Engineering welcomes readers' comments. Letters must include the writer's full name, address, organization, and years of ISPE membership. If published, letters may be edited for length and clarity. Send correspondence to ssandler@ispe.org.

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By Jim Breen

ISPE and Information Sharing


Jim Breen

I hope 2019 is bringing exciting challenges and fulfillment to your personal and career goals.

Like 2018, 2019 will have its uncertainties and opportunities but our industry will continue to evolve to bring new life-saving therapies to patients around the world. This presents a tremendous opportunity for ISPE to provide leadership to highlight the technologies that will drive better outcomes for patients and prepare our membership for these evolving changes.

I recently had the opportunity to attend ISPE Biopharmaceutical Manufacturing Conference on 10–12 December 2018 in Huntington Beach, California. Manufacturing company owners, regulators, equipment vendors, and service providers shared information on how they are addressing the evolving needs of the industry in continuous, CAR-T, and oligonucleotides manufacturing.

Presenters focused on the speed of changing requirements in these new areas as, in some cases, the changes mean new standards are developing. Presenters also emphasized how we as an industry need to continue to work together to drive common platforms across our industry to allow us to bring these therapies to market quicker.

At the Biopharmaceutical Manufacturing Conference, we had a great turnout to our Women in Pharma® Roundtable Discussion—over 75 women and men attended and a panel shared their career and life experiences. (See more coverage of the WIP event on page 14 and the Biopharmaceutical Manufacturing Conference on page 38.) The audience was very engaged during a breakout session that followed the presentations for all attendees to discuss how to address common workplace issues.

We at ISPE are committed to bringing relevant and timely information and training to our members to help them prepare for the new world of changing technology, business models, and workforce requirements.

I encourage you to get involved in ISPE at the chapter or affiliate level and help make our professional society the best it can be.

We look forward to seeing you at our upcoming conferences in 2019. The next ISPE Biopharmaceutical Manufacturing Conference 18–20 June in Boston, Massachusetts, will focus on cutting-edge technology that is shaping our industry and will demonstrate the skill sets you need to participate in this transformation.

The 2019 ISPE Europe Annual Conference 1–4 April in Dublin, Ireland will have as its theme Driving and Leveraging Innovation for Pharma. This promises to be an outstanding event in Ireland, which will have several new biologics facilities coming online over the next few years. Our Irish affiliate is working to make this event the largest Europe ISPE conference ever. (For more about the ISPE Ireland Affiliate, see the profile on page 8.)

As always, I encourage you to get involved in ISPE at the chapter or affiliate level and help make our professional society the best it can be. Only with member involvement and dedication can we drive our society and industry to the highest levels.

Jim Breen is 2019 ISPE International Board of Directors Chair; Vice President, Lead Biologic Expansion, Janssen Pharmaceuticals; and adjunct professor at Drexel University. He has been an ISPE member since 2000.

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ISPE IRELAND AFFILIATE: 30 YEARS AND GROWING

Mike McGrath

It is an exciting time for the pharmaceutical and life sciences industries in Ireland. The country has firmly established itself as one of the world's centers of excellence and the number one European location for pharmaceutical and life science investment. It is equally exciting for ISPE's Ireland Affiliate, which enters its 30th anniversary year as the host of the 2019 ISPE Europe Annual Conference with strong membership levels and a new organizational structure to support its growth plans.

From left to right, Liz Dooley, Eamon Judge, and Sue Cooke

A ROBUST INDUSTRY

Ireland is an island in the North Atlantic with a population of 4.8 million, located just west of the United Kingdom. The island is divided between the Republic of Ireland (officially named Ireland), which covers five-sixths of the island, and Northern Ireland, which is part of the United Kingdom.

With direct employment surpassing 30,000 people, a strong level of ongoing capital investments, and a large and well-educated workforce, the pharmaceutical industry in Ireland is robust. The country is home to over 120 pharmaceutical companies active in the areas of drug discovery, development, manufacture, and sales. While there are two main clusters of companies in Dublin and Cork, pharmaceutical companies are spread throughout the country. All the industry's top multinational corporations have a presence in Ireland, which in 2014 was the world's seventh largest exporter of pharmaceutical products, accounting for €39 billion in annual exports (approximately $44.6 billion USD) [1].

Over the last 10 years, the country has seen approximately $10 billion USD of capital expenditures in new facilities, representing one of the largest investment waves in the world. "If I look across the country at the moment, there are three $500 million-plus projects," said Eamon Judge, EMEA Major Project Planning Leader at Eli Lilly and Co., and the Chair of the ISPE Ireland Affiliate. "There are also five $300 million projects, almost all of which are focused on large molecule APIs."

Ireland actively encourages investment in the country through its Industrial Development Agency (IDA) and offers advantageous tax rates for foreign companies. It also benefits from its membership in the European Union and its proximity to the United Kingdom.

STREAMLINED COMMITTEE STRUCTURE

As the pharmaceuticals and life sciences industries flourish in Ireland, the ISPE Ireland Affiliate looks ahead to its 30th anniversary year with a new organizational structure designed to best serve its members.

Founded in 1989, the Ireland Affiliate covers the Republic of Ireland in its entirety. It currently serves approximately 750 members, of which 400 are actively involved in Affiliate activities. Through this membership, approximately 100 companies are represented. "Membership numbers have been fluid over the past two years," said Liz Dooley, Director of Operations at Janssen Sciences Ireland and the Vice Chair of the Ireland Affiliate. "We have two key focus areas around membership: to increase membership by 25% and to reduce churn by 50% by December 2019. And we have several initiatives to ensure we achieve these objectives."

Part of those initiatives is to convince YP, who often let their student memberships lapse, to become full members. For this, the Affiliate has a very strong YP group. "Our YP group is a liaison with the educational sector, and they try to engage with people earlier to explain to them what life in the pharmaceutical and life sciences sectors is like in Ireland," said Sue Cooke, Director, Strategic Consulting Group at DPS Group and the Affiliate's Secretary. "They are

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a very well-respected group and we see the value of their energy and ambition and helping to grow our group as well."

Indeed, education is a key growth factor for the Affiliate and for the Irish pharmaceutical industry. Ireland has one of the youngest and most highly educated populations in Europe. This provides a deep pool of talent for the sector, which continues to benefit from high levels of investment in third-level (university or technical college) education.

"About 80% of Irish high school students go to third level, and many of them are doing STEM-based subjects supporting our industry," said Judge.

A focus in the last year has been to revamp the Affiliate's committee structure. Under Judge's leadership, the Affiliate has taken a critical look at how the Affiliate is structured in comparison with other Affiliates in Europe and the United States.

"We had conversations with people on the committee of the D/A/CH (German, Austria, Switzerland) organization and the Nordic (Sweden, Norway, Denmark) Affiliate as well as a number of Affiliates in the United States," said Cooke. "We did some benchmarking of how those committees were structured, how they operate, and some of their lessons learned. We took that information to our Board and streamlined our structure."

Previously, the Affiliate had one large committee with 30 to 40 members, where it was thought the large number of members would be able to share the Affiliate's workload. However, many committee members did not have a specific role and consequently, much of the work was handled by a handful of people.

The Affiliate's new structure features an Executive Committee with a Chair, Vice Chair, Treasurer, and Secretary. Under the Executive Committee are several subcommittees, each with its own Chair, Vice Chair, and supporting members. The Chair of each committee is responsible for establishing a committee charter. There are currently four subcommittees: Events, Marketing, Membership, and Young Professionals.

A FULL SLATE OF EVENTS

Late in each year, the Ireland Affiliate establishes its event calendar for the next year. There is a mix of daylong seminars, evening seminars, and breakfast meetings. To help attendance and share budgets, several seminars are a collaboration with other industry groups, such as the International Society of Automation or Engineers Ireland.

The seminars have a specific theme, with national and international subject matter experts invited to speak. Most seminars are held at an industry hub so that site visits or tours can be included in the agenda, which often drives interest in the event.

The evening seminars are regionally based, with key hubs in Limerick, Dublin, Cork, and Waterford. These events are typically supported by local subject matter experts.

"We have primarily focused our activities around education and networking events in recent years," said Judge. "And we have been successful in extending those out to include running the European Biotech Conference in Dublin in September 2017. And in April 2019, we'll be the host Affiliate for the 2019 ISPE Europe Annual Conference in Dublin 1–4 April."

"We are delighted to have been chosen for the Europe Annual Conference," said Cooke. "It is a great vote of confidence for us and provides us the ability to attract new people and to bring more Irish speakers to the podium."

The ISPE Europe Annual Conference will focus on core areas that continue to drive, challenge, and shape pharma manufacturing: Facilities of the Future; Pharma 4.0 & Implementation in Pharmaceutical Operations; Quality Risk Management, Process Validation, Continuous Process Verification and GAMP®; and Project Management and Engineering.

Reference

1. Industrial Development Agency Ireland. *Bio-Pharmaceutical Industry Ireland.* Accessed December 11, 2018. https://www.idaireland.com/doing-business-here/industry-sectors/bio-pharmaceuticals

Quick Facts: Ireland Affiliate

Founded: 1989
Region: Republic of Ireland
Membership: 750

Contacts

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Eamon Judge, Eli Lilly and Co.

Vice Chair
Liz Dooley, Janssen Sciences Ireland

Treasurer
Kieran Coughlan, Life Science Consultants (LSC)

Secretary
Sue Cooke, DPS Group

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Emer Somers, Pfizer Ireland


LeAnna Pearson Marcum

HOW TO START MANAGING EXPECTATIONS

I have always held myself to a high standard and kept high expectations for myself. I always thought that setting this high bar for myself would push me harder, make me better, and ultimately help me succeed. However, when I didn't meet the expectations that I had set, I was so hard on myself. I would lie awake at night replaying where I went wrong over and over in my head, and all this did was make it worse.

In comes the art of managing expectations. While I am still working on this daily and pushing myself to make it a practice, I wish I would have started this so much earlier in my career. I hope the tips below can help you too. I plan to start a discussion thread on the YP Community of Practice board and I hope to hear more about how others manage expectations. I will also be discussing the ways that I have struggled with some of these myself and how I grew from it.

ACTION STEPS

1. **Honesty.** This seems like an obvious step but, in reality, it can be hard to be honest with yourself and others about what you or they can really achieve. This also goes the other way, as you need to ensure that you have rapport that allows someone to be honest with you without getting upset with what they have to say.

2. **Transparency.** To me, this is not the same as honesty, but transparency and honesty are strongly linked. Being transparent is giving someone all the facts they need to see the situation.

3. **Accountability.** I realize that earlier I described how hard I was on myself, but you still need to hold yourself and others accountable when something does not meet expectations. This is not to say that one should be punished or scolded; rather, take the opportunity to see where things could have gone better and learn from the experience.

4. **Failure.** Go ahead and accept it—failure is part of growth. It has taken me years to embrace that failing is not the end of the world and that it is just an opportunity for me to learn. In many cases where I have failed, I have made amazing strides afterward.

5. **Never assume anything.** This should go unsaid, but we all do it all the time. It takes such a small amount of time and effort to ask a question for clarification. For some, this is outside of your comfort zone, as you might be worried that your question is "silly," but this goes back to having an open rapport with yourself and those around you.

6. **Communicate, communicate, communicate.** This might be my last tip, but it is really the biggest part of expectations. If you don't communicate, then you can't be upset or disappointed when your expectations are not met. This includes updates on expectations, where you might see a potential issue in meeting something, or even when you have had a failure.

Just remember that expectations are not a one-way street. Sit down with those from whom you are expecting something, or those who have expectations of you, and talk about them.

LeAnna Pearson Marcum is a QAV Manager with bluebird bio in Durham, North Carolina, and the 2019 ISPE International Young Professionals Chair. She has been an ISPE member since 2009.

It takes such a small amount of time and effort to ask a question for clarification.


Marisol Hydock

THE MEDIUM AND THE MESSAGE

Marisol Hydock

Teamwork and collaboration are becoming increasingly critical in today's professional arena. The drive to produce innovative, disruptive products calls for interdisciplinary teams. To function effectively, these diverse groups require creative problem-solving, conflict resolution, and interpersonal skills. Even the hiring process has become centered on these skills, which have traditionally been called "soft skills." All these attributes are impacted by the ability to work effectively with many different personality types and work styles. Although it sometimes takes a little workplace psychology, stepping out of your comfort zone to understand what makes your coworkers tick can lead to greater success and foster a culture of collaboration all around.

The first step toward working effectively with others is understanding their preferred type of communication. Do you know people that never seem to answer their emails? Maybe they get an overwhelming number of emails daily or maybe they are just "old school" and prefer a phone call over an electronic message. Or perhaps you've asked a complicated question that's difficult to answer in an email. Try giving them a call; you might be surprised at how much faster your coworker answers your questions or completes your request.

Conversely, you might work with a new college grad who is comfortable with technology. If you have a quick question, perhaps a text will suffice without cluttering their inbox. Additionally, try to learn if your recipient likes all the details or just the highlights. Adapting your means of communication to the preferences of the person you're contacting usually leads to faster results.

Once you establish an effective means of communication, there may still be behaviors that hinder collaboration. If these are truly bothersome (pick your battles!), then it's important to discuss your issue with your coworker in a constructive manner. Make sure you don't just complain about what's wrong, but provide ways to improve the situation. If your coworker is the sensitive type, you may want to use the "sandwich" approach: Place your suggestion for improvement between two compliments about positive aspects. On the other hand, your coworker may be very blunt and objective. It may be best with this type to just cut to the chase.

Don't forget to also explore external factors that may affect a person's performance or interactions. Most important, make sure to keep your suggestions between you and the recipient and do not gossip about your grievances with other coworkers. Keep in mind that while most employees want to do well and provide valuable contributions, individual team members will still be diverse in their interests and personalities. Embrace these differences—success isn't found in uniformity. A team needs gregarious, outgoing, and creative types as well as quiet, analytical, and thinking types. Use your differences as an opportunity to learn something new or improve skills that you may lack. Sometimes working effectively is just a matter of approaching a situation with the right mindset!

Marisol Hydock is Integrated Solutions Sales Manager for Sartorius Stedim North America, Inc. She has been an ISPE member since 2013.

Adapting your means of communication to the preferences of the person you're contacting usually leads to faster results.

From left to right, George S. Millili, Peter Millili, and George P. Millili.

FAMILY TIES: MEET THE MILLILIS

Many members think of ISPE as a family of professionals, colleagues, and friends. Two of ISPE's active members, George and Peter Millili, have taken this a step further; they've made ISPE part of their family.

George Millili, 65, joined ISPE in 1997 and has been a very active member ever since. Currently Global Co-Chair of the ISPE Regulatory and Quality Harmonization Committee, he has also chaired the Global PQLI® and numerous other committees. In 2015 he was awarded ISPE's Joseph X. Phillips Distinguished Achievement Award, which honors an ISPE member who has made significant contributions to the industry. His son Peter Millili, 36, grew up attending ISPE events with his father. "From when I was in fifth or sixth grade, I knew I had a passion for science and he gave me the opportunity to go to ISPE meetings," said Peter. "I would go play at the pool while he was at the meetings, but it gave me exposure to meet different people and to hear about the things going on at the meetings."

That interest only increased as Peter grew older, recalled George. "Peter would go to the career seminars and go with me to sessions and he would get to meet people and learn how the industry works."

NAVIGATING A CAREER PATH

Growing up in the Philadelphia area, Peter got his introduction to working in the pharma industry with a job at a local pharmacy when he was in high school. He later did a summer internship at DuPont Merck Pharma, a joint venture at the time, where he had his first opportunity to work in a lab.

In 2000, Peter enrolled at Drexel University for a joint bachelor's–master's program in chemical engineering. With his father's encouragement, he also joined ISPE. "I was involved in starting the Student Chapter there and I participated in one of the local student poster competitions," he said. "I also got to go to my first national meetings as a member, which was great, and started navigating my career path." His father joked that since Peter joined at such a young age, by the time Peter retires he will likely be ISPE's "most tenured member."

The Drexel program offered students industry experience through six-month "co-op" internships. "While I was doing my master's research, I had the opportunity to start networking for my first co-op," Peter explained. He worked at other co-ops during his five years at Drexel, and then went on to the University of Delaware, where he earned his PhD in chemical engineering. "Through my engagement with ISPE, I got my first job at Merck in West Point, Pennsylvania, through a gentleman from ISPE named Brian Lange."

"ISPE is indispensable," George agreed. "It knows the pulse of engineering and manufacturing technology and quality in the industry. It has the technical know-how within its membership and can influence the positive direction of the industry in those areas. It allows members and organizations to interact with regulators. And I have found in my years at ISPE is that you also develop lifelong friendships."Peter's first full-time industry position started in 2010 in Merck's vaccine division. George was part of the company's commercialization development division at that time. "There wasn't a lot of interaction, but it was good to work on the same site," said George. "I was always there to answer questions, to mentor Peter, or to make some contacts that he needed in the beginning. But quite quickly, he didn't need that anymore; he took over for himself."

In 2013, Peter moved to Bristol-Myers Squibb (BMS), once again through the networking contacts he made at ISPE. "I learned more about the industry at ISPE and met some folks who brought me over to BMS, in particular another mentor who I knew through both family connections and the society," Peter said. Peter is currently the Associate Director, Biologics Drug Product Manufacturing Science and Technology, at the BMS

> "ISPE is indispensable. It knows the pulse of engineering and manufacturing technology and quality in the industry."

facility in New Brunswick, New Jersey. His responsibilities cover technology transfers in bringing new products to market, managing a team working with external manufacturing partners to ensure products are effectively produced, and managing a lab to support new commercial products.

He also continues to maintain an active ISPE presence, notably as a member of the Process Capability subteam of the PQLI® technical team. He has also presented at multiple conferences on formulation design, process development, and large-molecule technology transfer.

"I'm proud of Peter," said George. "He is an energetic, personable leader; over the years he has really developed a good technical discipline around the technical principles as well as the engineering principles that go along with it."

TIME TO GIVE BACK

In a career that has spanned 40 years, George has constantly shown his passion for not only the technical aspects of the pharmaceutical industry but also how it can positively affect those it serves: patients. His specialties are product development, scale-up, and technology transfer of pharmaceutical products. He has a bachelor's degree in pharmacy from Temple University and a PhD in pharmaceutics from the Philadelphia College of Pharmacy and Sciences. He is currently a Senior Principal Technical Advisor at Genentech, where he spends about a third of his time advising on technical issues, with the remainder focused on "external relations in the way of outreach to the industry and regulators and influencing positive change in the industry in technical and quality practices."

"He is someone who cares passionately about what he does," said Peter of his father. "He really cares about helping patients. He cares about the people he works with and is very dedicated to that. He's also a lot of fun to be around. He's always the one making jokes and giving everybody a hard time; that's his style, it's his approach. He's one who is always putting family first, which you can see with me. He has helped me and taught me and made sure I was on the right path through my life, both professionally and personally. He's the greatest mentor anyone could ever have."

A key theme throughout George's career has been the opportunity to give his knowledge and understanding back to the industry. "My motivation continues to be to see our industry continuously evolve in the areas of improving manufacturing technology, and ensure good science- and risk-based thinking, which results in high-quality product for the patient," George said. "I also want to continue mentoring young professionals, the engineers and scientists, to do things the right way for the patient. If we start mentoring them from the beginning, we can hope that those principles stay with them throughout their careers."

ISPE continues to benefit from the family ties that George and Peter Millili have brought to the society. And if history repeats itself, ISPE may welcome a new generation of Millilis in about 20 years: both Peter and his brother (also named George) welcomed newborns in late 2016.

—Mike McGrath

2018 ISPE Biopharmaceutical Manufacturing Conference:

CHALLENGES, STRATEGIES, AND SUCCESSES

at Women in Pharma® Roundtable Session

WIP Roundtable presenters and session planners (photo courtesy of Janette Buechler)

Six women shared stories about building their diverse pharmaceutical industry careers, including challenges encountered along the way and their recommendations for other women in the profession, during a roundtable session on Women in Pharma®. The Roundtable opened the second day of the 2018 ISPE Biopharmaceutical Manufacturing Conference in Huntington Beach, California, on 11 December 2018.

Participants were Cindy Capeloto, Site Director, Quality Management, Shire; Amie Clarke, Senior Director, Corporate Security and Crisis Management, Gilead Sciences, Inc.; Rose Doolittle, Senior Director, Pharmacovigilance CAPA Center of Excellence, Johnson & Johnson; Lisa Rappl, Associate Director, Asset Quality Lifecycle, BioMarin Pharmaceutical, Inc.; April Shiflett, Process Development Principal Scientist, Amgen, Inc.; and Melody Spradlin, Senior Director, Facilities Engineering, Gilead Sciences, Inc. Session leaders were Michele Levenson, Senior Program Manager, Validation, at Pharmatech Associates, Inc., and Vivianne Arencibia, President, Arencibia Quality Compliance Associates LLC.

CAREER BREAKTHROUGHS AND BALANCE

Shiflett and Capeloto discussed the challenge of how to break through in one's career and find balance with personal lives.

"The first thing that helped me was the willingness to take risks in picking the first job, asking for specific projects, speaking up in meetings, and sharing what I had to offer," Shiflett said. "People saw I was capable of pushing things over the finish line. Sometimes I am the only woman at the table. You have to be able to be comfortable with that." Her advice to other women coming up in the profession: "Ask for those projects, look for the opportunities that you can take on."

Shiflett shared how a change in her work-life balance happened several years ago with the birth of her son. Thanks to women mentors, she came to understand that getting her job done is key—it does not require an accounting for every moment of her day. She puts in the nights and weekends necessary to keep work on track and she is fulfilling her work role.

Capeloto, who is married with three children, observed that "there's no perfect recipe," for career development. "We all do it differently." A total 14 career moves have included many promotions, including a change made while she was seven months pregnant with her third child.

Having a family should not be an excuse for not moving forward with your career, Capeloto said. "Take a leap, challenge yourself, get out of your comfort zone. People get in their own way; they say 'it's not the right time' due to kids, pregnancy, family issues. My suggestion: take the leap. If you are not in a challenging role, probably the role won't get you where you want to go."

For work-life balance, she said, "I'm very strategic with my time. When I look at the company's goals, I look at what will transform the group—I have the right and capable team around me and behind me. I follow the Three Ds: develop myself and my team, which will help you get time back; delegate to that team; and deliver on results if you want to move within the organization." She urged attendees to consider "what will you have (to show) when you go for the next job? Don't be a passenger on the bus—be the driver."

GLOBAL AND GENERATIONAL COMMUNICATIONS

Being able to communicate across the various generations and with people in multiple locations is key to career success. Clarke noted that "with different generations and individuals in workforce, it is best to be direct. Approach people, topics, and meetings from the bottom line up front." Rather than spending time explaining why there is a meeting, she suggests getting down to the business of the meeting and meet only when necessary. "I meet in person with my team when I don't want the topic to get lost over the internet," she said.

Having older teenagers has helped Clarke to develop active listening skills that are very helpful in the workplace. Other tips: "Don't apologize if you don't need to," and "Overcoming egos is a big issue no matter what industry you are in."

Rappl's experience has included working for several global companies and she agreed that communication—both verbal and nonverbal—can have a great impact on relationships. Even something as simple as how introductions are handled can be important. She suggested regular interactions and "try to understand local colloquialisms. For instance, we say 'opening a deviation'; in Ireland they say 'raising a deviation.' Adapt to their styles so they are more comfortable with you." Also helpful for building bonds is to "try to find something in common with everyone you work with; a hobby, a shared interest. It goes across all generations and gives you something to connect on."

COPING WITH INDUSTRY CHANGE

Change from mergers, acquisitions, and buyouts can work for an individual's career and can also help lay the groundwork for integrating new departments while creating common purpose.

Diversity of experience—through various companies of different sizes, experiences with reorganizations, closings, downsizings, and acquisitions—has paid tremendous dividends for Doolittle's career. "The more you learn and do, the more value you create. Think of a career lattice, not a career ladder. I've moved laterally or even taken a step down to learn something new. It's a marathon, not a sprint, so think about the long term not the short-term win or promotion or pay increase if that pigeonholes you into a corner that will be hard to get out of."

Embracing change and seeing the opportunities will help you to identify the right moves for you, Doolittle said. "Let go of the fear and inertia that come during a difficult period. Evolve or become extinct."

The strength in this approach will help to build a common purpose when creating a new group during a transition. Know your strengths, and those of your team, Doolittle recommended. "You build respect by recognizing the value your team members bring to the table," she said. This also contributes to building culture: the behaviors you value and devalue will influence the team culture. Consider what you want to change or enforce in the culture, then take actions to support them.

Spradlin also experienced many changes at companies she worked for, which prompted her to move into different roles at other companies. She has worked in a range of positions and companies and in each instance, has considered: "What can I control, and not? Your standards and your core values are in your control. The mission may change, so pause, think about it, and make the most of it."

Demonstrating resiliency in times of change helps to create a common purpose, she said. "Walk the talk, be curious, understand the drivers for change. Hold yourself accountable for demonstrating these." Being able to adapt and figure out your options, where you may need to retool with more training, more networking, or other options, is critical.

—Susan Sandler, Editorial Director

Wanted: WIP Success Stories

Pharmaceutical Engineering is looking for more stories about Women in Pharma®. Can you recommend someone who should be profiled? Would you like to cover a WIP event for PE? Contact Susan Sandler, Editorial Director, at ssandler@ispe.org for more information.

GENERICS: INDUSTRY PERSPECTIVES FROM FOUR LOCALES

The market for generic drugs continues to grow. Consider these developments:

- The US FDA approved a record number of generics in 2018 [1].
- Generics are taking an increasing share of the value market around the world. In North America between 2006 and 2016, volume grew from 52% to 70% while value rose from 16% to 23%. And a record 86% of prescriptions were reportedly dispensed as unbranded generics in 2017 [2].
- The global generic drug market was valued at around $244.5 billion USD in 2017, growing at a compound annual growth rate of around 8% during 2010-2017 [3].
- One estimate anticipates a compound annual growth rate of more than 10% from 2018 to 2022 [4].

In recognition of the growth and importance of generics to the pharmaceutical market, *Pharmaceutical Engineering* takes a look at what's happening in some very diverse global markets. Four articles provide "snapshots" of developments with generics, biosimilars, the drug shortage problem, and expansion into nondomestic markets, just to name a few trends. A technical case study of an innovative approach to lyophilization using QbD to revalidate a commercial injectable drug product as part of a transfer to a new line starts on page 52.

The Generics Cover Story in this issue of PE contains four articles:

(1) India: Highlights of some changes in India that demonstrate the growing commitment to quality and GMP by PE freelance writer Emily Burke.

(2) China: Information about regulatory reforms in China and predictions from market observers about the impact on quality by PE freelance writer Emily Burke.

(3) Japan: Tsunehiro Togashi, Managing Director of CM Plus Singapore Pte. Ltd., works in Japan and other Asian markets. He gives an overview of established generics producers in Japan and their journey to expand into the Southeast Asia market and beyond.

(4) The Philippines: Richard Simon R. Binos, Health Systems and Market Access Officer of the Pharmaceutical & Healthcare Association of the Philippines, provides a look into the burgeoning biosimilars market.

VARIED VIEWS

Each article provides an overview as described above to expand ISPE members' knowledge and understanding about the activities

and trends impacting colleagues in other countries. Each article offers different viewpoints and varied approaches.

These articles are not meant to be all-inclusive about the respective countries and are limited to exploration of generics and/or biosimilars. One author (Burke) is an industry observer, while the others are part of the action—these different views provide a variety of insights and information for PE readers.

These profiles do not encompass a complete worldview of the generics market. They provide a unique perspective and may bring new information and updates to ISPE members about activities in the important sector of generics.

PE welcomes additional submissions on generics topics and comments. More information about generics and biosimilars will help all members around the world to learn more about the progress that is being made with the production of these drugs.

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India: From Generics to Biosimilars

India has become a major producer of generics drugs and is now the largest exporter of generics in the world [1]. These exports go to over 160 countries, including the United States, Australia, Russia, and nations in Asia, the Middle East, Africa, and Latin America. Forty percent of generics demand in the US is met by Indian companies [2]. India's top manufacturers are also entering the biosimilars market, with more than 50 biosimilar products approved by the Central Drugs Standard Control Organization (CDSCO), India's pharmaceutical regulatory body. The market for Indian biosimilars has been largely domestic or emerging markets, but manufacturers are setting their sights on the lucrative EU and US markets.

However, quality issues remain a challenge, which manufacturers are working hard to address. Quality concerns will play an especially important role in the global acceptance of Indian biosimilars, due to their more complex manufacturing process. Following lapses in quality standards and data-related issues as pointed out by the US FDA, Indian drug makers have invested in modern technologies and automated processes and have mostly adopted world-class operating systems to ensure deviations are minimized, according to Vikas Dandekar, Editor, ET Prime, published by *The Economic Times of India*. Maintaining consistency, being inspection-ready at all times, and maintaining a culture of quality are ongoing challenges.

According to Dandekar, large companies are leading the way in creating a "culture of quality" by implementing changes such as electronic batch records, daily staff meetings to understand how better quality can be assured and standardized, and identifying the root causes of quality issues to fix problems where they originate. Automation is being introduced wherever human intervention can be eliminated.

One company that has led the way in creating a culture of quality is Zydus Cadila. After addressing concerns surrounding aseptic procedures expressed in a 2015 FDA warning letter, the company has had zero citations in three subsequent audits, said Dr. Ranjana Pathak, President of Global Quality, Medical Affairs, and Pharmacovigilance at Cipla Pharmaceuticals. One strategy Zydus Cadila has used to improve quality manufacturing is the GEMBA technique, a strategy that encourages management to visit the manufacturing area for direct observation of procedures and processes in place.

Pathak stated that a culture of quality at Cipla is being built by way of learning and development. Individuals are sent for both external and in-house training, and the company has created Learning Academies for chemists, microbiologists, and production operators. "This has proven to be very beneficial to the 'do it right first' concept," said Pathak, although he conceded that "our work is not complete—this journey is arduous and long." Pathak added that the company has also improved transparency by making quality-related data sharing a top priority. Monthly Quality Council meetings are held to discuss findings of internal audits and results of all key quality indicators so that the company can course-correct where needed and stress the need for accountability and ownership.

GMP GROWTH

The Indian government has expressed interest in joining the Pharmaceutical Inspection Convention and Pharmaceutical Cooperation Scheme (PIC/S). Membership is open to any regulatory agency

that has a system of Good Manufacturing Practices (GMP) inspection controls in place that is equivalent to the requirements of current PIC/S members [3]. This interest signifies a growing acknowledgment of the need for transparent compliance with the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) quality guidelines such as ICH-Q10, which provides guidance on implementing quality systems to ensure successful implementation of GMP throughout the product life cycle.

Another key step toward integration of GMP guidelines by Indian manufacturers is the recent draft update by the CDSCO of Schedule M. Several changes have been brought about to streamline drug regulatory mechanism in India. Recently, draft Drugs & Cosmetics (Amendment) Rules, 2018, to upgrade Schedule M of the Drugs & Cosmetics Rules, 1945 on "Good Manufacturing Practices and Requirements of Premises, Plant and Equipment for Pharmaceutical Products" [4] and the draft guidelines on "Good Distribution Practices for Pharmaceutical Products" [5] have been released. Once firmed up, both will be significant steps toward ensuring quality standards, according to Kanchana TK, Director General of the Organisation of Pharmaceutical Producers of India, an advocacy body that represents research-based pharmaceutical companies in India.

STANDARDS EXPANDED

On 3 April 2017, the Drugs & Cosmetics Rules were amended to require bioequivalency testing of generic drugs that fall into Category II (low solubility and high permeability) or Category IV (low solubility and low permeability) in the biopharmaceutical classification system. This means that generics manufacturers are now required to demonstrate that the rate and extent of their product's absorption is not statistically different from those of a reference product when administered at the same molar dose. This brings the CDSCO in line with almost all other regulatory authorities, including the FDA and the European Medicines Agency (EMA). The rationale behind requiring bioequivalency testing for generics lies in the fact that even though the chemical structure of the active pharmaceutical ingredient of a generic drug is identical to that of the reference product, the formulation may be different, which could affect absorption and therefore impact both safety and efficacy.

In 2012, India issued Guidelines on Similar Biologics. The standards set forth in this initial guideline were relaxed in a 2016 revision [6]. "Biologics continue to be treated almost like a chemical product and are regulated under the Drugs & Cosmetics Act, 1940, and the Drugs & Cosmetics Rules, 1945," Kanchana said. Marketing approvals for a biosimilar product are granted on the basis of data available from other countries and based on similarity being established in India by way of comparative clinical trials. The only additional requirement for biosimilars manufactured in India is the requirement for preclinical approval by the Review Committee on Genetic Manipulation. To ensure the quality of all biologic products, it is critical that the CDSCO move toward regulating them under a separate set of regulations, said Kanchana.

While drug regulations are evolving, India has a long way to go.

Despite the lack of strong guidelines for biosimilars, some Indian companies are meeting global standards for biosimilar production, Dandekar pointed out. After receiving observations from the FDA regarding its biosimilars processes, Indian drug maker Biocon was able to quickly make corrections and go on to gain several FDA biosimilar approvals, with filing from its partner Mylan.

While drug regulations are evolving, India has a long way to go. Further, it is only through strict implementation and enforcement of these changing regulations that the quality standard of drugs can be ensured, said Kanchana. And to release the product into the global market, Indian companies must meet international standards, which recent cultural changes should ensure that they do. According to Dandekar, the industry has already demonstrated a serious commitment to consistent drug quality through multiple efforts ranging from training of staff to investing in facilities upgrades. One area of training of particular importance is the collaborative effort between CDSCO and the FDA to train additional Indian FDA inspectors of pharmaceutical manufacturing facilities [7]. These trainings will help to ensure that there are sufficient numbers of inspectors on the ground who are versed in international techniques for conducting inspections. The Indian government is investing in hiring additional inspectors and enhancing their training through programs such as the FDA collaboration.

—Emily Burke, PhD

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China: Pursuing Quality for Generics & Biosimilars

Over the past several years, Chinese regulatory authorities have signaled an increased awareness of the need to improve quality standards for both generic and biosimilar drugs. In 2015, the China Food and Drug Administration (CFDA) (now NMPA, National Medical Product Administration) issued technical guidance on the development and evaluation of biosimilars [1], and in 2016, the State Council General Office issued the Opinion on Conducting Evaluations of the Quality and Efficacy Consistency of Generic Drugs, which laid out an industry-wide overhaul of generic drug quality by requiring a retroactive and ongoing generic consistency evaluation (GCE) [2]. What will these and other reforms mean to the Chinese generics and biosimilars landscape?

REGULATORY REFORMS FOR GENERICS

Bioequivalence studies had been required for generic drugs since 2007 regulatory revisions. However, these bioequivalence studies were often unreliable due to a lack of an official reference drug list and a lack of Good Clinical Practice (GCP) and regulatory oversight, calling into question the quality of generic drugs approved prior to the 2016 reform. Now, legacy generics as well as new generics must be demonstrated to have the same quality as, and be biopharmaceutically equivalent to, the officially listed reference drug, which is typically the innovator or branded version of the generic drug.

According to Jifeng Lei, CEO of Anbison Inc., Chinese pharmaceutical companies now fully understand the regulatory and technical requirements that are in line with the FDA and the European Medicines Agency (EMA) in terms of pharmaceutical equivalence and bioequivalence. Essentially, the generics applicant must demonstrate that their product becomes available at the site of drug action at the same rate and to the same extent as the reference product when administered at the same dose and under the same administration route. Bioequivalence studies are conducted in NMPA-qualified hospitals, with sample analysis occurring at qualified analysis organizations according to GCP guidelines. An intensive site inspection is conducted for every application for those sites by NMPA inspectors, and the bioequivalence requirement is referenced to the FDA-published general guidance as well as the specific product bioequivalence guidance. This increased focus on generics quality may help to account for a growing global demand for China-produced generic drugs. In 2017, Chinese drugmakers won approval for 38 generics, up from 22 in 2016 [3].

As generic quality increases as a result of the Generic Drug Quality and Efficacy Consistency Evaluation policy, competition for off-patent branded drugs will no longer draw premium prices. At the same time, companies that are unable to keep up with these new rigorous standards will be left behind, resulting in consolidation of the sector.

According to Lei, many Chinese pharmaceutical companies are now focusing on pharmaceutical redevelopment to make their marketed drug products bioequivalent and pharmaceutically equivalent to the reference product so they can survive in the marketplace. Product and process design, process performance monitoring, process qualification, bioequivalence, and the Common Technical Document are becoming hot topics within the Chinese pharmaceutical industry. At the same time, according to Lei, the NMPA is cracking down on false data in the application dossier, and top management and scientific talent in the industry are now more likely to be focusing on the technical side—development and manufacturing—rather than on the sales side.

There is still a significant need for more contract research organizations focusing on pharmaceutical development and bioequivalence studies.

ONGOING QUALITY WORK

There is still a long way to go for the quality consistency/therapeutic equivalency evaluation of generic drugs in China. After three years of effort, only a small portion of the marketed generic products have gone through intensive reevaluation, said Lei. But state owners, patients, physicians, drug regulatory authorities, and payers are all making drug quality consistency and consistency of therapeutic effects a priority, and implementation of ICH Q10 standards is considered a must.

Consistent application of ICH Q10 standards will also be critical to bring Chinese biosimilars to the global marketplace, according to Daotian Fu, PhD, General Manager of Livzon Mabpharma Inc. Currently, no true biosimilars have been developed by a Chinese biopharma company. Due to the complex structure of biologic drugs, the bar for a biosimilar designation is much higher than that of a generic small molecule drug. Although a generics manufacturer can demonstrate that the structure of their drug is identical to that of the reference product, the biosimilar manufacturer cannot. Because of this, both the FDA and the EMA require biosimilar manufacturers to perform head-to-head clinical trials of a biosimilar product against the reference product to ensure that differences in structure that may occur as a result of variations in the manufacturing or formulation process do not result in differences in drug safety or efficacy.

For Chinese biopharma companies to produce biosimilar products that will be competitive both at home and globally, strict adherence to these ICH standards of clinical testing is necessary. These efforts will be guided by regulatory reforms and guidance at the NMPA such as the 2015 guidance on biosimilars development. Additionally, said Fu, the Pharmaceutical Quality System is currently being established by Chinese pharmaceutical manufacturers, and quality standards are being implemented throughout various stages of life-cycle management.

BIOSIMILARS ARE COMING

A number of biosimilars are in late-stage development by Chinese biopharmaceutical companies, said Joe Zhou, PhD, the CEO

of Genor Biopharm. These include biosimilars of the following reference products: anti-CD20 antibody rituximab (Rituxan), one of the most effective CD20-targeted treatments for non-Hodgkin lymphoma and also approved for chronic lymphocytic leukemia and rheumatoid arthritis; adalimumab (Humira) and infliximab (Remicade), anti-TNF-alpha agents approved for a variety of inflammatory and autoimmune disorders; trastuzumab (Herceptin) for HER2-positive breast cancer; bevacizumab (Avastin), an anti-VEGF for the treatment of various cancers; and pembrolizumab (Keytruda), a checkpoint inhibitor therapy that helps to activate cancer patient's immune systems. Zhou agreed that Chinese biopharma companies with global ambitions are becoming more vigilant in following quality guidelines set by the ICH, FDA, and EMA. Five of the top Chinese companies pursuing biosimilar development are 3SBio, Qilu Pharmaceuticals, Shanghai Fosun Pharmaceutical Group, Tonghua Dongbao Pharmaceutical Co., and Beijing ShuangLu Pharmaceutical Co. [4].

With one of the world's largest domestic markets and increasingly global ambitions, attention to quality and international standards can only mean significant growth and increased competition among Chinese biopharma companies in both the generic drug and biosimilar markets.

—Emily Burke, PhD

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Japan: Generics Leading Expansion

Tsunehiro Togashi

In Japan, off-patented drugs are not always converted to generic drugs but may remain on the drug list as off-patented-drug products. These are customarily classified into three groups: patented drugs; off-patented drugs ("long-listed drugs"); and generic drugs. The government of Japan aims to increase the use of generic drugs to 80% by 2020, and has enacted various measures to achieve that target [1]. Increased medical expenses due to the aging population have been a major driver of these initiatives. Because of these measures, the use of generic drugs already increased to 65.8% in 2017 from 39.9% in 2011 (see Figure 1) and there is a projected goal of 80% generics by 2020.

Generic drug companies have succeeded in increasing their presence due to the government's commitment to greater use of generics. However, this growth is limited globally because there are fewer prospective "seeds" for new generics and the domestic market demand is likely to reach a saturation point soon. Developing the overseas market is a way to break through this stalemate.

For example, certain companies in Japan have advanced into the US, the world 's largest market; in 2017, Sawai Pharmaceutical, one of the biggest generic drug manufacturers, acquired an American generic pharmaceutical company, Upsher-Smith; in July 2016, the second-largest generics manufacturer, Nichi-Iko Pharmaceutical, acquired Sagent Pharmaceuticals, Inc. (which makes biosimilars).

EXPANDING MARKETS

Of all potential foreign markets, the Asian market is the most promising due to cultural and geographic proximity. With the exception of companies with competitive patented drugs such as Takeda, Astellas, Daiichi Sankyo, Eisai, Otsuka, and Mitsubishi Tanabe, Japanese pharmaceutical companies had not shown a keen interest in the Asian market. Generally, those companies have sold patent or off-patent brand products but have not attempted to manufacture or be engaged in the business of generic drugs at all.

The following are examples of other Japanese pharmaceutical companies that have successfully penetrated overseas markets.

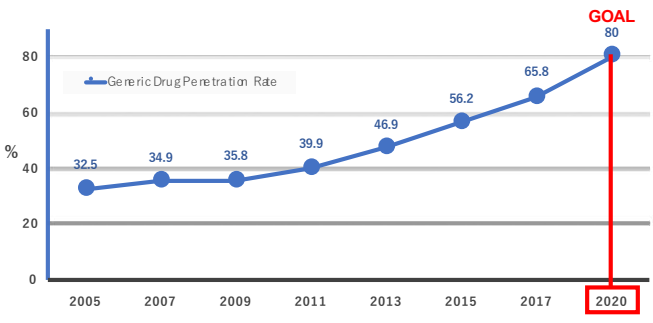
Meiji Seika Pharma Co., Ltd.

Meiji Seika Pharma is a pharmaceutical subsidiary of the long-established Meiji Group. Meiji Group is widely known for its food brands. Its pharma subsidiary has outstanding strength in antibiotics and generic drugs. More than 40 years ago, Meiji Group established PT Meiji Indonesian Pharmaceutical Industries and began to produce sterile lyophilized products of aseptically filled drugs as well as solid dosage drugs. The company now distributes these products in Indonesia, Malaysia, Singapore, and Thailand and has started to export penicillin products to Japan.

Meiji also established Thai Meiji Pharmaceutical Co., Ltd. in 1979. Since then, Thai Meiji has manufactured and sold solid dosage products (mainly antibiotics), including over-the-counter (OTC) and veterinary medicines. It has also been engaged in drug exports as a contract manufacturing organization (CMO) with their Japanese headquarters and other Japanese companies.

In February 2015, Meiji acquired an Indian CMO/CDMO giant, Medreich, to start CMO services. In October 2017, using the production

Figure 1: Generic drug growth in Japan, recent and projected.



Source: Ministry of Health, Labor and Welfare
The report for "2017 Basic Economic, Fiscal Administration & Reformation Policy" approved by the cabinet on June 9, 2017

Note: The year numbers here have been converted from those as per the Japanese era.

and development capability of Medreich, it established Me Pharma as a subsidiary of Meiji Seika Pharma to supply generic drugs to Japan. With the tremendous production capacity of Medreich, Meiji is expanding sales in Japan and other parts of Asia, including B2B business, focusing especially on products expected to be fast growing in the future, such as those for lifestyle-related disease and the digestive system.

Taisho Pharmaceutical Co., Ltd.

Taisho is a top Japanese company for OTC medicines including popular energy drinks. Its prescription drugs, including antibiotics and osteoporosis medications, account for one-third of its sales. It is noteworthy that Taisho's OTC products are also manufactured in its own factories in Indonesia, Malaysia, and Mexico. In 2016, despite the then-sluggish growth of the Japanese pharmaceutical market, Taisho moved to invest substantial capital to form a business alliance with one of the largest Vietnamese pharmaceutical companies, Duoc Hau Giang Pharmaceutical JSC (DHG). Taisho owns 34% of DHG shares. Taisho has been transferring manufacturing technologies and GMP know-how to DHG, aiming to expand markets for both DHG products and its own products in Vietnam and elsewhere in Asia. It seems likely that, in addition to exporting its own products from DHG back to Japan, Taisho may also undertake CMO business for other Japanese companies.

Fuji Pharmaceutical Co., Ltd.

Fuji Pharma possesses a strong brand and technical know-how in obstetrics and gynecology drugs and radiology. Fuji Pharma is currently deploying in strategic areas a unique synergistic development model of "Brand × Generic × CMO," where Fuji proceeds simultaneously with production of branded drugs, generic drugs, and CMO. Major shareholders of Fuji Pharma are the founder's family and Mitsui Trading Co. With the contribution by Mitsui Tracing Co., Fuji Pharma acquired OLIC, Thailand's largest CMO, in 2012. Then Fuji Pharma built an injection drug production facility to export products back to Japan as well as distribute them in Thailand. Expansion of producing and selling products, and partnering with other companies, in other Asian regions is anticipated.

Nipro Pharma Co. Ltd.

Nipro Pharma has been engaged in CMO business, as well as manufacturing and sales of their own generic drugs. Nipro built the first factory in Hai Phong, Vietnam's third largest city, and in 2015 started operation of the first ampule drug production building that conforms to J-GMP, EU-GMP, CGMP, and PIC/S GMP. The vial (liquid/lyophilized) drug production facility began operation in 2016. In the future, corresponding to the needs of CMO customer companies, it plans to expand production lines to include oral drugs and external drugs. In 2016, Nipro Pharma formed a capital alliance (acquiring 20.4% of voting rights) with Mekophar (Mekophar Chemical Pharmaceutical Joint-Stock Company). Nipro has made strenuous efforts to provide technical transfer to enhance Mekophar's quality assurance system and upgrade its production scale. This further strengthened the partnership and enhanced the cooperative relationship, and now Nipro is providing drugs at a competitive price level to Asian markets.

Nippon Chemiphar Corporation

Nippon Chemiphar Corporation is a pharmaceutical company that mainly produces generic solid dosage drugs. In order to manufacture its own products in Vietnam, Nippon Chemiphar established a fully owned subsidiary, with the first plant expected to start production by the end of 2018. Nippon Chemiphar will export the products to Japan as well as to the Asian region in the near future. The company predicted the production cost should be 30% lower than in Japan.

Nichi-Iko Pharmaceutical Co., Ltd

Nichi-Iko is a leading generics company in Japan, ranked second to Sawai Pharmaceutical in sales. Nichi-Iko has been showing enthusiasm toward Asian market development. In Thailand, Nichi-Iko launched 17 products and partnered with DKSH in 2010, Biolab in 2013, and Bangkok Lab in 2015. In 2013, Nichi-Iko partnered with Hanoi Pharmaceutical in Vietnam. In 2018, Nichi-Iko formed business alliances with Lloyd Laboratories, a pharmaceutical company in the Philippines, its subsidiary distribution company InnoGen Pharmaceuticals, and Sunward Pharmaceutical in Singapore and Malaysia. These alliances strengthen Nichi-Iko's support in drug registration applications, distribution, and sales networking for their products in each country.

SUMMARY

Some top companies have taken bold risks and advanced into the Asian region with their respective strategies. Meiji Seika Pharma has a long history in Asia and has accumulated sales and production know-how, so it should be safe to say that it is one step ahead of other companies.

All the other companies discussed in this article are taking similar steps, which are twofold: first, transfer manufacturing technology of their own pharmaceutical products to partner companies through capital investment, M&A, etc.; second, renovate facilities and systems to ensure production meets Japanese quality

standards, factory operations conform to PIC/S GMP, and products can be exported back to Japan. With the exception of Nichi-Iko, all other companies discussed are focusing on quickly establishing production bases elsewhere in Asia that can satisfy Japanese quality standards to export products back to Japan. This trend is likely to continue because exporting to Japan can bring about a considerable profit margin.

In the meantime, other companies have started to provide contract manufacturing services in Asia for Japanese and global companies while simultaneously marketing their products together with partner products in the Asian region. To make this business model successful, each company must smoothly engage other Japanese companies in the alliance and implement a win-win strategy to conquer Asian markets.

CONCLUSION

Strategic actions taken in the market can be classified into four approaches: (1) invest capital to build the company's own factory; (2) form a joint venture with a local partner; (3) take over existing assets by merger and acquisition; and (4) form an alliance or association without ownership of assets.

With the exception of Nichi-Iko, which has taken a unique strategy to form an alliance/partnership rather than obtaining its own assets outside Japan, the other companies have used one or more of these strategies. In options (1) through (3), the final goal is to become not only a reputable generic company but also a qualified CMO that is prepared to flexibly meet any global standards.

How should late entrants to the Japanese market proceed? This question is critical to all of the domestic companies in Japan because the available market remains at the same level or shrinks unless they develop a new market outside Japan. The Southeast Asian markets will be enjoying economic growth due to increased population and enrichment of medical insurance. According to our estimate, the pharmaceutical market size in Southeast Asia should increase up to 50% of Japan's within 5 to 10 years, and we project that half of that market will be in generics.

In general, approaches (2) and (4) should be reasonable and most viable as they are cost- and time-effective solutions. However, the most suitable solution will depend on the types of drugs to be produced, the economic situation in the foreign market, the technical capability of the partner, and, more importantly, the mindset of trust to be cultivated with the partner.

With the Japanese government's continued desire to reduce drug prices, signs of other changes in the health market such as the enactment in Indonesia of the national health insurance market, and the growth of overall medical expenditures rising fast along with growth of gross domestic product, more changes are coming.

About the author

Tsunehiro Togashi is Managing Director of CM Plus Singapore Pte. Ltd., a consulting firm providing professional services for engineering and GMP consulting in pharmaceutical facilities in Japan and other Asian countries. He also serves as Founder and Group CEO for the holding company of CM Plus Group, which includes a network with subsidiary and liaisons/partnerships throughout China, Thailand, the US, Singapore, Vietnam, and Indonesia. The company group headquarters relocated in 2018 from Japan to Singapore. Togashi has 30 years of experience in pharmaceutical facility projects. He holds a B.Eng. (Civil) degree and a BA in Economics, both from Tokyo Metropolitan University. He has been an ISPE member since 2002.

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The Philippines: Biosimilars—Opportunities & Challenges

Richard Simon R. Binos

It is the duty of the government to improve access to safe, effective, and quality medicines for its constituents. Various approaches are taken by different countries to achieve this; for the Philippines, the approach is through the active promotion of generics. Under Philippine laws, it is a policy of the state to promote "effective competition policy in the supply and demand of quality affordable medicines" through the use of generics medicines [1,2]. By making generics available, the supply of medicines is ensured, and the medicines will be more affordable with greater competition.

"Generics" or "multisource pharmaceutical products" are off-patent versions of small-molecule therapies that demonstrate therapeutic equivalence to innovator products [3,4]. This definition, however, does not cover large, complex molecules such as biologics. Similar biotherapeutic products (SBPs), or biosimilars, are similar in terms of quality, safety, and efficacy to an already licensed reference biotherapeutic product (RBP).

While both generics and biosimilars are approved on abbreviated pathways [5], they are not equivalent. Active ingredients of generic medicines are structurally the same; biosimilars, however, are structurally different and are produced through sophisticated biotechnology processes such as recombinant DNA [6]. The methods of establishing "equivalence" for generics and "similarity" for biosimilars also differ. Therapeutic equivalence is demonstrated through bioequivalence using in vitro or in vivo studies, whichever is applicable. Similarity is established through comparability exercises on various parameters to determine the absence of relevant differences, as complemented by appropriate nonclinical and clinical data [7].

While opportunities have opened, better availability has yet to be realized.

LEGISLATION FOR QUALITY

The objective of the 1988 Philippine generics legislation is clear: to improve access by making available high-quality treatment options that are safe, effective, and affordable. Pursuant to this, the Philippine Food and Drug Administration (FDA) implemented Administrative Order No. 2014-0016[8], which provided regulatory guidance for the registration of biosimilars.

By adopting internationally accepted guidelines, marketing authorization holders are able to submit more or less the same evidence that they used to register their biosimilar products in "pioneer" regulatory authorities such as the EMA and the US FDA.

While opportunities have opened, better availability has yet to be realized. As of June 2017, three years after instituting the regulatory pathway, only three biosimilar products had been registered. A number of industry challenges can be discerned from the policy and its implementation.

Classification of Existing Biological Products

The Philippine FDA requires that when it receives a marketing authorization renewal for an existing biological product, evidence of similarity with an RBP must also be submitted unless the biological product is already classified as such. This is challenging for the industry since not all currently registered biological products were classified as either RBP or SBP during their development and initial registration. Thus, they may not have the necessary evidence to support their classification.

Scope of Regulation

The scope of the policy states that the biosimilar concept applies to "all biological drug applications except for vaccines, plasma-derived products, and their recombinant analogues." Reconciling this with the definition of biological products means that comparability studies must be submitted for modified animal tissues, high-molecular-weight hormones, and the products of genetic engineering or other new biotechnological techniques. This runs counter to other regulatory best practices, as not all products may be classified as a biosimilar, especially biological products that are difficult to characterize.

Administrative Challenges

Currently, the length of the Philippine FDA regulatory reviews ranges from two to four years, which is heavily attributed to the limited manpower complement. While there is industry interest in submitting applications that follow internationally aligned requirements (and a number of companies have already done so), long queueing time affects the availability of these products in the market.

Conditional Approvals and Post-marketing Commitments

To sustain interest, the Philippine FDA may consider conditional approvals for new biosimilars with limited evidence. This is common in the EU, provided that post-marketing commitments are met. This is an incentive for investing in research and development not only for biosimilars but also for other innovative medicines.

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IDENTIFYING GLOBAL THEMES IN CLINICAL STUDY PARTICIPANTS'

Experience with Investigational Medicinal Products

Esther Sadler-Williams, Kristen DeVit, Chie Igushi, Lynn Wang, Samantha Carmichael, Nova Getz, and Ken Getz

This article examines patient preferences in one facet of clinical research: the experience related to the use of investigational medicinal products (IMPs). As patients have become more involved and informed in their healthcare choices, the "voice of the patient" has been increasingly incorporated into the drug development process. Given that the success of a clinical study relies on the recruitment, retention, and compliance of participants, all stakeholders—sponsors, investigator sites, and clinical study supply providers—need to understand patients' mindsets and participation experiences throughout a study. Patient-centric knowledge can help improve the investigational process, support adherence, and ultimately create a comprehensive ecosystem for engaging patients who participate in clinical research.

Using data collected from North America, Europe, China, and Japan, this article provides a consolidated analysis, highlighting regional differences and similarities to help clinical trial stakeholders make more informed decisions in the design and implementation of IMPs in global studies.

THE STUDY'S GROWING HISTORY

Seminal research on patient perceptions of IMPs was first conducted in 2012 by the Patient Survey Project Team at the ISPE's Investigational Products Community of Practice (IP CoP). With survey results from 1,425 clinical trial participants (predominately in North America), the team analyzed respondents' opinions about their experiences with IMPs and published suggestions for improvement [1].

Although these findings were intended to help improve the patient experience and better align medicine kit design with the needs of the patients, the study's collaborators wanted to expand the survey to a globally diverse population. With an adapted survey run in 2015, they targeted a larger geographical scope. The team first expanded to Europe and China, publishing those consolidated results in 2016 [2]. Around the time of that publication, a team in Japan started gathering data from current and past clinical trial participants. The research teams have now received and analyzed data from 1,473 participants in Japan to create new averages with previously collected data in 2017.

Given that clinical supply practices have not drastically changed since the original survey was completed in 2013 in North America, the study collaborators' combined data can be compared and used as a benchmark across the four regions.

OBJECTIVES

With data collected from Japan and compared to data from North America, China, and Europe, the survey sponsors wanted to identify global themes and regional differences as they related to the use of IMPs. Other goals of the survey and its

Table A: Patient Demographics

	North America (2013)		China (2014/2015)		Europe (2014/2015)		Japan (2017)	
Participating in a clinical trial	Currently	31%	Currently	68%	Currently	40%	2016	45%
	< 6 months ago	23%	< 6 months ago	16%	< 6 months ago	11%	2015	23%
	> 6 months ago	46%	> 6 months ago	16%	> 6 months ago	49%	Before 2015	32%
	Female	60%	Female	43%	Female	49%	Female	28%
	Male	40%	Male	57%	Male	51%	Male	72%
Top three therapeutic areas	Diabetes	12%	Diabetes	23%	Neurological	23%	Heart disease*	40%
	Respiratory	9%	Heart disease	16%	Cancer	17%	Diabetes	18%
	Pain	9%	Cancer	16%	Heart disease	14%	Hyperlipidemia	14%

*(Hypertension, cardiac angina)

resulting publications included:

- Increasing the industry's understanding of the patient experience with IMPs
- Determining if there are any noticeable differences in patient experiences
- Providing stakeholders with valuable data sets to support correct decision-making relating to the use of IMPs
- Fostering collaboration between global regulatory agencies, facilitator organizations, and stakeholders involved in the clinical trial process

METHODOLOGY

In each region, the survey reused many of the same questions from the original North America study. However, some questions were eliminated from the surveys that followed in China, Europe, and Japan to focus on key themes recognized in the original survey. Some other questions were slightly reworded to account for cultural differences in translation. The methodology varied among geographic locations as described next. The teams relied on agencies, site management organizations, and patient advocacy groups that had access to patients mostly through clinical trials, pharmacies, and research nurses. Access to appropriate patient populations was instrumental to the survey's success, with patient anonymity being strictly controlled. See Table A for details about patient demographics.

North America

For North America (N = 1,425), 48 questions in an electronic survey were given to patients that had taken part in a clinical trial in their lifetime and taken their medication home (to ensure a participant was not from an in-hospital study).

Europe

For Europe (N = 109), the study was conducted electronically and in English only, with 48 questions adapted from the original study in North America. The small sample size in Europe was attributed to several factors. First, the survey was delivered only in English, which may not be the primary language of potential participants. Second, as a generalization, Europeans tend to be a little more reserved and are more reluctant to either openly praise or criticize than in North American culture. Third, participants were excluded if they had not participated in a clinical trial that involved IMPs. In addition, not all patients responded to every question; thus, the figures show varying N for the European study population. The results were reanalyzed for this publication; therefore, they slightly differ from the referenced publications.

China

For China (N = 1,935), the survey contained 44 questions modified from the original study in North America, which were translated into Chinese. Data were collected via mobile or paper versions, depending on patients' preferences. Surveys were conducted in person at study sites.

Japan

For Japan (N = 1,473), the survey focused on 18 key questions, which were designed based on the questions from the survey in Europe. Working with the University of Tokyo, an online survey was sent to 2,688 adult patients (> 20 years old) who enrolled in clinical trials conducted from 2013 to 2016 in Japan. Those patients were extracted from the survey panel of INTAGE, Inc. The data collection period was March 7–9, 2017. The response rate was 54.8%. The survey designers reduced the number of questions to increase the chances that the participants completed the entire survey. The data were collected in an online format.

RESULTS

The following section discusses the results, outlining the range of criteria used throughout the surveys.

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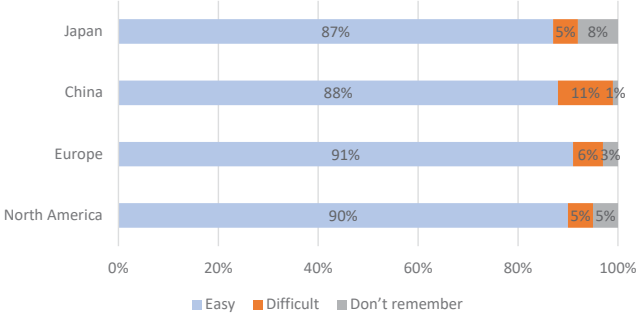
Table B: Top Three Forms of Medication Received*

	North America (2013)	China (2014/2015)	Europe (2014/2015)	Japan (2017)
Bottle	42%	47%	29%	14%
Blister	30%	37%	37%	71%
Syringe	15%	14%	20%	12%

*Other medications included topical and inhaled forms.

Figure 1: Overall Ease of Use. Easy = Participants that selected options "very easy" or "somewhat easy." Difficult = Participants that selected options "somewhat difficult" or "very difficult."



Ease of Medication Use

When asked if it was easy to use their medicine kit, the clear majority of participants in all four studies found their medication "somewhat easy" or "very easy" to use. Each study had a high number of participants that reported their medicine kit was "somewhat easy" or "very easy" to use: 87% for Japan, 88% for China, 91% for Europe, and 90% for North America.

Kit Design

Participants were asked a yes/no question: "Did the design/layout of the medicine kit help you take your clinical trial medicine on schedule?" Although we noted some significant differences in regions (Figure 2), overall, 86% of Japan study respondents stated that the medicine kit design helped take medicine on schedule. For the participants using only bottles (although this was a much smaller percentage of the overall survey total), 91% said that kit design supported taking their medicine on schedule. Thus, in Japan, whether bottle or blister packaging is used, design is a key component to supporting the patient taking their medication on schedule.

The participants in China were split evenly: 46% said the kit design was helpful and 46% said it wasn't. This could be because the respondents in China heavily value their direct interactions with site staff for medication scheduling, a statement that can be supported by a later question in the survey about reminders to take clinical medication. In that question, 77% said that it was helpful or very helpful to receive "instructions from my physician/nurse/pharmacist every time I visit the hospital or medical center" as reminders for taking a medicine on schedule.

For survey participants in Europe, 43% said kit design was important to taking clinical trial medication on schedule, but the same percentage (43%) found kit design unimportant. This was evaluated further by reviewing the top three forms of medication received: blister packs, bottles, and syringes. Of the cohort using blister packs, only 31% answered "yes," 38% answered "no," and the remaining 31% answered "couldn't remember." Those using bottles had an equal split (45% each) between "yes" and "no"; for those using syringes, 23% said "yes" and 30% said "no."

In North America, the majority of participants (60%) answered "yes," 30% answered "no," and the remaining 10% answered "couldn't remember." When separated by the medicine forms, the percentages differed. For those using bottles but not blister packs, 51% said "yes," 37% said "no," and 11% answered "didn't remember." For respondents using blister packs and not bottles, 75% said "yes," 20% said "no," and 5% answered "didn't remember." For those using syringes and not blister packs or bottles, 48% said "yes," 35% said "no," and 17% answered "couldn't remember."

Taking Medicine on Schedule

To better understand any issues with taking medications on schedule, the participants were asked what would help remind them to take their clinical trial medication. They were asked to rate several options on a scale from 1 to 4, where 1 indicated "not at all useful" and 4 indicated "very useful." In other translations of the survey response options, "useful" was replaced with "helpful."

In China, the participants preferred instructions from their clinician at every visit and only indicated a slight preference in helpfulness in the other categories (Figure 3a). In Japan, most participants found all methods useful but cited individually organized daily or weekly dosing units in the kit as the most helpful (Figure 3b), which could be attributed to the high use of blister packs. The participants from Europe indicated a strong preference for dosing instructions on the label (Figure 3c), similar to results from participants in North America (Figure 3d).

Evaluating the results on a global scale, "dosing instructions on the label" (73%) and "verbal instructions from my physician/nurse/pharmacist" (69%) were cited as the two most useful

Figure 2: Kit Design Supported Taking Medicine on Schedule

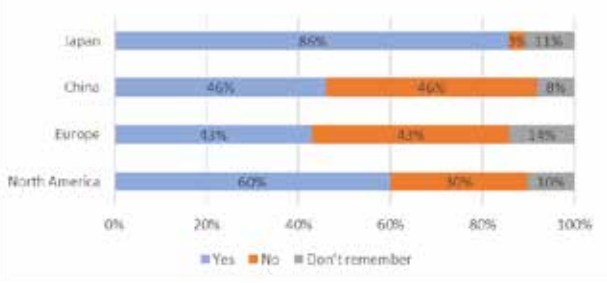


Figure 3a: Usefulness of Instructions in China

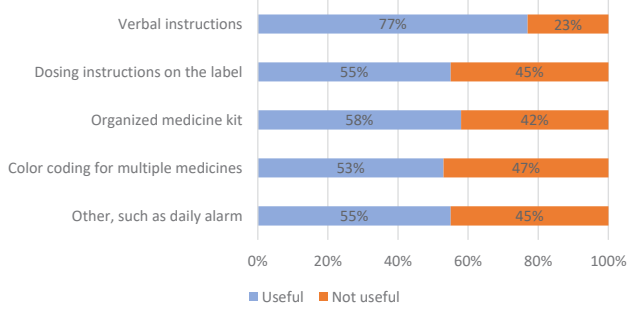


Figure 3b: Usefulness of Instructions in Japan

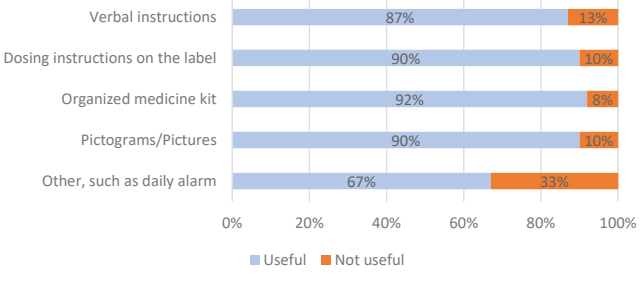


Figure 3c: Usefulness of Instructions in Europe

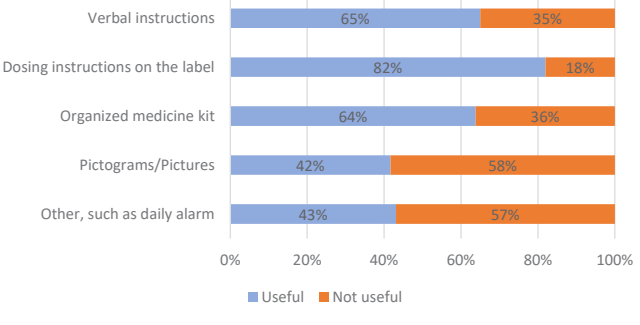
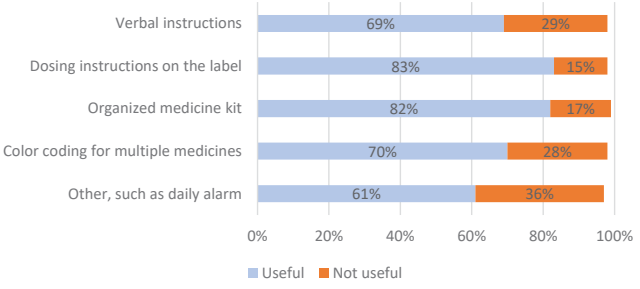


Figure 3d: Usefulness of Instructions in North America. Useful = "Very useful (4)" and "Useful (3)." Not useful = "Not so useful (2) and "Not at all useful (1)." (The figures in the parentheses are the respective rating scales.) Note: 1%–3% of the North American participants did not answer parts of the question, so the totals do not equal 100%.



mechanisms to help participants take their clinical trial medication. Using an organized medicine kit, such as trial medication organized in individual daily or weekly dosing units, was also cited as important or very important by 66% of global respondents.

Most Helpful Form of Instruction

Survey participants were asked to think about how they "learned to use, take, and store the clinical trial medicine," and rate the helpfulness of various methods. Combined results from Europe, North America, and China show a slight preference (84%) for "someone showing/telling you" how to take clinical trial medication as compared with "an opportunity to ask questions" (82%). Slightly less preferred methods were to receive an "explanation of the label" (68%) and "receive extra documentation" (64%) (Figure 4). These data confirm the ongoing need for person-to-person explanations, which can be supplemented by printed material.

Packaging Preferences

Respondents in Japan and Europe preferred to receive their medications in blister packs, whereas respondents in North America preferred bottles. Respondents in China had a relatively equal distribution between the different kinds of packaging.

The packaging preferences tended to align with the packaging use reported in the clinical trial in which the respondent participated (Figure 5). For example, 71% of survey respondents from Japan were using blister packs and 14% were using bottles in their clinical trial. Of the group that was only using blister packs in their clinical trial (n = 878), 71% preferred blister packs, 22% had no preference, and only 7% preferred bottles. For the respondents only using bottles (n = 134), 66% preferred bottles, 17% preferred blister packs, and 17% had no preference.

Of the survey respondents in Europe who used blister packs (37%), 70% preferred blister packs in their clinical trial and 23% specified no preference. Only 3% of blister pack users in Europe preferred bottles. In the North American survey, of the 482 respondents who only used bottles, 59% preferred bottles, 8%

Figure 4: How Helpful Were the Following to Help You Learn How to Use Your Clinical Trial (CT) Medicine? Averaged percentages from Europe, North America, and China mentioning "very helpful" and "somewhat helpful." This question was not asked in Japan.

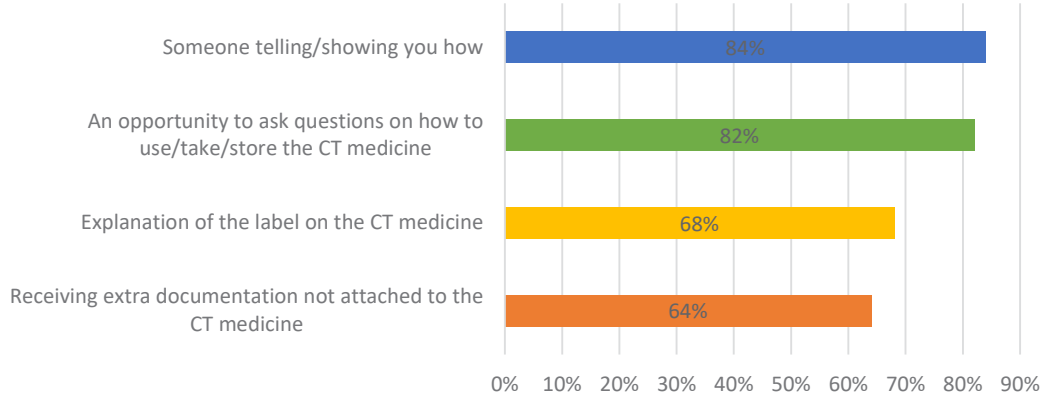
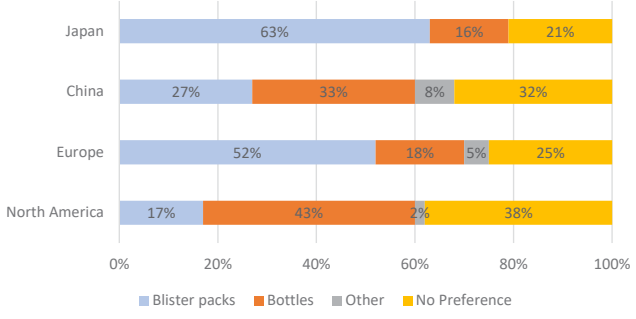


Figure 5: Medication Form Preference



preferred blister packs, and 33% had no preference. However, of the 339 respondents who only used blister packs, 38% preferred bottles, 34% preferred blister packs, and 27% had no preference. For respondents who used both bottles and blister packs in their clinical studies, 48% preferred bottles, 25% preferred blister packs, and 28% had no preference.

In a related question asked only in North America, Europe, and China, participants were asked if they kept their medicine in its original container. This has been a concern in the industry because patients may remove their medication from the clinical trial kit provided, thus risking incorrect dosing. However, participants in these three regional studies reported similarly encouraging responses: 86% of participants in Europe, 84% of participants in China, and 86% of participants in North America kept their medicines in the original container.

Most Important Characteristics of an IMP

Survey participants were asked, "How important is each of the following medicine kit characteristics to you when thinking about its effect on your overall experience in your clinical trial?" and "Can you indicate the importance of each characteristic on a scale of 1 (not at all important) to 4 (very important)." In North America and Europe, participants overwhelmingly rated "ease of use" and "clear instructions" as the most important characteristics of their IMP kits (Figure 6a). In China, participants did not indicate a strong preference for IMP characteristics as compared to North America and Europe.

In Japan (Figure 6b), this question was translated to be better understood by the participants as "Would you like to request that sponsor companies improve the following areas?" The participants selected their desired level from 4 ("very much") to 1 ("not at all—meets expectations").

Reuse and Return Behaviors

Participants were asked if they returned their used and unused clinical trial medicine to their medical center. The results across Europe, China, and Japan were consistent with the results in the original North America study, which found that an unacceptable percentage of participants did not return unused medication to the clinical sites. This is a result that the industry needs to mitigate against globally (Figure 7).

The high percentage of "returned on request" results for the China study may reflect the participants' interpretation of the question and represent those participants that returned supplies as they were "requested" to do so by the clinical site. These findings may also highlight that in-person communication is important and that patients may require explicit requests from their clinical site to return unused medication.

In Japan, participants could also indicate additional choices like "can't remember" and "none were remaining" when describing their return behaviors. In China and Europe, participants could select "returned on request."

Supplementing this question, the survey team in Japan also

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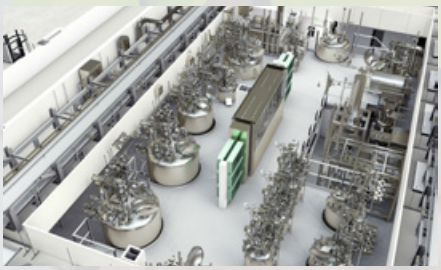

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Figure 6a: Medicine Kit Characteristics Ranked as "Very Important." This figure shows percentages for participants answering "4 (very important)." Survey participants in China were not asked about "information included on label" as a characteristic but were asked about "clear instructions."

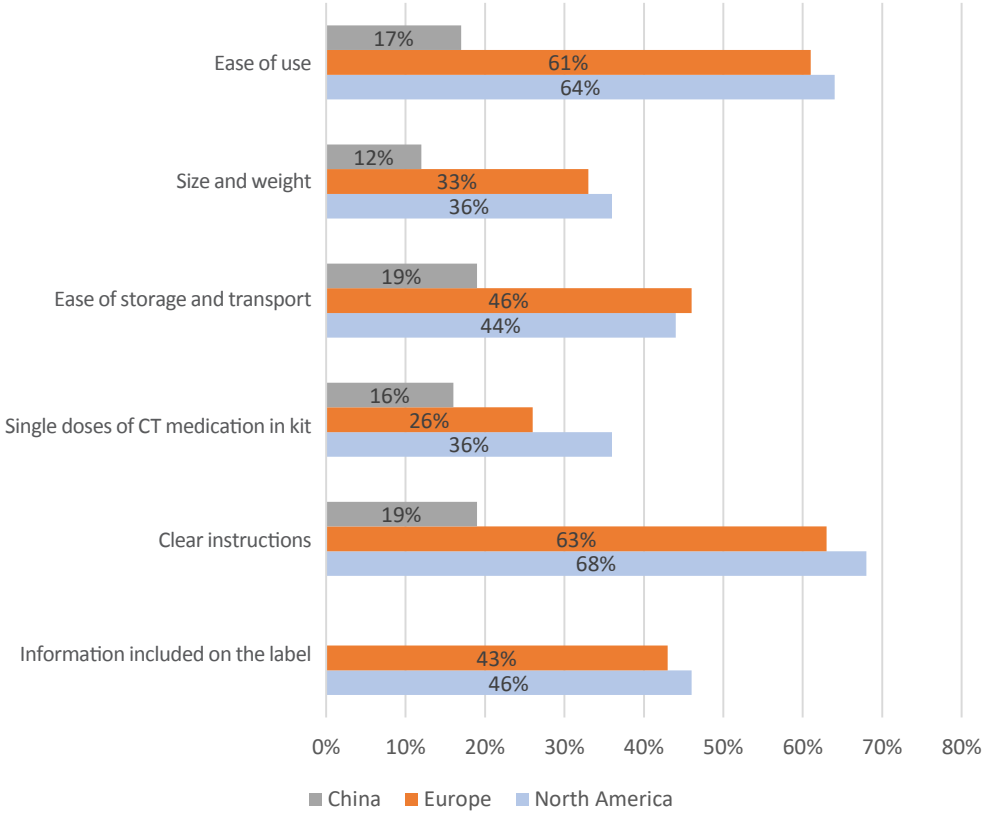


Figure 6b: Participants in Japan Requesting Sponsors to Improve the Following Areas. This figure shows the percentage of participants that selected "4 (very much)" in Japan for the characteristics listed.

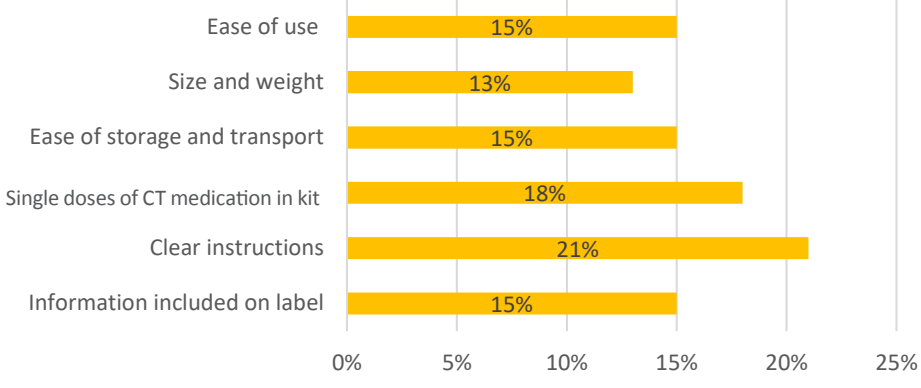
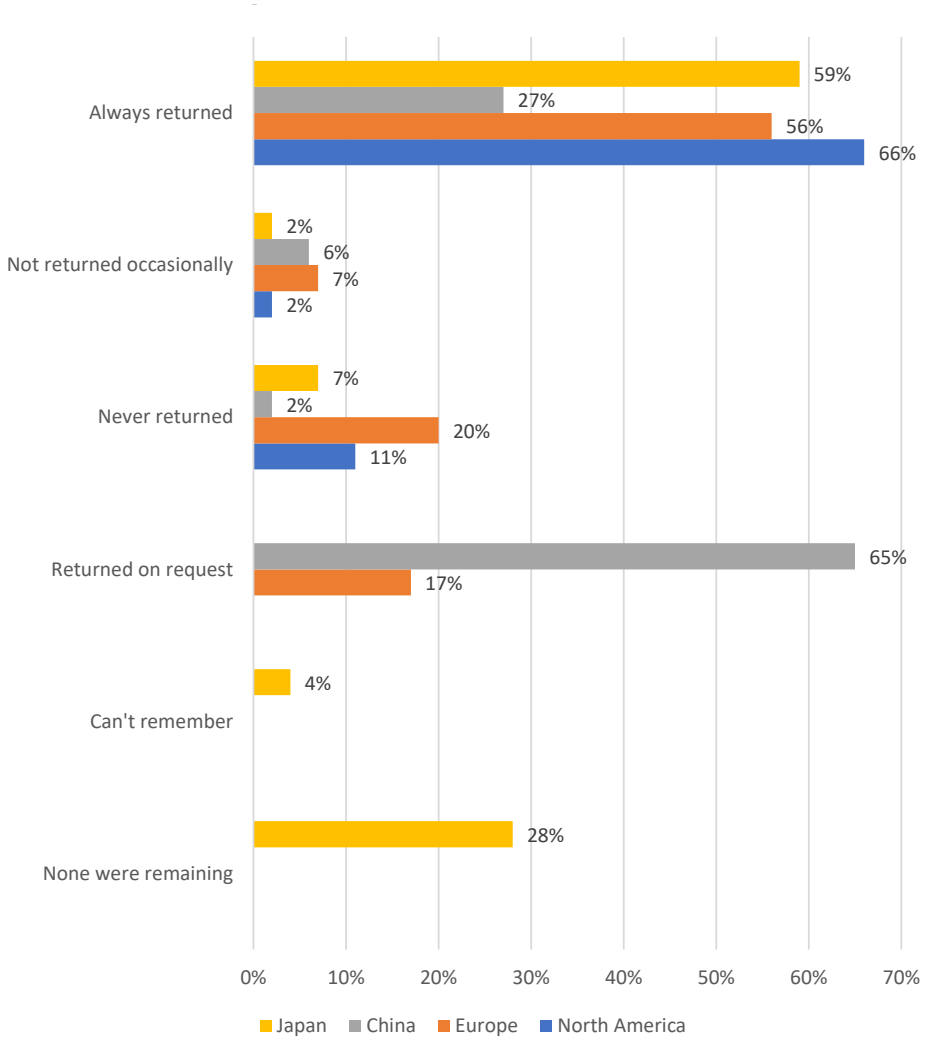


Figure 7: Return of Trial Medications



asked the group of participants who answered, "not returned occasionally" or "never returned" (9% of total surveyed population), why they kept unused clinical trial medicine. In this 9% of the total survey population, 34% of these participants said that the sites "never asked for a return," 32% said they had no visit scheduled to return the medication, 22% forgot to return it, and 12% said they wanted to keep unused medication for future use if they received the same diagnosis.

Pictograms and Booklets

The researchers wanted to understand if the booklet labels and pictograms serve as an effective way to communicate medical information to patients. These studies were also intended to help evaluate booklet labels, an area of intense focus in clinical trial design.

In Europe, 75% of survey participants reported that they had not seen pictograms on their kit but 41% found that text and pictograms together were helpful. Regardless of whether they had seen pictograms on their medication, nearly all the participants from Europe were able to identify four common pictograms correctly.

In China, 82% of respondents found the pictograms at least "somewhat helpful." These data correspond to the original 2013 survey in North America, in which most survey participants found the same pictograms "helpful." In Japan, survey participants were given slightly different questions. They were asked if they opened and read the booklet label. Also, 65% said they had opened and read the label of each container at least once, whereas 21% had done so on some, but not all, containers. In this survey, 7.1% said they never opened or read the booklet label and 6.5% reported reading the booklet label every time.

In comparison to pictograms, the booklet label seemed to have limited use to participants. Half of the survey participants in Europe said they had never opened or read the booklet label. In China,

Figure 8: Images Identified by Survey Participants: 1. Store between 2°C and 8°C; 2. Do not freeze; 3. Protect from moisture; 4. Protect from light.

55% said they relied on instructions from the booklet label; however, 17% said they never opened their booklet labels. Although these data showed a geographic difference, the results indicate that patients frequently prefer and rely on verbal information from the clinical site rather than booklet labels.

Survey participants who did read their booklet labels found it easy to find their language and read the information; most participants in the Europe survey found that the text size was large enough to read. In Japan, survey respondents were asked about how easy it was to find their language of choice in the booklet label. Further, 83% reported that it was "very easy" or "somewhat easy" and 11% reported it was "somewhat difficult "or "very difficult," whereas 6% reported "could not remember."

Home Delivery

Patients often have to travel long distances to participate in studies. To improve patient recruitment and retention, some sponsors are considering ways in the future to send IMPs directly to patients' homes to help ease participant burden. The survey team wanted to gauge patients' future preferences for this. Participants were asked, "If it was possible to have repeat prescriptions or refills of your clinical trial medicine delivered to your home, how helpful would you find this?" More than 75% of respondents in North America, Europe, and China reported that having IMPs delivered directly to their homes would be helpful; in Japan, it was 85% (Figure 9).

Medicine Kit Size

From the outset of this work, size, storage, and ease of transportation of IMP kits were expected to be of concern to patients. Survey participants in North America, Europe, and China were asked about their thoughts on the size of the medicine kit as it concerned transportation and its ease of storage at home. Most of the respondents in these three regions (>80%) said their IMP kit was "very easy" or "somewhat easy" to store. Similarly, more than 70% of global participants said their medicine kit was easy to transport based on its size. Although the same question was not directly explored in Japan, as shown in Figure 6b, only 13% of participants in Japan expected improvement on size and weight for their medication kits. Thus, from the survey results, it was therefore surprising, but reassuring, that there appeared to be general satisfaction observed in these regions regarding kit size and weight for storage and transportation purposes.

Information Delivery Preferences

To gauge patients' preferences for the way they would like to receive additional information, participants were asked, "In addition to receiving information from your healthcare worker, tell us how useful would it be to receive information in the following ways?" They could rate the usefulness of various communication methods in a clinical trial.

Participants in most regions indicated a strong preference for email, followed by text messages (Table C). It is interesting to note, however, that email was the most preferred method in Europe, North America, and Japan, but least preferred in China, potentially because email is not significantly used as a daily or instant electronic communication tool in China.

To gauge interest levels of using other communication methods as reminders, participants in China were asked, "How interested would you be in receiving an electronic device along with your clinical trial medicine to remind you to take your medicine and document that you have taken your medicine?" and 66% of the participants said they would be "very interested" or "somewhat interested" in an electronic device as a reminder system.

In Europe, participants were asked a related question on communication: "How interested would you be in receiving electronic or telephone reminders each time you need to take your clinical trial medicine?" and 44% said they would be "very interested" or "somewhat interested" in such reminders.

DISCUSSION AND KEY FINDINGS

Retention and compliance of clinical trial participants is crucial to drug development research, but IMP professionals, as well as study sponsors and suppliers, do not interact directly with participants and may be unaware of the patient experience as it relates to using trial medications. This series of four regional studies aimed to compare specific clinical trial preferences, help inform industry about these patient preferences, and ultimately develop global guidelines for patient-centric design of IMPs and create best practices for communicating their proper use.

Ease of Use

One of the most important characteristics of a medicine kit cited by participants was ease of use. The original study in North America suggested a high level of satisfaction with the ease of use of IMPs, which was also reflected in the expanded surveys in Europe, China, and Japan. These results could suggest that our industry is adequately meeting the needs of patients. However, given that ease of use was reported as a highly valued quality of a medicine kit, sponsors and suppliers must continue to ensure their IMPs support patient compliance efforts by meeting end users' needs. Clear instructions were also cited as an important characteristic in an IMP, emphasizing the essential role of in-person communication with clinical research staff to verbally explain the use of the medication.

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Figure 9: Perceived Helpfulness of Delivered Medications

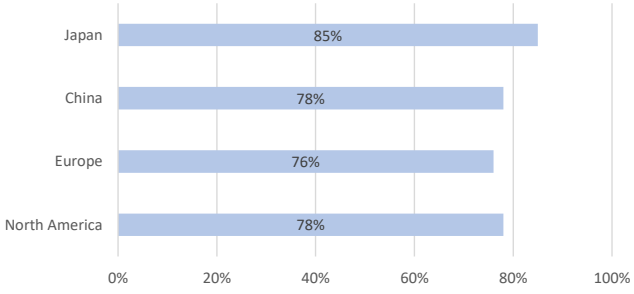

Table C: Preferences for Communication Methods After Face-to-Face

Region	Top 2 Delivery Methods Preferred
Japan	1. Email 2. Postal mail
China	1. Text 2. Postal mail
Europe	1. Email 2. Text
North America	1. Email 2. Text

The Role of Kit Design

The kit design plays a role in supporting taking medicine on schedule, but there are strong regional differences. Depending on the type of packaging, such as blister packs, bottles, and syringes, the design may also play a role to support taking medication on schedule. Other methods, like organizing medicine kits in daily or weekly dosing units or color-coding, might help supplement healthcare workers' efforts to ensure adherence to medication schedules. With the exception of the results from respondents in Japan, where there was a high percentage of blister pack users, all other regions indicated that kit design did not strongly support taking medicines on schedule, citing this as an area for potential improvement to strengthen compliance.

Primary Communication Methods

Maintaining compliance with the study protocol relies on strong communication with participants. Dosing instructions on the label and verbal instructions provided at the site or with a pharmacist are still considered very useful to global study participants.

Written Communication

Booklet design is an important issue for regulators, who are concerned that patients do not read booklet labels; a concern expressed by some is that medicine kits are often returned with unopened booklets. Although a majority of respondents in Japan reported reading the booklets, nearly half of the respondents in China and Europe said they never opened or read the booklet label. A potential explanation for this result could be that some clinical sites are obliged, for a variety of reasons, to add their own study label to IMPs; this could be the label that patients read and remember. Clinical trial stakeholders should keep these findings in mind and not rely on patients to read the booklet, but rather ensure that comprehensive verbal communication is employed at the time of a study visit.

Pictorial Communication

Pictograms serve as another vehicle for communication, especially regarding storage information. In these studies, nearly all participants from Europe were able to identify four common storage-related pictograms correctly. A majority of participants from China found the pictograms at least somewhat helpful. These data correspond to the original 2013 survey in North America, in which most survey participants found the same pictograms helpful.

Electronic Communication

In terms of strengthening ongoing communication with clinical trial participants, email and text message were listed as preferred methods after face-to-face communication in the clinic. Although data on reminder preferences were not collected in Japan or North America, the participants in China and Europe indicated some level of interest for electronic or telephone reminders to take their medication. Because adoption of mobile technologies has grown over the past few years, the preference for electronic reminders may change and should be further explored among clinical study participants.

Returning Unused Medications

It is assumed that all clinical site staff communicate the need for the timely return of all unused medications. The majority of participants across all four surveys report either returning or using all the medication. However, a concerning percentage of participants reported the intent of retaining or using unused and/or unreturned medication. Clinical trial stakeholders must determine how best to recover or account for all unused medications.

Delivery Methods

In considering how to ease the burden on patients in obtaining medication refills, home delivery was of interest across all four regions. In North America, this was a particular wish of younger participants, who may be short on time. In this arm of the survey, elderly participants placed a strong value on visiting the clinical site and having an opportunity to receive medication and information directly from the study staff or a pharmacist. Age was not collected in the China or Japan surveys, but it would be a valuable data point to collect in any future survey to understand whether this sentiment aligns with North American participants.

CONCLUSION

In ongoing efforts to incorporate patient-centric practices into clinical research, study sponsors, IMP suppliers, and clinical sites need to consider how to best support patient retention and compliance by evaluating the patients' overall ease of use with the medication and by facilitating clear, consistent communication regarding instructions.

Regardless of the medication packaging, the instructional label, face-to-face explanations about the usage, and return of medication are essential to support clinical trial participants. Compliance may also be boosted by incorporating secondary measures, such as sending reminders through email or text messages. These methods of communication may not be widely employed, but would be accepted by study participants if employed in a secure manner through the clinical site. Finally, participants find their current medications easy to transport and store, but would also welcome home delivery of their medications.

Ever-improving, modern-day communications will facilitate a greater dialogue between patients and IMP professionals. The production of patients' clinical medication supplies can function as a two-way process by first accessing the needs and preferences of the trial patient population and then determining the best design and delivery method. Ensuring that communication continues throughout the trial to accommodate any learning and modifications needed to assist the patient will also improve retention and compliance. Coupled with new advances in clinical supply manufacturing methods, the industry can expect shorter lead times to prepare and deliver medications, enabling more flexibility in the clinical supply chain.

The implementation of direct-to-patient (DTP) supply models may also improve patient recruitment and adherence to medications. Although this more-user-friendly approach offers many benefits to study participants and clinical research sites, employing a DTP model also requires a well-coordinated effort between regulators, legal teams, clinicians, and logistics providers.

Supporting a patient-centric supply chain and balancing cost considerations is not an easy feat. With these global survey results, the ISPE team and its supporting sponsors hope that this article will create greater awareness about patients' current usage and encourage stakeholders to evaluate the specific needs of patients as they relate to their study. Using this article as a guide, stakeholders can implement best practices in the design of IMPs and communication of their use to ensure greater patient safety, increase compliance in their studies, and create more consistent data in clinical trials.

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Japan team members: Chie Igushi, Pfizer; Hiroaki Ishii, Mitsui Soko; Kaoru Ide, Toray; Akihiro Shiga, UCB Japan; Chiaki Yamauchi, Nippon Boehringer Ingelheim; Hirofumi Suzuki, Bayer; and Robert Kamphuis, Pfizer.

ISPE administered the survey and aggregated the responses; NHS, NIHR, and EUPATI disseminated the surveys to patients through clinical trials pharmacies, research nurses, or patient advocacy groups; the Robertson Centre for Biostatistics, University of Glasgow, analyzed and reported on the resulting data.

The Europe team partnered with three agencies that had access to patient groups: UK National Health Service (NHS), UK National Institute for Health Research (NIHR), and European Patients Academy on Therapeutic Innovation (EUPATI). In China, the ISPE China IP CoP partnered with Drug Information Association China to enlist five site management organizations to collect responses: Hangzhou Tigermed Consulting Co., Ltd.; LinkStart; Medkey Med-Tech Development Co. Ltd.; SMO ClinPlus; and WuXi Apptech. In Japan, the ISPE Japan IP CoP enlisted cooperation of the professor to collect responses: Professor Kaori Muto of the Institute of Medical Science, The University of Tokyo.

Further Reading

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About the authors

Esther Sadler-Williams is Managing Director of her own clinical supply training and consultancy company, SimplyESW, an organization that supports clients in enhancing team skills as well as conducting improvement projects to optimize clinical supply chain delivery. As a pharmacist, she has over 35 years' experience in various GMP and GCP pharmaceutical fields, including managing groups of CRAs and medical writers, as well as more laterally providing contract services for clinical supplies including packaging, labeling, and distribution with Almedica, Aptuit, and Catalent. She has been invited to speak on various clinical supplies topics at many international meetings and in addition is a past Chair of ISPE's EU Investigational Products COP as well as being a lead author for several publications and guidance documents. She has been an ISPE member since 1999.

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BIOPHARMA GROWTH AND REGULATORY PERSPECTIVES

The 2018 ISPE Biopharmaceutical Manufacturing Conference on 10–12 December in Huntington Beach, California, provided information about future-oriented developments in the burgeoning area of biopharmaceutical manufacturing—and also shared insights into the achievements that are already underway. Regulatory perspectives on how new developments are being assessed were provided by several FDA speakers.

The future was the focus of ISPE's third biopharma conference, with a look at developing technologies and presentations from FDA speakers with information about how to move forward in obtaining approvals for innovative technologies.

Some trends in the biopharma industry were noted by Andre Walker, Principal, Andre Walker Consulting, and chair of the conference program committee, at the conference's opening plenary.

"We used to talk about monoclonal antibodies, and now we will talk about new modalities," he said, noting that biopharma is moving toward "turbo-charged" manufacturing, like what is possible with continuous manufacturing. "Our job is to make it compliant and an economic reality for the patients," Walker said. "We've gone from small molecule to large, now we're going even larger to complete cells." But new modalities are also "going smaller" as pharma companies that previously strove to keep viruses out of their facilities are retooling to manufacture them. He also anticipates a coming together of the typical small molecule/large molecule divide. For instance, experience with organic solvents is rare in biopharma plants, but "you need them to make nucleic acid therapeutics, and potent compound experience is essential when producing antibody drug conjugates."

Left to right: Timothy Moore, opening plenary panelists, Steven Oh.

Continuous downstream biopharma is in its early stages, Walker noted—some work has already been accomplished, although not in commercial usage yet, and companies large and small are investing in its development. He encouraged attendees to take the lessons learned from small molecule developers into the biologics continuous manufacturing (CM) space. "It's up to us to use the regulatory path (small molecule developers) cleared for us to make it a reality. New people, new skills, and new processes are needed."

FDA AND EMERGING TECHNOLOGIES

In the opening plenary session on 10 December, Steven S. Oh, Deputy Director, Division of Cellular and Gene Therapies, Office of

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CONFERENCE HIGHLIGHTS

- Address the challenges of manufacturing new modalities: innovations in process technology, equipment design, infrastructure, and operations being implemented by established and start-up firms to safely produce these novel therapies.
- Examine case studies demonstrating substantial increases in output, quality, and dramatic reductions in cost and risk helping large and small manufacturers to remain competitive.
- Explore innovations that are changing the biopharmaceutical manufacturing landscape such as rapid bioburden measurement, PAT and soft sensors, process intensification, and continuous processing.
- Learn about the emerging best practices that are solving supply chain challenges in Viral Vector, Oligo, and ADC production.

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Regulatory Panel Discussion With Q&A

The closing session of the 2018 ISPE Biopharmaceutical Manufacturing Conference on 12 December 2018 was an Industry and Regulatory Panel Discussion led by Joseph Famulare, Vice President, Global Compliance and External Collaboration, Pharma Technical Quality, at Genentech/Roche.

Panel participants were Patricia Hughes, PhD, Branch Chief, Division of Microbiology Assessment, FDA/CDER; Ingrid Markovic, PhD, Senior Director, US Pharma Technical Regulatory, Genentech; Steven S. Oh, PhD, Deputy Director, Division of Cellular and Gene Therapies, Office of Tissues & Advanced Therapies (OTAT), CBER/FDA; and Juan Torres, PhD, Senior Vice President, Global Quality, Biogen.

Torres addressed how to move from a process model being informational to being part of the control strategy. Once a functioning model is developed the specifics of how it will be utilized in the control strategy and how it will be maintained over time must be conveyed to the regulators for their approval. There is a continuum of thinking on this, depending upon the model's criticality within the overall control strategy. Hughes agreed that the model is a "tool in our toolbox" for creating a complete overall control strategy.

Torres continued by considering whether there is a need for a backup to the model. Batch approval is from multiple inputs, and details of this scenario need to be considered in the control strategy. "This will be an even a bigger question if you automate a model to take action based on a process deviation," he noted. Hughes said, "Yes, that would be a problem." Oh noted that he is a proponent of advanced control methods, especially for cell and gene therapy. "Bring multiple tools to bear to achieve process control" was his view.

Hughes said that sponsors should not be afraid of new methods such as Raman spectroscopy or rapid (instantaneous) micro even though these might be more sensitive and will give more information than you have had historically. Integrating these new tools into systems provides opportunity for expansion of knowledge and continuous improvement.

Torres agreed, noting that industry must take risks. The only way to learn if anything works is to try to make it a reality. You have to invest in technologies such as virus gene sequencing for viral contamination detection. Markovic agreed and thanked the FDA for actively promoting these new technologies. "The ultimate goal is speed, flexibility, cost."

"There are some efforts in the cell and tissue engineering space to advance new technologies, which could include continuous manufacturing, plus QC methods," Oh said. NIIMBL (National Institute for Innovation in Manufacturing Biopharmaceuticals) and BioFab are two organizations that coordinate efforts to develop new technologies.

Famulare asked Oh about structures in CBER for promoting new technologies. Oh said that many cell and gene products start out with advanced technology. CDER has an emerging tech team, but CBER does not. It does have a group who are coming up with even newer advanced testing methods. At the time of the conference, the group had been in existence for six months. Oh suggested using the INTERACT program or having a direct conversation with the relevant office based on technology.

Hughes said that at CDER, a lot of reviewers are not up to speed on the new technologies. They have a center of excellence for this and are trying to understand these new technologies, and they want information from industry to help them understand.

Torres asked whether there are methods for cross-agency alignment on new technologies. Hughes said through FDA's Program Alignment there is connection between CDER and the inspectors

In response to an audience question about where FDA recommends companies should go to get a read on regulators' stance on best practices for new technologies, Hughes said that meetings, conferences, and publications are good sources. "Worst case is to see it first in an IND application," she said. "Connect with agencies early for direct information." Markovic suggested ICH as being helpful, noting Q12 is under review and Q13 jut initiated for continuous manufacturing. Hughes added that including information explaining new technology in the application can be very helpful.

Torres noted that there is room to expand intercorporate collaborations such as BioPhorum Operations Group (BPOG). Hughes lauded BPOG and noted some FDA representatives "have been invited." Oh added that although FDA is excited about interacting, it is mostly for education and FDA does not endorse any technology.

In response to an audience query about rapid microbial detection technology in cell and gene therapy, Hughes said the criticality of sterility is key, and likely of huge value for autologous therapy due to production to patient dosing timelines. Oh said standards are being developed to help with implementation and the National Institute of Standards and Technology is doing so as well.

Famulare asked if rapid micro could be used on existing processes. Hughes was enthusiastic about this and said, "bring them on!" FDA has already approved many, she said.

Famulare asked if parametric releas, which has been accepted for terminally sterilized product, was possible with regards to aseptic processes given some of the newer technologies coming providing stringent controls. Hughes responded that "Ten years ago no, never, but today, why not, but it's our (industry's) job to provide proof." She said many companies are using CMOs, and there are concerns about shortcuts being taken using the same technology for a variety of different products.

Several issues were discussed related to post-approval. Oh said that CBER has prelicense inspection as part of BLA review, and product specialists would accompany inspectors for a PAI. Post license, the inspection goes to ORA, team biologics, and usually a product specialist comes as well. Markovic said she appreciates the close relationship between inspector and product reviewer.

Famulare noted that Q12 says robust quality system and robust inspection history would enable a more streamlined change for a manufacturer. Torres asked what constitutes a robust quality system and said agreement is needed on that, perhaps metrics? Famulare said ISPE has an active initiative, Advancing Pharma Quality. Torres said that his peers had a willingness to share more metrics if it would enable quick innovation approval. Markovic added, "You need a robust quality system, but also robust product knowledge, and a platform of prior knowledge." She advocates a combined holistic approach that the three must be taken together to ensure quality.

Tissues & Advanced Therapies, CBER/FDA, provided details about some of the FDA's activities in support of innovative and emerging technologies. Early interaction with the FDA on biopharma product development is encouraged through INTERACT (Initial Targeted Engagement for Regulatory Advice on CBER producTs, formerly pre-pre-IND interaction), which can garner early FDA feedback.

Oh described recently approved cell therapy and gene therapy products, including the following.

- Provenge (sipuleucel-T): Autologous T-cell immunotherapy for treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer.
- Luxturna (voretigene neparvovec): Adeno-associated virus vector-based gene therapy for treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy.
- Yescarta (axicabtagene ciloleucel): CD19-directed genetically modified autologous T-cell immunotherapy for treatment of adult patients with relapsed or refractory large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma.
- Kymriah (tisagenlecleucel): CD19-directed genetically modified autologous T-cell immunotherapy for treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

He outlined guidance and resources of interest to biopharma product developers, including Expedited Programs for Serious Conditions—Drugs and Biologics (2014); 21st Century Cures Act Regenerative Medicine Therapies (2016); Expedited Program for Regenerative Medicine Therapies for Serious Conditions: Draft Guidance for Industry; and a website with information about the regenerative medicine advanced therapy (RMAT) designation and early FDA interactions.

RMAT status designation may be sought from the FDA for drugs that are regenerative medicine therapy, which includes cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products. Oh said that 22 RMAT designation requests have been granted as of 13 June 2018; six are pending, and 33 have been denied. The denials tend to be for administration reasons such as an inactive IND or no preliminary clinical evidence submitted or insufficient preliminary clinical evidence.

REGULATORY REVIEW

During the plenary session on 11 December 2018, Oh presented on "GMP Considerations for Cell and Gene Therapy and Viral Vectors."

Oh outlined some unique CMC challenges presented by cell and gene therapy products. With autologous therapies (one lot treats one patient), specific concerns include product tracking and segregation, high product variability, limited material or time for testing, short shelf life, manufacturing logistics, and scale-out. On allogeneic cell bank-based products, specific concerns include donor eligibility, qualification of cell banks, reproducibility of replacement bank, stability of cell banks and intermediates, and scale-up. Common concerns to both products include mechanism of action, material qualification, challenges establishing specifi-

cations, appropriate manufacturing facility, product shipping/handling, and major manufacturing changes.

Phase 1

Phase 1 for cell and gene therapy projects emphasizes safety considerations, Oh said. Expectations are preclinical animal studies conducted using the product manufactured as it will be used for clinical studies; safety of source material, reagents, and processing; safety testing (sterility, endotoxin, mycoplasma, identity, purity, viability, etc.). Some in vitro proof of concept data should exist, as well as demonstrated ability to manufacture the product. Specification should be established to ensure minimum quality, and product sponsors should have preliminary shipping and stability data.

Donor testing and screening for infectious diseases are required for human cells, tissues, or cellular or tissue-based "351" products when source material is collected from allogeneic human donors. CBER guidance documents provide additional detail on what infectious disease must be tested, when donors must be tested, how they are tested, the types of test kits, and where testing must take place. In addition to donor blood testing, donor screening via medical questionnaire must be performed. Donor eligibility screening and testing requirements often differ by country. For example, non-US countries may not use FDA-licensed test kits or CLIA-certified labs, or they may not perform all the nucleic acid and antibody-based testing required. Consult with the FDA early in product development if using source material from non-US donors. Ancillary materials to be aware of include:

- Research-grade reagents. Where packaging states "not for clinical use, for research purposes only," Oh said the reagent can be used in CGT manufacturing only if properly qualified and to use the highest grade available.
- Human-derived materials. Human serum albumin requires the use of licensed products, and for autologous or pooled human serum, there are donor eligibility issues.
- Animal-derived materials. Adventitious agents, BSE/TSE issues for bovine materials require attention to the country of origin and age of the herd.
- "Serum-free" media do not always solve the problem.

GMP considerations outlined by Oh include the following:

- For Phase 1, there is more flexibility in how CGMPs compliance is achieved. The suitability of a facility depends on the nature of the product—not all state-of-the-art facilities are ideal for every product.
- GMP may "improve" the product, but mostly it allows the product sponsor to control product quality and safety, and to help ensure manufacturing consistency.
- GMP cannot prevent manufacturing errors from happening but can help ensure that controls are in place to catch them and take appropriate corrective actions.

Phase 2

In Phase 2, Oh said that sponsors often focus on clinical and statistical design, but manufacturing is also important. Phase 2 manufacturing is often "on autopilot" but it may be a good time to implement a major manufacturing change prior to Phase 3 studies. CMC expectations are higher for Phase 3 studies (identity, stability, manufacturing consistency/product comparability). Consider further product characterization and revision of release specifications during Phase 2, and consider manufacturing changes that might be needed to accommodate larger trials. Understand critical quality attributed (CQA), critical process parameters (CPP), and key process parameters (KPP).

For product development, work backward

- Step 1: MOA—How is the product supposed to work in the patient?
- Step 2: TPP—What would you have to study clinically to assess safety and efficacy based on MOA, and what properties does the product need (product labeling)?
- Step 3: CQA—What critical properties do you need to control to achieve the desired safety and potential efficacy?
- Step 4: CPP—What processes need to be controlled to achieve CQA?
- Step 5: KPP—What controls do you need to achieve a consistent process?

Next, Oh outlined establishing specifications. Specifications are defined in ICH Q6B and Q11 as "critical quality standards (CQAs) that are proposed and justified by the product sponsor and approved by regulatory authorities. ... Specifications are chosen to confirm the quality of the DS and DP rather than to establish full characterization and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the DS and DP." The full product characterization includes testing not performed on every lot. CQA includes product properties where specifications have not yet been established (e.g., potency) or the product sponsor is not sure if it is truly critical (e.g., additional cellular marker).

Phase 3

Oh likened Phase 3 to commercial manufacturing being on training wheels. At Phase 3, the product sponsor should be using as close to the commercial process as is feasible for registration studies. Potency assays should be in place, CQAs should be identified and appropriate specifications should be in place. CPPs should be well-defined—Phase 3 is critical for demonstrating manufacturing consistency. Additional stability data should be collected, but some details are still being worked out to prepare for commercial production.

He noted CQA and CPP are not meant to be static—these should be continually evaluated and revised as needed. This is important, Oh stated, but revise cautiously since tremendous impact is possible on the product. Additional product characterization data may indicate a better way of ensuring quality. Clinical outcome data may provide clues as to what product properties are most important, and additional manufacturing experience may guide CPP and CQA.

Expedited pathways

Expedited pathways present challenges: fast-advancing clinical

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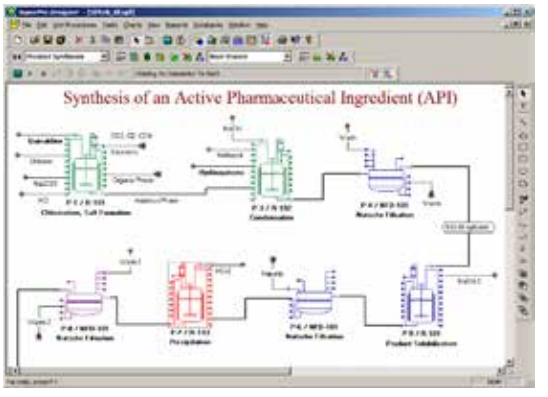

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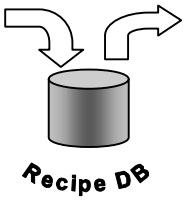

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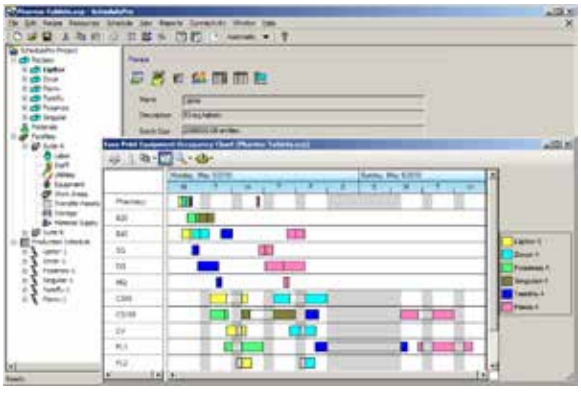
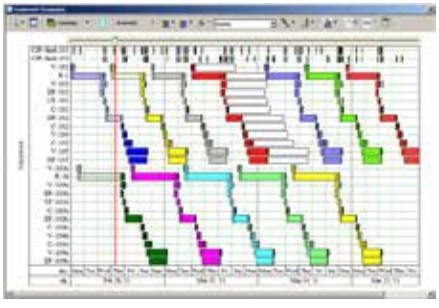


Migrate to SchedulePro to model, schedule, and debottleneck multi-product facilities



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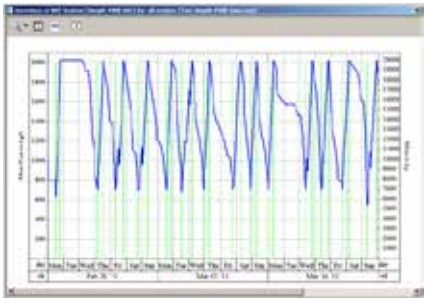

Managing inventories for input, intermediate, and output materials

SuperPro Designer is a comprehensive process simulator that facilitates modeling, cost analysis, debottlenecking, cycle time reduction, and environmental impact assessment of integrated biochemical, bio-fuel, fine chemical, pharmaceutical (bulk & fine), food, consumer product, mineral processing, water purification, wastewater treatment, and related processes. Its development was initiated at the Massachusetts Institute of Technology (MIT). SuperPro is already in use at more than 500 companies and 900 universities around the globe (including 18 of the top 20 pharmaceutical companies and 9 of the top 10 biopharmaceutical companies).

SchedulePro is a versatile production planning, scheduling, and resource management tool. It generates feasible production schedules for multi-product facilities that do not violate constraints related to the limited availability of equipment, labor, utilities, and inventories of materials. It can be used in conjunction with SuperPro (by importing its recipes) or independently (by creating recipes directly in SchedulePro). Any industry that manufactures multiple products by sharing production lines and resources can benefit from the use of SchedulePro. Engineering companies use it as a modeling tool to size shared utilities, determine equipment requirements, reduce cycle times, and debottleneck facilities.

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programs with a timeline that is truncated can mean planning for CMC for commercial scale, for example, or comparability studies needed for scale-up may not be ready yet. Start to think early about planning/conducting CMC changes, "even during Phase 1 if that is what it comes down to."

Challenges affecting CGTPs (current good tissue practices) on expedited pathways include limited manufacturing experience (comparability studies are not statistically powered, and not enough retention or test samples are available); limited in-process testing (process variables and CPPs are not known); limited assay development (potency, purity) (assays are not qualified, and reference standards not established or adequately characterized); limited product characterization (CQAs not known); limited knowledge of product- and process-related impurities; and limited product stability data collected.

Oh outlined a product life cycle approach to potency measurement. Stepwise assay development includes investigation of biological activity and development of a relevant potency assay. He noted that expedited development does not change the regulatory requirements for a validated measure of biological activity before clinical studies to support safety and efficacy for licensure. Considerations for potency assays at the final cell product level include biological potency assay/mode of action (e.g., cell killing); cytokine production; transduction efficiency; vector copy number. At the vector substance level, biological potency assay/mode of action; infectious titer (critical for MOI determination at the transduction steps) in target cell and/or surrogate cell line.

Process changes

Process changes during the product life cycle are to be expected, and not all of the changes that come will be planned. The product sponsor is responsible to plan for change, report and implement change, and demonstrate product comparability using risk- and science-based approaches. "This is risk-based, so risk assessment is key," Oh said.

Some examples of process changes include changes in manufacturing steps, starting materials, reagents, vendors, cell culturing conditions, purification scheme, master cell bank, scale-up or scale-out, automation of the process, and manufacturing site.

Comparability study design insights shared include side-by-side studies of "old" versus "new" product if feasible; comparison to historical data may be acceptable if justified; use relevant, well-qualified assays with predefined acceptance criteria; define acceptable levels of variability using proper statistical methods established prior to the study; discuss comparability protocol and analysis methods with FDA prior to study. If comparability cannot be demonstrated by analytical methods, FDA may require additional preclinical studies or clinical trials.

CONTINUOUS MANUFACTURING AND FDA

Patricia Hughes, Branch Chief, Division of Microbiology Assessment, FDA/CDER, provided some background on recent steps taken by FDA to support innovative technologies during her plenary session presentation on 12 December 2018.

Finalized guidance from CDER in September 2017, Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization, provides industry with information to support early input by the FDA, including presubmission questions and proposals for emerging technology to the Emerging Technology Team.

New developments that Hughes highlighted include single-use systems (SUS), CM, and PAT including Advanced and Rapid Microbial Methods (ARMM). CM in particular shows promise for biopharma through significant improvements in cell line development, cell expansion, cell transfers and protein expression, and reduced microbial contamination rates due to use of SUS in spite of the very long perfusion processing times and complex perfusion operations.

Next in CM: integration of both drug substance upstream and downstream operations; continuous processing from the bioreactor to purification; and continuous chromatography steps. The FDA fully supports this approach, she noted, and indicated that partially integrated continuous biomanufacturing processes have been approved using ballroom design facilities.

Hughes noted that microbial monitoring is still mostly offline although the industry is working to develop and implement ARMM. She is looking ahead to aseptic improvements that integrate ARMM with separation technology such as isolators and closed RABS (restricted access barrier systems), automation that eliminates human/process interaction, and equipment designs that minimize risks during transfers.

FUTURE TRENDS

Timothy Moore, Executive Vice President, Technical Operations at Kite, a Gilead Company, shared the views of a company involved in biopharma development in a presentation during the opening plenary on 10 December 2018 on "Cell Therapy—The Future." Yescarta is one of the first CAR-T therapies to be commercialized. CAR-T and T-cell receptors (TCRs) are cell therapy platforms utilizing receptors engineered to recognize tumor cells and trigger a targeted immune response.

There is much opportunity for development, Moore noted, in areas such as establishing efficacy against hematological cancers for patients with limited options, expanding indications in earlier stages of hematological cancers, exploring solid tumors, rapidly evolving technologies, and leveraging a platform for targeted therapies in other indications.

Challenges faced include complex and resource-intensive manufacturing technology; each patient is a unique batch, requiring chain of identity and chain of custody; adverse events need to be minimized and managed; variability in incoming patient cells reduces manufacturing consistency; and timing and scheduling are critical.

He outlined the ultimate goals for product development: products with excellent safety and efficacy profiles; innovative therapies for patients with hematological and solid tumors; and

scalable manufacturing process to lower the cost of goods and meet market demands.

Moore noted that there are many new entrants to the cell therapy space in both autologous and allogeneic sectors, and many new entrants are expected to reach commercial status as soon as the second half of 2019. Companies entering the market must continue to manage a complex pipeline and scale commercial operations effectively to stay competitive. CAR-T and TCR are the platforms being used, utilizing receptors engineered to recognize tumor cells and trigger a targeted immune response.

With development, cell therapy knowledge is evolving. Moore talked about his company's product, Yescarta, a treatment for non-Hodgkin lymphoma that obtained US approval in October 2017 and EU approval in August 2018. Kite is working to reach patients earlier in the course of treatment and is investigating new indications, including mantle cell lymphoma and follicular lymphoma. The company is also studying combination with other immune-oncology agents with the goal of improving efficacy.

Kite is developing KITE-585, which targets B-cell maturation agent expressed in multiple myeloma; this is now in Phase 1 clinical trials as an investigational treatment for multiple myeloma. Another program aimed at solid tumors is also in development: KITE-718 is a cell therapy engineered to express TCRs that target MAGE A3/A6 proteins, frequently found in bladder, esophageal, head and neck, lung, and ovarian tumors; KITE-718 is in Phase 1 clinical trials, and Kite is partnering with the National Cancer Institute to help accelerate TCR research.

Future trends in cell therapy development, Moore said, will focus on automating manufacturing processes, business systems that support the move to cell therapy maturity, end-to-end tracking identity and materials, and end-to-end connectivity. Moving from centralized to decentralized manufacturing models will increase the reach of cell therapy, and manufacturers will need to address attributes including allogeneic versus autologous, feasibility of process and raw material controls, technology options, compliance and regulatory requirements, staffing needs and training, and economic viability.

—Susan Sandler, Editorial Director

Disclaimer: This is a brief and informal synopsis of information from US FDA during presentations at the ISPE 2018 Biopharmaceutical Manufacturing Conference on 10–12 December 2018. It has not been vetted by any agency and does not represent official guidance or policy of the FDA.

Paul Fiorio

Jean-François Duliere

Andy Hopkins

Jörg Zimmermann

2018 ISPE EUROPE ASEPTIC CONFERENCE:

Focus on Biologics Technology

More than 200 attendees from manufacturers and key suppliers attended ISPE's first European conference on aseptic manufacturing in the old capital of the Austro-Hungarian monarchy, Vienna. Austria is a hot spot for biopharmaceutical manufacturing with a number of global manufacturers or subsidiaries of major pharmaceutical companies. The 2018 ISPE Europe Aseptic Conference's focus was on the latest developments in aseptics, the main technology for biologics.

KEYNOTE PRESENTATIONS

Jörg Zimmermann, Pharma Vetter GmbH

Key trends and developments were presented by Jörg Zimmermann, Vice President at Vetter Pharma (see Figure 1). These included increasing regulatory difficulties and cost pressures for European life sciences companies; growth in specialty medication, especially anti-infectives, oncology, and nervous system disorders; maturing personalized medicine with falling prices; and technology companies entering the health field.

Along with these trends is a change in the conception of health care, Zimmermann said, from caring for the sick to prevention, healthy behavior, and real-time care. About 75% of healthcare spending is now for noncommunicable disease, especially cancer, cardiovascular, chronic respiratory diseases, and diabetes.

Genomics, metabolomics, and proteomics information is leading to new drug discoveries and personalized medicine. Big data and mobile apps for healthcare are on the rise with over 20,000 apps available already. Supply chain issues are a challenge for life science companies in forecasting demand and building flexible and reliable supply chains.

Zimmermann predicted the prefilled syringe market will double between 2014 and 2024, and polymer syringes will enter the markets. For comparison they have already 60% market share in Japan. Also, needleless systems will have more market share as they are painless and so are more appealing to patients.

Paul Fiorio, Novartis

With the example of KYMRIAH for autologous immunocellular therapy, Paul Fiorio, Global Pharma Compliance and Inspection Head at Novartis, discussed the new manufacturing process of a CGT (cellular and gene therapy) product.

KYMRIAH is a one lot per patient process, as patient-specific cellular material is collected under nonaseptic conditions. The microbial bioburden load is dependent of the patient, equipment, and environment conditions. The components for this process are received by qualified and certified suppliers. Measures to reduce bioburden are numerous. The product is manufactured under aseptic conditions and includes the connections between different fittings and syringes and capping/uncapping of sterile ports on bags and containers. Each formulated bulk material is sterility tested with a test for detection of foreign organisms before release. Key controls to aseptic processing cover processing components, personnel, and environment.

Genomics, metabolomics, and proteomics information is leading to new drug discoveries and personalized medicine.

An interesting question-and-answer session followed and posed the questions as to whether new regulation is needed, as the product cannot be called "sterile," and is the term "aseptic processing" still correct? A clear statement from Andy Hopkins, Expert GMDP Inspector at MHRA, clarified the MHRA viewpoint: "The fact that a product comes from a nonsterile starting material does not really matter."

Jean-François Duliere, Chair of ISPE Annex 1 Commenting Group

Numerous comments from various parties were submitted, collected, bundled, and forwarded on behalf of EMA, to the MHRA

Figure 1: Key trends and developments discussed during Zimmermann's presentation.

01 **Increasing regulatory and cost pressure**
Cost pressure and regulatory difficulties are becoming an increasing hurdle also for European Life Sciences companies, impacting the way healthcare firms develop products

02 **Specialty medicine as growth driver**
The focus on specialty medicine within the Life Sciences sector will grow; with a major focus on anti-infectives, oncology, and nervous system disorders

03 **Maturing personalized medicine**
The prices for personalized medicine are falling, companies are increasingly focusing on this segment

04 **Tech companies meet health companies**
Companies from other sectors, e.g. telecommunication, technology, retailers and food manufacturers are entering the ring

05 **Our conception of healthcare is changing**
Healthcare is changing from "care for the sick"to prevention healthy behavior and real-time care

06 **High spending for non-communicable diseases**
Around 75% of healthcare spending is spent on non-communicable diseases, especially cancer, cardiovascular and chronic respiratory diseases and diabetes

07 **"Economics" leading to new drug discoveries**
The increasing availability of genomics, metabolomics, and proteomics information leads to a row of new drug discoveries and personalized medicine

08 **Big Data and mobile health on the rise**
With approx. 20,000 healthcare smartphone apps available and Big Data making real-time information and analysis possible, Big Data and mobile health are finding their way in the Life Sciences sector

09 **Supply chain is becoming an issue**
Life Sciences companies try to find better ways to forecast demand and build flexible supply chains, necessary due to global unrest

10 **Implantable sensors**
Advancements in nanotechnology will integrate mobile health even more in our lives

Source: CatCap GmbH 2016, M&A Report: The European Life Sciences Industry 2015

rapporteur, Andy Hopkins. Jean-François Duliere, Chair of ISPE's Annex 1 commenting group, presented a comprehensive overview of the most considered topics.

Various comments went to the Annex 1 link to nonsterile products. There were concerns that Annex 1 could be used globally for nonsterile products. Additional arguments addressed Quality Risk Management with many references to QRM in Annex 1. The word "risk" is mentioned 92 times, indicating its importance to the commenters. Regulators indicate that QRM has been formally required since 2013 after release of ICH Q 9 in 2005.

Andy Hopkins, MHRA

Andy Hopkins, Expert GMDP Inspector for MHRA, provided input about 140 sets of comments on Annex 1 that have been received from industry. All comments have been reviewed. Hopkins noted that there is a certain lack of understanding that Annex 1 does not affect just Europe but also applies to PIC/S and WHO. In addition, Annex 1 covers many types of manufacturing including API, single-unit batch processing, and others. Comments are to a certain extent controversial, ranging from "too prescriptive" to "not prescriptive enough."

He pointed out that QRM is not a new requirement but already had been formally requested since 2013. Hopkins pointed out that a genuine dialogue between regulators and industry is needed and should be far more open than currently is the case. Training by industry associations such as ISPE and others is key.

"Bad design" but "good monitoring" is like testing things into compliance and not the right approach, he said. He also noted that contamination control strategy is not a new requirement as mentioned in chapter five in 2015.

Andy Hopkins's statement and conclusion about QRM in aseptic processing: "Design the processes, procedures, and facilities not to contaminate the product. Design the monitoring system to detect any deleterious trend and/or failure. Keep reviewing and developing as new information about your processes, procedures, and designs comes to light. Keep developing as you become aware of new technological advances."

ADDITIONAL PRESENTATIONS

After the keynote presentations, the conference continued with four dedicated tracks:

- Track 1: Quality & Regulatory: Annex 1, Quality Risk Management and Data Science
- Track 2: Isolator, Barrier, Robotics and Manufacturing High Potent Drugs
- Track 3: Aging Facilities—The Way to Facilities of the Future
- Track 4: Decontamination, Sterilisation, Transfers, E-Beam, Stoppers, RTU, and Disposables

Due to positive feedback from participants, including regulators, about the program, including the presentation content and speakers, the D/A/CH Affiliate committee has committed to repeating the conference within the next two years.

—Thomas Zimmer, Vice President, European Operations

ISPE D/A/CH Affiliate members with John Bournas, CEO and President of ISPE.

Happy 25th Birthday, D/A/CH Affiliate

At the conference, the ISPE D/A/CH Affiliate (Germany/Austria/Switzerland) celebrated its 25th anniversary. Gunter Baumgartner, Chair of the Affiliate, pointed out the high level of growth in affiliate membership in recent years with a high global retention rate. The Affiliate currently has over 1,300 members. The D/A/CH Affiliate has provided a long list of successful events, seminars, trainings, and Young Professional and Student activities. The Affiliate received the Affiliate and Chapter Excellence Award at the 2018 ISPE Annual Meeting & Expo in November, which celebrated the work of the D/A/CH Affiliate. An anniversary celebration dinner at the old Renaissance Palace Ferstel in Vienna included past D/A/CH chairs as honorary guests.

New Paths and Old in the Japan Affiliate's US Plant Tour

Akihiro Matsuki and Michael J. Lucey

In conjunction with the 2018 ISPE Annual Meeting & Expo in November in Philadelphia, the ISPE Japan Affiliate held its annual pharmaceutical plant tour. The tour extended over four days from 29 October to 1 November. The group visited four US plants—three in California and one in Indiana.

A total of 20 professionals from across Japan participated, including Affiliate Treasurer Hiroshi Sakai, Head of Secretariat Akihiro Matsuki, and Adjunct Director Michael J. Lucey, who jointly led the Organizing Committee of Affiliate Board Members.

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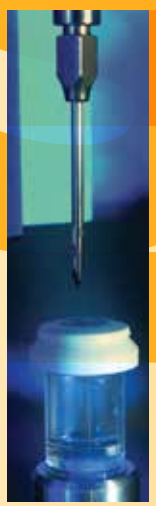

Members of the Japan Affiliate enjoyed four plant tours before attending the 2018 ISPE Annual Meeting & Expo.

The tour team included eight members from pharmaceutical companies, eight from engineering/construction companies, and four from equipment manufacturers.

The group visited Shire in Los Angeles; Boehringer Ingelheim in Fremont, California; Novartis in San Carlos, California; and Eli Lilly in Indianapolis. Then they traveled to Philadelphia to attend the ISPE Annual Meeting & Expo. The following are highlights from the individual plant tours.

SHIRE

The 2018 tour team's first visit was the Shire Los Angeles manufacturing plant. Tour members saw the new QC laboratory as well as the Building 8 purification manufacturing facility, which were selected as category winners of the ISPE 2018 Facility of the Year Award (FOYA) in the two categories of "Operational Excellence" and "Facility Integration & Overall," respectively. The newly constructed QC lab functions as a control lab for next-generation plasma-derived therapy, for which global demand is increasing. The design achieved an open and efficient development environment by incorporating a Lean process flow and an improved work environment for the employees. Building Information Modeling (BIM) was used to design the Building 8 manufacturing facility. The philosophy is that maintainability and operability should be taken into consideration at all times. An optimal facility has been realized through a real-time review during construction with feedback from designers and the manufacturing team to the facility design. At the 2018 Annual ISPE meeting on 6 November, it was announced that Shire's Los Angeles Building 8 manufacturing facility was the Overall Winner for the 2018 FOYA.

BOEHRINGER INGELHEIM

The team next visited the Boehringer Ingelheim biomedicine manufacturing facility in Fremont, California. Following the overview presentation, the team saw the production line and this was highlighted by the host's professionals during the facility walkdown, which comprises six processes: cell culture, harvesting, initial purification, final purification/formulation, filling, and warehousing, with two lines dedicated to the first four processes. A full and unobstructed view of the production line from the visitor's corridor is a major advantage, enabled by the glassed-in design. With the adoption of mobile single-use equipment, the highly flexible character of the facilities was recognized by all. At the time of the visit, an additional 12 kl SUS culture tank was being installed. At the close of the tour, a networking reception was provided by host company representatives, which itself offered a further opportunity for quality questions and answers. The lasting impression left with the visitors is the host's strong passion for biomedicine manufacturing.

NOVARTIS

Novartis's Technical Research and Development (TRD) facility and production facility is in San Carlos, California. The production line for the aminoglycoside antibiotic "TOBI" (tobramycin) is composed of a solution adjustment unit, spray dryer, homogenizer, powder loader, and other units. High-potency active pharmaceutical products are manufactured and isolators are adopted for the powder loader and inspection unit. The TRD facility and the commercial manufacturing facility are laid out at the same site. It was clearly noted by the visiting team that this made for good communication. Moreover, Novartis has demonstrated its own initiatives in all design processes, from the characteristics of pharmaceutical products to the design of production equipment and inhalers. The host company takes great pride in its products.

ELI LILLY

The tour team's final stop was Eli Lilly's continuous manufacturing facility in Indianapolis, the 2017 ISPE FOYA Winner. Members observed the operation of the continuous direct compression process and small molecule production line. The direct compression process is the simplest process for tablet manufacturing. Eli Lilly uses simulation techniques and experimental approaches in evaluating fluctuating factors, and their quality management strategy has been established using process analytical technology tools and modeling techniques. Given the interest in Japan in all aspects of continuous manufacturing, this visit was a timely one, permitting the opportunity for an enhanced understanding of Eli Lilly's approaches to quality management.

CONCLUSION

The tour was realized through the cooperation of the host plants as well as friends of the Japan Affiliate in the ISPE organization. For this, the authors and the Affiliate wish to express sincere gratitude.

On a lighter note, and maximizing the opportunity of being in the US, visits were made in free time available to a Napa Valley winery and the Indianapolis 500 Race Course and Museum. All of this made for a highly interesting time, as well as being most educational for all.

For a further widening of the network of members in Japan, the Affiliate holds a reunion every year for all participants in the US pharmaceutical plant tour over the many years of its history and displays the tour in poster form at the Winter Meeting in December.

About the authors

Akihiro Matsuki, Mitsubishi Chemical Engineering Corporation, is Head of Secretariat for the Japan Affiliate. Akihiro has over 20 years of experience as a pharmaceutical manufacturing facility engineer. He has been an ISPE member since 2012.

Michael J. Lucey is Sales Development Manager at JGC Corporation, Japan, and Adjunct Director of the Japan Affiliate. Michael has worked for more than 30 years as Japan-based Sales Development Manager for the Global Marketing Division of JGC, covering areas of the company's international business. He has been an ISPE member since 2001.

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QUALITY BY REDESIGN OF A LEGACY PRODUCT

Case Study

Sasha Nikolić, PhD


Sasha Nikolić

In recent years, the concept of quality in the pharmaceutical industry has evolved from the idea of testing the quality to designing the quality. The fundamental idea is very simple; it is necessary to understand the material and process variables that determine the final product's quality from the beginning of product development. Such an approach permits an in-depth understanding of the product and guarantees its quality by adjusting process variables based on known variability of input materials and intermediate manufacturing phases. The strategic thinking is based on the fact that processes might change or drift over time, which gave birth to the well-known quality by design (QbD) approach [1].

BACKGROUND

The concept of QbD has been successfully implemented in many industries for decades. However, it required time before it could be implemented in the pharmaceutical field, mainly due to the lack of regulatory harmonization among different countries and regions. To ease the implementation of QbD, and generally harmonize the quality concept, ICH released several guidelines, ICH Q8–Q11 [2–5], which provide a general framework for QbD application to drug substance and drug product science- and risk-based development and manufacture.

CASE STUDY REVIEW

Since the release of ICH guidelines, several case studies were published on how to apply the key elements of QbD to product development for both chemical and biological/biotechnological entities [6–9]. Furthermore, in collaboration with the Pharmaceutical Control Services of the Health Department of the Catalan Government, the ISPE Spain Affiliate published a case study about the application of QbD to legacy products [10]. In this article, a case study of QbD applied to a lyophilized injectable drug product is presented. The product has been already marketed by Laboratorio Reig Jofre since 2008 as a generic version of a reference drug product in different markets, including Europe (EU), Israel, South Africa, Hong Kong, Vietnam, and Georgia.

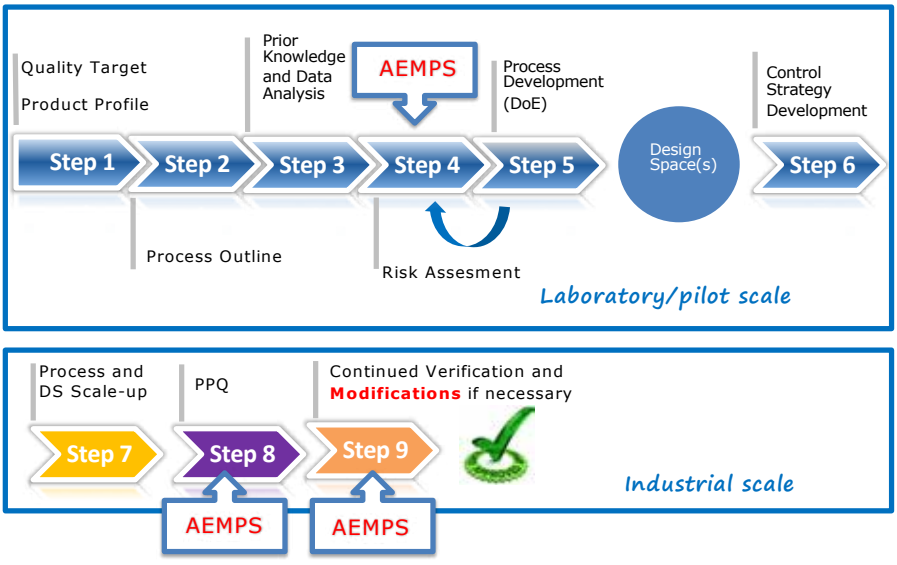
The introduction of a new larger freeze-dryer, which drove an increase in batch size to match the new machine's full capacity, inspired this project. At the same time, it was determined useful to review knowledge gained during initial development and routine manufacturing (approximately 3–5 batches per week for 8 years), and propose improvements where necessary, applying a risk-based approach throughout the process. This would generate the first set of variations, compared to the already-approved dossiers. Furthermore, at the same manufacturing site, a new manufacturing zone with increased capacity for sterile injectables was to be constructed, with plans to transfer the product to this new manufacturing area, with larger freeze-dryers. This will represent the second group of future variations.

Variation classification depends on each country's regulation, but in most of the cases, at least several major variations will be necessary. In Europe, these changes are classified as Type II variations (also taking into account that freeze-drying is considered a nonstandard manufacturing process). Approval and implementation of such changes usually require up to 2 years. To reduce this time, and make the product manufactured with the new process and/or in the new facility commercially available sooner, an additional variation can be filed to include a Post-approval Change Management Protocol (PACMP), according to the current European legislation. This document lists the foreseen changes as well as proposes a strategy for evaluating and mitigating potential impact on product quality.

AEMPS COLLABORATION

If supporting data and strategy are sufficiently sound, from both a scientific and a risk management point of view, it is possible the

Figure 1: Schematic representation of the project, in which steps are internal (company) tasks and milestones correspond to steps to be finished before each meeting with AEMPS.



regulatory authorities will downgrade the variation type—in this case from Type II to Type IB, or even IA. If approved, this permits for faster evaluation of the proposed changes with a consequently shorter time for commercial implementation. Although appealing, this approach is not commonly used to introduce future variations. Considering the complexity of the aforementioned changes, it was decided to contact the Spanish national health authority Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) and share with them the details of the project plan and proposed strategy.

The initiative was well accepted by the AEMPS. In an initial meeting, a QbD approach was proposed for the revision and redevelopment of the product. It was accepted that the scope of the subsequent meetings would be the first group of variations, i.e., QbD-based variations and the introduction of a PACMP. At the same meeting, Laboratorio Reig Jofre proposed a working strategy that included several meetings between Laboratorio Reig Jofre and AEMPS to review previous project milestone outcomes and coevaluation of the strategy to be implemented for subsequent milestones. Figure 1 provides a schematic representation of the milestones and proposed meetings.

SCIENTIFIC ADVICE MEETINGS

The formal meetings with AEMPS were categorized as scientific advice meetings. This categorization of the meeting was proposed by AEMPS given that throughout the project, extensive statistical data treatments were foreseen, as well as the use of novel analytical techniques. This way, the data would be evaluated while being generated, making it easier to evaluate the final documentation that would support the formal variations, once applied for. The first formal meeting was organized to review the proposed experimental strategy, mostly the type of experimental designs, variables, and corresponding levels and ranges to be studied, to support the creation of the corresponding design space. For that purpose, all historical data were previously statistically assessed for the whole period since the first commercial batch to provide information about the current manufacturing process's state of control and identify the improvement needs.

Generally, the manufacturing process was under control. However, it was found necessary to improve the bioburden analysis sampling strategy, because isolated out of specification (OOS) results were obtained for this in-process control. The root cause in all occasions was found to be sample manipulation in a grade C environment. For this purpose, and in collaboration with the filter provider, a new filtration system was designed: a preassembled and gamma-irradiated system that contains sampling bags with aseptic disconnectors to avoid any sample manipulation prior to its analysis. Furthermore, the overall sterility assurance is increased by design.

QUALITY ASSESSMENT

An extensive and comprehensive risk assessment was performed to define the following:

1. Quality target product profile (QTPP), critical material attributes (CMA), critical quality attributes (CQA) of the intermediate products of each unit operation and of the finished product, and the critical process parameters (CPP) (For CQA and CPP examples, see Tables A and B, respectively.)
2. Experimental strategy for all manufacturing unit operations

Table A: Examples of the evaluated CQAs and surrogate parameters (parameters that correspond to an analytical result; several surrogate parameters may be evaluated together to describe one CQA)

Critical Quality Attribute	Surrogate Parameter
Appearance	Visual appearance
	Degree of color
Identity	Match the product main molecule
	Match the salt
Appearance of reconstituted solution	Opalescence
	Absorbance
Reconstitution time	Reconstitution time
Finished product pH	pH
Residual moisture content	Residual water
Purity	Related compounds
	Main compound assay
Extraneous particulate contamination	Subvisible particles
	Visible particles
Sterility	Sterility
Pyrogenicity	Bacterial endotoxins
Hermeticity	Tightness

Table B: Examples of evaluated CPPs, for each process unit operation

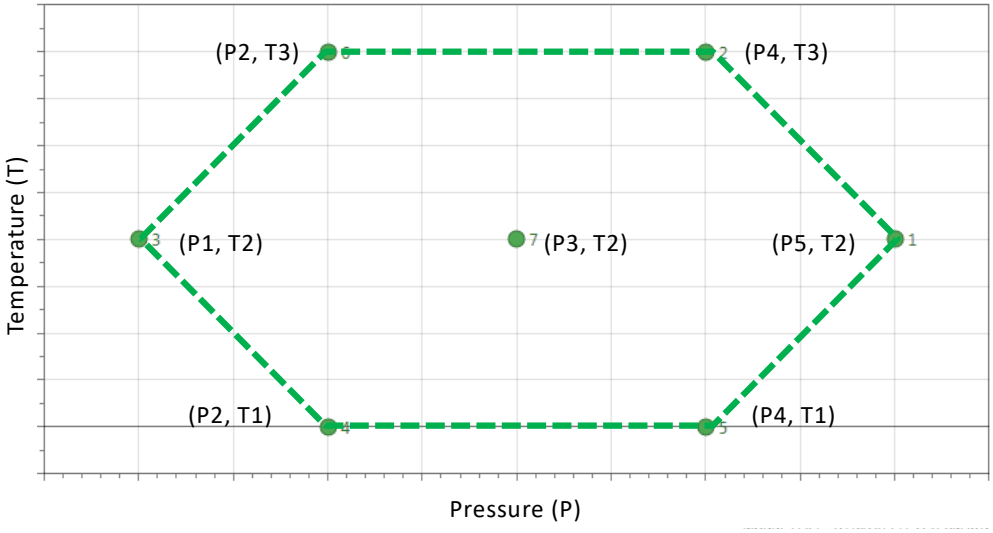
Unit Operation	CPP
Compounding	Stirring speed
	Stirring time
	Cooling jacket temperature
	Final volume adjustment
Filtration	Filtration pressure
	Filtration temperature
	Filter-solution contact time
	Filtration time
Solution collection	Cooling jacket temperature
Filling and pre-stoppering	Pump volume setting
	Nitrogen blowing pressure
	Filling speed
Freeze-drying	Loading temperature
	Soak time
	Freezing temperature
	Freezing time
	Primary drying time
	Primary drying pressure
	Primary drying shelf temperature
	Secondary drying time
	Secondary drying pressure
	Secondary drying shelf temperature
	Nitrogen backflush pressure
Crimping	Crimping station height

For the freeze-drying process, as an example, it was found necessary to investigate the impact of the variability of the CPPs (such as the shelf temperature and chamber pressure, once the endpoint of the sublimation was guaranteed) on the product quality, for all CQAs that may potentially be affected, such as aspect, reconstitution time, purity (assay and related compounds), and residual moisture content (RMC). The current freeze-drying cycle, as described in the dossier and applied in routine, had only fixed set points, and no structured data were available for any other combination of the set points. Taking into account that energy input changes from one freeze-dryer to another, even with theoretically same set-point values, and that the future freeze dryers (new manufacturing area) will be loaded by an automatic loading and unloading system, thus without trays, the risk of failure (affectation of one or more CQAs) due to the modified energy input was considered high.

A detailed experimental strategy was presented to define the experimental region. AEMPS suggested that a list of all possible Design of Experiments (DoE) were presented, along with the one chosen, to better describe the benefits and drawbacks of each potential DoE matrix. The aim was to find the most appropriate DoE that could maximize the significant information while reducing the number of experimental runs. This was completed also taking into account the duration of freeze-drying processes (more than 2 days, in this case). Further, it was proposed and accepted to study primary drying (sublimation phase) and secondary drying (desorption phase) separately. This was done by first assessing the impact of the variability of the CPPs related with secondary drying (temperature and duration) while keeping the primary drying conditions fixed (those corresponding to the already approved and routinely applied for this product).

A total of three runs was necessary (at three different temperatures for secondary drying, with a 10°C difference among runs). The pilot-scale freeze-dryer was equipped with a sample thief, so in each run it was possible to extract samples at different timepoints without disturbing the process and while maintaining the process conditions as unchanged (apart the secondary drying duration) of all samples from the same run. The assessed CQAs were RMC, purity (assay and related compounds), and appearance (to evaluate the possibility of collapse during secondary drying, being the product amorphous). The duration range was set between 3 h and 16 h. The maximum evaluated duration was way above the current routine duration, but it was decided to assess the impact of addi-

Figure 2: Graphical representation of the DoE experimental domain for primary drying. The exact values are omitted for confidentiality reasons. Instead, pressure (P) and temperature (T) levels are indicated as P1–P5, and T1–T3, respectively.



tional time that may be added due to operational reasons (currently, night shifts have limited number of permitted operations).

In all the cases, the CQAs complied with the specifications, and no significant variability was observed among runs and extractions. All the results of RMC were comprised between 0.4% and 0.8% (specification: NMT 5%). Likewise, the purity (assay, and individual and total related impurities) was not affected by increasing temperature and process time within the experimental region. No shrinkage was observed, so collapse during secondary drying did not occur. It was also confirmed, in evaluating the reconstitution time, that it may increase due to collapse either in primary or secondary drying. These results permitted the conclusion that the experimental region also represented the design space region for this part of the freeze-drying process at pilot scale. For further studies, i.e., DoE for the primary drying, the center point conditions for the secondary drying temperature and the shortest duration were set as fixed.

The following experimental task was the assessment of the impact of primary drying CPPs variability on selected CQAs, such as appearance (collapse) and reconstitution time. At the same time, with primary drying being the longest step, it was decided to evaluate the impact on the duration, with the aim of choosing the shortest, and thus most cost- and energy-effective process, while guaranteeing quality. Figure 2 provides the Doehlert DoE experimental domain representation [11, 12]. This kind of DoE permits the study of two factors, pressure and temperature; in this example, at different number of levels, five and three, respectively. It is also possible to extend the experimental domain in different directions, and new factors may be added, if necessary. The estimation of main effects and all first-order interactions, as well as quadratic effects, is possible without confounding effects. The central point conditions coincided with the currently established conditions that had been set during the initial development, based on the thermal characteristics of the solution, such as glass transition of the freeze concentrate and the collapse temperature, assessed by differential scanning calorimetry and freeze-drying microscopy, respectively. These conditions were used for the three replicates to assess model quality.

After the nine experimental runs, and analysis of the corresponding CQAs, it was concluded that the experimental region could also describe the design space for the primary drying part of the freeze-drying process at pilot scale. As no statistically significant differences were found as outcomes of all cycles, it was not possible to model the CQAs as function of the CPPs. However, significant differences, in the range 16 h to 30 h, were observed in terms of process duration, as a function of pressure and temperature.

Along with the freeze-drying studies, experimental strategy was also applied to elucidate the impact of variability on other unit operations, such as compounding. In this case, CPPs that were varied systematically were stirring speed and temperature, to evaluate their impact of solubilization kinetics, foam formation, and degradation. Also, the new sterilizing filtration system was subject to experimental studies, in collaboration with the filter provider.

DATA EVALUATION

Once all the experimental work regarding the manufacturing process was finished, a comprehensive data evaluation was performed. It permitted the reassessment of the initial risk designation for each unit operation, taking into account the new findings. The aim was to describe the mitigation actions, including the

pilot-scale design space (for freeze-drying) and normal operating ranges (for other unit operations), and to propose a formal risk-based control strategy for the scale-up exercise, for all unit operations.

After defining the control strategy and corresponding sampling plan, a full industrial-scale batch was manufactured to verify the newly developed process and corresponding design space. For freeze-drying, the proposed strategy for design space scale-up consisted of applying a cycle at the upper edge of the design space (P4 + T3, Figure 2) for primary drying, and at the lowest temperature and shortest duration of secondary drying. The rationale is based on the fact that all other, less aggressive, primary drying conditions (combinations of pressure and temperature) will yield satisfactory results if the upper edge is proven acceptable. For secondary drying, the combination of temperature and duration was chosen as possibly worst case in terms of desorption effectiveness and uniformity throughout the freeze-dryer. In all the cases, the endpoint of each phase was guaranteed by appropriate process analytical tools, the same as those used at pilot scale. For all unit operations, process data were collected continuously and compared with the corresponding acceptable ranges.

The analytical results, related with all CQAs, complied with specifications and were comparable with those at pilot scale. This confirmed that the design space could also be successfully applied at the industrial scale. At this stage, the first phase of manufacturing process validation [13] was considered finished and data were shared with AEMPS during the second formal meeting. At the same time, a process performance qualification (PPQ) strategy proposal was submitted for preevaluation. It was based on the risk reassessment after process scale-up. The number of full-scale batches to be manufactured was defined as at least three, where the final number of batches necessary to define all process phases as qualified would be based on statistical evaluation of the data to assess intra- and interbatch variability and process capability [14].

PPQ EXERCISE

An extensive sampling plan was proposed for secondary drying (RMC mapping), the only manufacturing phase where the residual risk of lack of uniformity among vials was still considered medium. Given the batch size, the number of samples (315 per N batches) was very high, considering the analysis by Karl Fisher titration. Therefore, an alternative analytical method, based on near-infrared spectroscopy, was developed and validated. It permits analyzing hundreds of samples in a very short time without any sample manipulation, allowing effective evaluation of manufacturing process quality without errors due to sample manipulation. Furthermore, as the analysis is not destructive, it can be used to follow the evolution of the same sample during stability studies, or to correlate RMC and other CQAs.

The PPQ exercise was executed in accordance with what had been agreed upon with AEMPS. For this purpose, three full industrial-scale batches were sufficient to qualify all manufacturing phases. The freeze-drying process that was applied for PPQ, and later in routine manufacturing, was within the design space, close to the conditions of the scale-up batch (pressure 10% lower; temperature 12.5% lower), to minimize the duration and permit for a safety margin. For the PPQ exercise, two freeze-dryers were used (one for each full-scale batch of bulk solution) to assess the impact of different freeze-dryers on the process and product quality. All CPPs were demonstrated to be under control; likewise, the CQAs complied with the specifications. The RMC mapping showed very good uniformity (0.4% to 0.8%, specification NMT 5%). The two freeze-dryers showed statistically significant differences in terms of RMC, but after the evaluation, it was concluded that there was no practical difference, i.e., no impact on product quality, between the processes performed in the two freeze-dryers. This permitted to further downgrade the residual risk identified for secondary drying to low. Thus, the control strategy proposed for routine manufacturing for this CQA was reduced to only three vials, randomly sampled from any of the positions in the freeze-dryer.

VARIATIONS EVALUATION

After executing the three PPQ batches, the data were summarized and shared during a third and final formal meeting with AEMPS. At the same time, the Continued Verification Strategy and a proposal of a PACMP were presented to AEMPS. The PACMP was prepared to anticipate the following:

1. Change of the vial type from molded to tubing, with consequent further increase of the batch size (in the manufacturing area)
2. Change of the manufacturing area with new and larger freeze-dryers, thus an additional increase of batch size

For each proposed future change (second group of variations), the exact aim was defined and agreed upon, as well as the failure mode and possible effects on the product quality. For every identified failure mode, necessary actions and experimental strategy were defined and the deliverables established, with the aim of downgrading the corresponding variation type. After adjusting the final text of the PACMP, it was submitted along with all other variations for evaluation. Given that the submitted documentation was previously evaluated during the formal meetings, the number of allegations was very reduced and these were focused on the dossier sections where the data were included, rather than the content or quality of the provided information. All variations, including the introduction of the design space, the routine use of PAT tools (such as endpoint determination for each batch by Pirani vacuum gauge), novel analytical techniques, and the PACMP were approved for routine implementation in only 6 months, significantly faster than in traditional applications where no previous communication with AEMPS is established.

This was an example of a win-win strategy. The same group of variations was presented in other European agencies (national procedures) and worldwide. The evaluation time was significantly longer in other European countries, with several groups of allegations in each of them, mostly focused on the definition of criticality and PACMP. In all cases, the variations were approved. On the other hand, in most non-EU countries, the evaluation was signifi-

cantly different due to lack of expertise about QbD terminology and principles, and/or absence of regulatory harmonization. Although the same documentation, adapted to regional requirements, was provided in all cases, it was not possible to obtain the approval of the PACMP in most non-EU countries.

CONCLUSION

It is clear that better harmonization among regions and countries is still required so innovation can be implemented in the life cycle management of pharmaceutical products. Therefore, any initiative in this field, such as the announced ICH Q12 guidance [15], will be very helpful.

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Sasha Nikolić, PhD, is Director of the Center of Excellence in Freeze Drying at Laboratorio Reig Jofre (Barcelona, Spain). He is a licensed pharmacist (University of Perugia, Italy) and he holds an MSc (University of Barcelona, Spain) and a PhD (University of Siena—University of Berlin), both in pharmaceutical technology. During his academic career, prior to joining Reig Jofre, he developed research activities in the field of application of nanotechnologies in dermal and ophthalmic drug delivery. During his postdoctoral studies at the University of Barcelona, he focused on freeze-drying as means of stabilization of nanosuspensions. In his current role, he focuses on freeze-drying and aseptic process development, as well as the implementation of quality by design and continuous process verification strategy development and improvement. Dr. Nikolić is also appointed as a lecturer for the postgraduate students at the University of Barcelona. He is author of various peer-reviewed papers and book chapters.

AUTOMATED PARTS WASHER

Factory Acceptance Test

Olivier Van Houtte, Paul Lopolito, Dijana Hadziselimovic, and Neo Aik Ann

It is a common practice in the pharmaceutical and biopharmaceutical industries to execute a factory acceptance test (FAT) for equipment involved with various drug manufacturing processes. The FAT is a project milestone in purchasing good manufacturing practice–compliant equipment.

User requirement specifications (URS), functional specifications (FS), and design specifications (DS) are all incorporated into the equipment design and manufacture, as shown in Figure 1. The FAT is performed in production-like conditions at the manufacturer's site, where testing equipment, utilities, and trained personnel are available to ensure that the equipment functions as designed. It is also easier and less expensive to correct issues or implement design changes at the manufacturer's facility. A well-planned and well-executed FAT can lead to an easy transition to site acceptance testing (SAT), qualification,* and continual monitoring of the parts washer after delivery [1–4].

Based on our decades of experience, this article presents best practices and critical items to avoid when planning for and executing an FAT for an automated parts washer. We also include a case study to illustrate the advantages of carrying out an FAT.

DOCUMENTATION

Documentation related to the equipment and the project can generally be provided in the manufacturer's format as long as the manufacturer meets some basic criteria [5]:

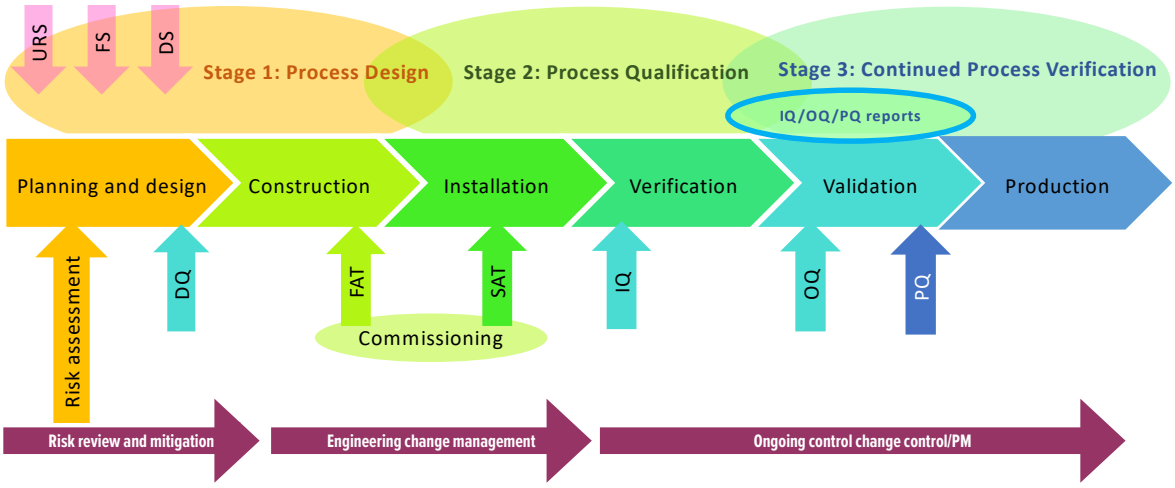
- Having an acceptable quality system in place (ideally approved by a third party)
- Demonstrating the necessary technical capabilities and expertise

* Instrument qualification (IQ), operational qualification (OQ), and performance qualification (PQ)

Table A: Instrument calibration checklist

Document	Acceptance Criteria	Pass/Fail	Initials/Date
Sump temperature transmitter and non-recirculated final rinse temperature transmitter and exhaust temperature transmitter	Transmitter calibration has been performed according to instruction 920-514-029 rev. _____	Pass/Fail	
Pump outlet pressure transmitter	Pressure transmitter calibration has been performed according to instruction 920-514-037 rev. _____	Pass/Fail	
Conductivity analyzer calibration	M300 analog outputs channels calibration has been performed according to instruction 920-514-031 rev. _____	Pass/Fail	
Conductivity sensor calibration	Conductivity sensor calibration has been performed according to instruction 920-514-034 rev. _____	Pass/Fail	
770 MAX analyzer and 500 TOC sensor	770 MAX analyzer and 500 TOC sensor have been set according to instruction 920-514-097	Pass/Fail	
777 MAX TOC analog output calibration	777 MAX TOC analog output calibration has been calibrated as per 920-514-163 rev. _____	Pass/Fail	

Figure 1: Life cycle approach: Design, qualification, and continued verification



- Following good engineering practices
- Having approval from a subject matter expert (SME) and quality personnel, at a minimum

Control system documentation is normally expected to follow GAMP® 5 Guidelines [6]. The more complete the FAT documentation, the easier it is to execute SAT, IQ, OQ, and PQ activities.

Project documentation is divided into two categories: predelivery and postdelivery.

POSTDELIVERY DOCUMENTATION

Postdelivery documentation, submitted to the end user after the FAT and any corrective follow-up actions are completed, is usually provided in paper or electronic format or both. Typical content includes:

- Operator/user manual
- Manufacturing and qualification documentation
  - General arrangement drawings
  - Rack and accessories drawings, if applicable
  - Welding procedure specifications
  - Procedure qualification report
  - Heat number certificates
  - Surface finish report
  - Welding map drawings
  - Welding logs
  - Material certificates
  - HEPA filter certificates
  - Chemical delivery system specifications, if separate
- Control system validation documentation
  - Software history
  - Hardware design specifications
  - Software design specifications
  - Software module specifications
  - Software module test specifications
  - Software module test report
  - System acceptance testing (software test documentation)
  - System acceptance test report FAT protocol

PREDELIVERY DOCUMENTATION

Predelivery documentation is submitted to the end user before manufacture to ensure that both manufacturer and end user have a common understanding of all requested equipment features, documentation, testing requirements, delivery time, etc. It is often divided into a written order-confirmation letter and submittal package. "Certified for construction" documents and drawings are sent for approval by the end user once the design of the equipment is complete. Standard submittal packages include the following:

- Transmittal letter
- Drawings showing the layout of the equipment, utilities, and installation requirements
- Process and instrument diagrams (P&ID)
- Recommended spare parts list
- General arrangement drawing showing the layout and location of the major components
- Wiring/electrical diagrams
- Functional specifications
- Project schedule
- FAT protocol (sometimes sent with the "certified for construction" or "issued for correction" package only)

The overall project schedule should reflect the 4–6 weeks that manufacturers typically need to develop the preliminary submittal package, and the 2–3 weeks that end users need to approve it.

Figure 2: Typical FAT table of contents

Table of Contents

Upon approval, the washer manufacturer implements end user comments, if any, and provides updated certified for construction drawings. Delays in issuing or approving these documents can have a negative impact on the unit lead time. Requests for alterations or modifications may also affect pricing and/or delivery time.

FACTORY ACCEPTANCE TEST

The FAT, an integral part of the equipment qualification program, is designed to challenge the unit to ensure that it functions as intended. The equipment is tested in conditions as close to real life as possible, using sophisticated bays that are capable of duplicating virtually any site conditions, including electrical configurations, utility supplies, and calibrated measurement devices.

The FAT also confirms that the equipment is manufactured according to the approved design drawings, technical specifications, and end user purchase order. A typical FAT may require 2–3 days of onsite attendance by end user representatives. The number of representatives may vary, depending on end user preference and objectives, but will generally include an SME from engineering and validation. Both manufacturer and end user understand that the unit documentation may need to be updated after the FAT and that final documentation will be issued after the unit is shipped.

FAT documentation contains elements common to standard operating procedures (SOPs) and other qualification documents, such as introduction, purpose, scope, responsibilities, overview, deviations, change control, corrections, test procedures, and results. FAT documentation should also include software version identification, P&ID, weld inspection checks, instrument checks, alarm verification, and coverage testing, if applicable (Figure 2). Finally, the FAT documentation is assigned a document number with the equipment number or serial number listed, as well as the document revision number.

Equipment Configuration Verification

This process confirms the installation of all unit options purchased by the end user. It is typically conducted via a P&ID walkdown, where all subsystems are depicted and explained, and main washer functionalities are identified. This is easily completed with one operator reading the P&ID and a second operator verifying that the drawing corresponds to the as-built configuration. Any deviations should be noted by redlining the P&ID and initialing and dating the edits. Once completed, both operators should initial and date the P&ID and personnel FAT record sheet. Figure 3 shows a typical P&ID of an automated washer.

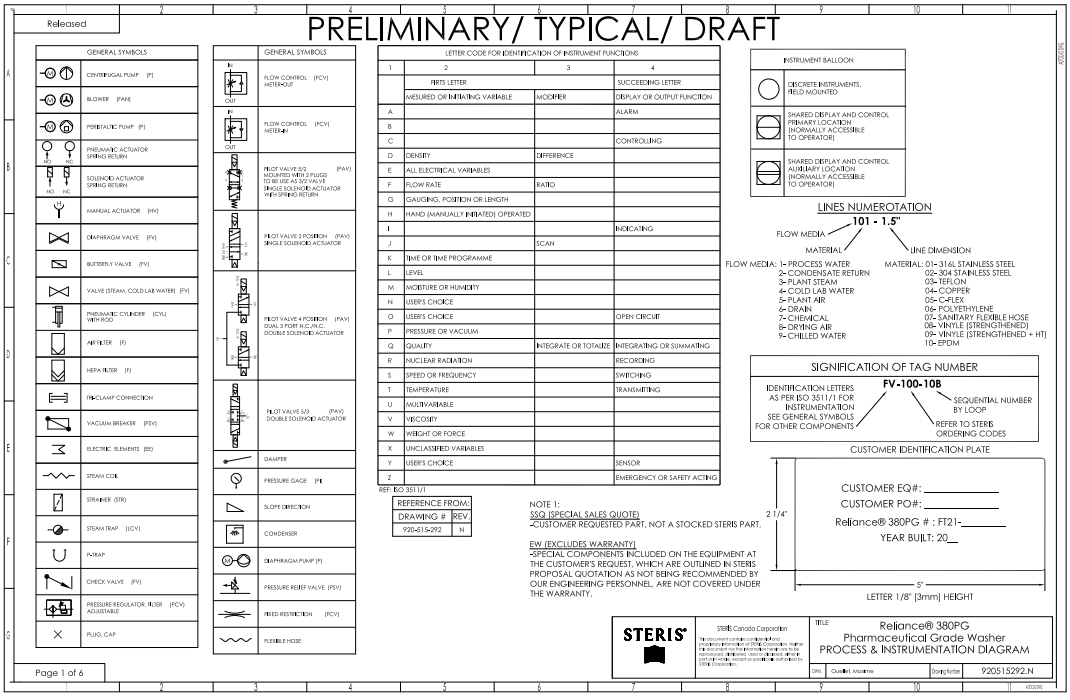
Documentation Verification

Next, operators must verify that all the documentation purchased by the end user has been supplied. Standard documentation normally comprises component booklets or cut sheets for nonproprietary parts such as valves, sensors, temperature transmitters, etc.; control system documents; manufacturing documents; and other documents such as user manuals, installation checklists, spare parts lists, and preventive maintenance schedules. Component booklets and control system documents should align with the ver-

Table B: Alarm and message testing

Communication Has Been Lost with Customer SCADA System	Acceptance Criteria	Pass/Fail	Initials/Date
While washer is idling (no cycle in process), disconnect the customer system cable and wait for the time set in the Communication Lost Alarm Delay field, in miscellaneous values.	Alarm is generated.	Pass/Fail	
—or—			
Enter service mode: In the miscellaneous value menu, set Communication Lost Alarm Delay to 30 seconds and exit service mode. Alarm shall be triggered in 30 seconds (maximum). Acknowledge alarm and once alarm has been tested, reenter service mode and set communication alarm delay to 0 seconds.	Once acknowledged, alarm is not monitored again until communication has been reestablished and lost again.	Pass/Fail	

Figure 3: Typical washer P&ID



ified P&ID drawing. The documentation title and revision number, once verified, are listed in the FAT documentation and a hard copy or electronic copy is filed. It is also usually possible to purchase extended documentation packages containing more detailed information.

Accessories and Racks

Because loading racks and accessories are essential for proper washer operation, it is critical to confirm that all the necessary accessories have been supplied. These include baskets, spindle headers, clips, and other items. Any drawings of the racks and accessories should be verified and documented with the revision number in the FAT documentation. A list of replacement parts should also be included. Any changes to the rack or accessory drawings should be documented as part of the FAT.

If end user racks are not available during the FAT for some reason, manufacturers may use test racks to perform wash cycles. Ideally, accessories should be ordered at the same time as the washers themselves; over the years, however, we have observed that washing equipment is often purchased prior to defining load configurations; this explains why dedicated end user racks are typically ordered at a later stage in the project. If the accessories arrive after the FAT is closed, then the SAT or qualification documents can be amended and applicable sections verified. If the accessories are elaborate, then a separate FAT can be scheduled to verify the design and performance of the accessories prior to shipment.

FACTORY SETUP VERIFICATION

Operational Readiness

Factory setup verification should be a review of software, electrical inputs, electrical outputs, instrumentation calibration/adjustment, and alarm/message testing.

Software: Demonstrate that the unit's software has been configured according to the options purchased. We recommend that the end user save a copy of the software version prior to starting the FAT execution and then again after completion of the FAT.

Electrical inputs: Verify input signals' electrical continuity by activating the input and confirming the response on the control display.

Electrical outputs: Verify output signals' electrical continuity by activating the appropriate output on the control touch pad and confirming the response of the output device.

Instrument calibration/adjustment: Verify that all instrumentation has been calibrated or set by the automated parts washer supplier or the instrument manufacturer. To demonstrate this properly, verify that each instrument procedure has been completed and the results documented as shown in Table A.

Alarm/message testing: Demonstrate the unit's proper response when alarm conditions occur. The condition that generates the alarm is simulated and verified on the operator interface panel. During the

Figure 4: Critical cleaning parameters

alarm and message tests, it is important to document the procedure to activate the alarm so it can be repeated during the SAT or OQ protocols, if necessary. It is also important to note any operator or equipment safety risks that may occur when a specific alarm or message is triggered. Alarms triggered through activation of code or software edits should be noted. Refer to Table B for a typical alarm test procedure.

Operational Tests

A cycle test performs a standard cycle to demonstrate the washer's proper operation sequence (prewash, wash, rinse). Each operational test should be repeated for each programmed cycle. If no specific cycles have been defined prior to the FAT testing, then run a standard test cycle, which includes typical concentrations, temperature, times, and final rinse water pH and/or conductivity to verify that each phase within the cycle is operational. Refer to Table C for a typical operational test procedure.

PERFORMANCE TESTING

Some type of performance testing at the factory is highly recommended, as it may significantly reduce the time required to complete PQ at the user site. These tests should ideally be performed using actual parts provided by the end user and the specific loading accessories that were ordered. When parts cannot be made available for the FAT, or if accessories are not available, representative components and accessories can be used. Two broad categories of performance tests can be completed during FAT: coverage and cleaning. These tests normally include a protocol and a report.

Table C: Operational tests checklist

Phase	Acceptance Criteria	Pass/Fail	Initials/Date
Initiate a light cycle			
Prewash 1 treatment			
Prewash 1 filling	Sump fills with PORT 1	Pass/Fail	
Prewash 1 recirculation	Recirculation time is 1:00 (MM:SS)	Pass/Fail	
Prewash 1 drain	Water is drained	Pass/Fail	
Wash 1 treatment			
Wash 1 filling	Sump fills with PORT 1	Pass/Fail	
Wash 1 heating	Water is heated to 150.0°F (65.5°C)	Pass/Fail	
Wash 1 preparing injection	"Preparing injection" is displayed for 10 s	Pass/Fail	
Wash 1 chemical injection	Chemical pump #1 is energized for 5 s	Pass/Fail	
Wash 1 recirculation	Recirculation time is 4:00 (MM:SS)	Pass/Fail	
Wash 1 drain phase	Water is drained	Pass/Fail	
Rinse 1 treatment			

Figure 5: Process parts covered with riboflavin

Figure 6: Process parts after rinse cycle

Figure 7: Parts covered with soil

Coverage tests use a riboflavin solution as soil. The solution is sprayed inside and outside the components that are to be cleaned; it can be dried or not. The components are then placed in the recommended accessory and processed in the washer using a rinse cycle. Once the cycle is completed, the components are inspected using an ultraviolet light. Any areas not properly covered by the spray system will be easily detected.

Cleaning tests can be performed using end user–provided parts and soil(s). The parts to be cleaned are coated with the provided soil(s), then placed in the recommended accessories and processed in the washer using a full wash cycle. The specific load pattern should be considered and indicated in the test conditions as well as the dirty hold time for the soil. The clean parts can then be inspected by the end user and, if needed, cycles and/or accessories can be modified to ensure satisfactory results. One of the main advantages

Performance testing at the factory may significantly reduce the time required to complete PQ at the user site.

Table D: Acceptance criteria used in laboratory testing

Criteria	Procedure
Visually clean	The cleanliness test is confirmed using large (typically 3 inch × 6 inch) stainless steel coupons. After the cleaning trial has been completed, the coupon is rinsed with tap water for 10 seconds and observed for cleanliness. A coupon is considered visually clean if no residue of the sample or detergent is visible on either side of the coupon.
Water-break free	A visually clean coupon is rinsed with deionized water and tested for water-breaks. The coupon surface is coated with deionized water for 10 seconds while at vertical orientation and the surface is examined as the film of water drains. If the surface is clean, the water will form a thin continuous film that uniformly coats the surface. This film will persist for as long as 30–60 seconds.
Pre- and post-cleaning weights	A visually clean and water-break-free coupon is air-dried at ambient temperature and then weighed on an analytical balance to determine its post-cleaning weight. The post-clean weight is compared with the weight of the dry clean coupon before coating. A large coupon is considered 100% clean by weight if its pre- and post-cleaning weights are within than 0.1 mg of each other. The coated coupon surface is approximately 100 cm^2 for wet samples and approximately 200 cm^2 for dry samples. The coated surface and sensitivity of the balance corresponds to < 0.5 $\mu g/cm^2$ or 1 $\mu g/cm^2$, assuming a uniform distribution.

Figure 8: Parts inspection after a wash cycle

of performing this test during the FAT is that the washer and/or accessories can be modified much more easily at the factory than they can at the final location.

Because sending soils is not always possible or practical, a third alternative may be considered: Many cleaning agent suppliers can perform cleaning tests to support cleaning agent selection and cleaning parameter development. Coupons, or parts coated with the soil(s) to be cleaned, can be sent to these suppliers for analysis. This process should ideally be performed in parallel with the development of the URS, FS, and DS of the automated parts washer design. Such an analysis, when combined with a coverage test performed during the FAT, provides a strong rationale that supports the selection of the cleaning agents, process parameters, and accessories, greatly reducing the risks of "bad surprises" during the PQ stage.

CASE STUDY: COVERAGE AND CLEANING TESTS

In this case study, the end user is a global registered FDA cosmetics company with manufacturing facilities in several countries. The company purchased an automated parts washer to process filling line components, move away from manual washing, increase throughput, reduce manual handling of chemicals due to safety issues, and improve general consistency in washing. A laboratory evaluation was carried out for a range of viscous skincare products.

The goal of the laboratory evaluation was to determine optimal cleaning parameters to remove the following products from stainless steel and polyester tanks and equipment by agitated immersion, clean-in-place (CIP) spray wash, and an automated parts washer cleaning application. The test soils included:

- Extra emollient night cream
- Lip mask
- Intense moisturizing cream
- Baby sunblock with an FDA-registered drug active
- Bulk concealer with an FDA-registered drug active
- Moist SPF 30-day cream with an FDA-registered drug active

Critical parameters analyzed during the laboratory evaluation included cleaning action, change in temperatures, variations in cleaning chemistry, changes in cleaning agent concentration, multiple cleaning steps, variation in rinse and wash times, and water quality (Figure 4) [7–9]. A coupon was considered clean if it

Figure 9: Cream residue on process part after wash cycle

was visually clean and water-break free, and if its precoating and post-cleaning weights were equal (0.0 mg residue), as shown in Table D [8]. Once cleaning parameters were developed for the stainless steel coupons, testing was performed on the coated parts provided by the end user in the washer itself.

End user parts were sprayed with a riboflavin solution at 0.2 grams per liter water and dried for 4 hours. Parts were then placed onto the customized rack and loaded into the washer. After a short cycle the rinsed parts were unloaded and inspected with a UV light for possible traces of riboflavin (see Figures 5 and 6).

PERFORMANCE TESTING

The end user provided the following products to be used as soils for the load items. These were determined to be the most difficult to clean based on a grouping strategy:

- Lip mask
- Baby sunblock
- Bulk concealer

The washer supplier recommended the following parameters based on the laboratory evaluation:

- Prewash of 2–5 minutes at 60°C–80°C
- Wash with 5% v/v alkaline detergent (80°C, 15 minutes)

Parts were then covered with the end user–provided soils (creams), loaded onto the customized rack, and processed in the washer using the recommended cycle. Once the cycle was completed, parts were inspected (Figures 7 and 8).

As can be seen in Figure 10, some areas were not cleaned properly. The root cause was found to be poorly positioned T-joints with openings that hadn't faced the washer side spay arms. This created areas where spray coverage was insufficient. The issue could easily be fixed by reorienting the components so that the problem areas could directly face the side spray arms. The loading procedure was updated to prevent the situation from reoccurring.

CONCLUSION

The FAT is a critical project milestone in the design phase of the life cycle model for an automated parts washer. The design of an automated parts washer is based on the URS, FS, and DS. The FAT also provides a unique opportunity for the end user to work closely with both the detergent and equipment suppliers to evaluate the washer and ensure it meets the intended design requirements. Detergent selection and cleaning parameters can be determined in parallel to the washer design and construction. The FAT allows end user personnel, under the guidance of equipment experts, to verify that the automated parts washer functions as intended. If issues occur or design changes are needed, they can be addressed during the FAT or added to a punch list for the equipment supplier, cleaning detergent supplier, or end user to be addressed prior to shipment or installation. A well-prepared and -executed FAT on an automated parts washer can reduce resources and time required for the development of SOPs and qualification testing.

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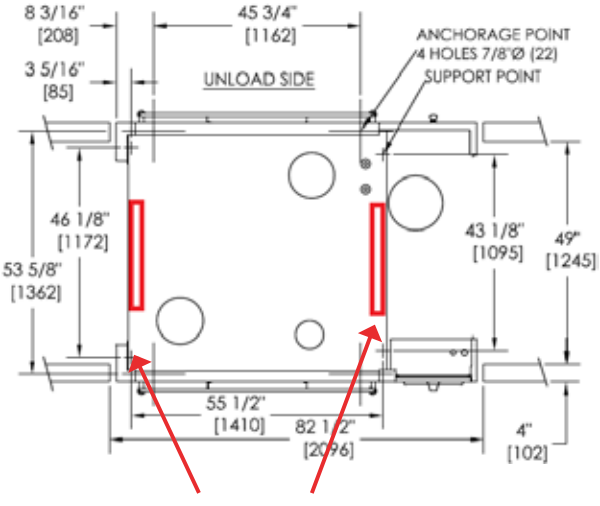
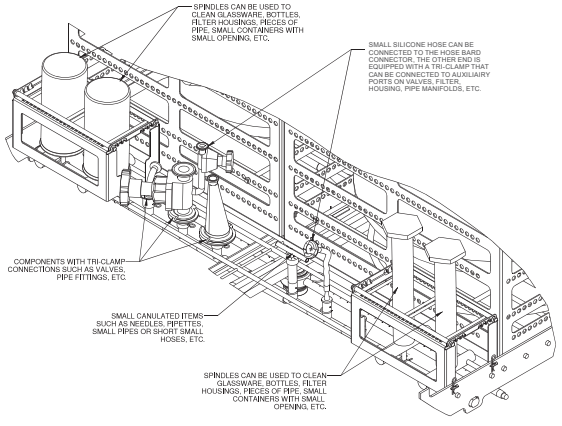
Figure 10: Misplaced process parts on wash rack



Spray arm locations



Opening of components should face the spray arms when possible

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PURIFICATION OF SYNTHETIC PEPTIDES

by Countercurrent Chromatography (MCSGP)—Economic Evaluation

Thomas Müller-Späth, PhD, Michael Bavand, PhD


Thomas Müller-Späth


Michael Bavand

High-pressure liquid chromatography employing the multicolumn countercurrent solvent gradient purification (MCSGP) process principle has been developed as a novel purification technology for peptides produced by chemical synthesis. MCSGP offers a step change in efficiency compared to batch high-performance liquid chromatography (HPLC) processing. With MCSGP, two identical reverse-phase (RP) columns are operated in countercurrent mode, with internal recycling of impurity-containing side fractions extracting continuously pure product and discarding impurities without significant product loss. Peptides can be purified at preparative/production scale with significantly higher yield without compromising target purity. The process also allows an up to 10-fold higher productivity with typically 80% lower solvent consumption, providing an overall attractive economical production scenario and allowing pushing of the boundary of economic synthesis of long peptides. Process scenarios are modeled based on experimental data showing that for 10 kg of peptide produced per year, the upstream and downstream savings can amount to millions of US dollars.

Most therapeutic peptides are synthesized through chemical solid-phase peptide synthesis (SPPS), generating synthesis-related product impurities that need to be removed by chromatographic purification steps. Reverse-phase high-performance liquid chromatography (RP-HPLC) is the method of choice to remove the impurities, often employing automated batch rechromatography steps (i.e., separate purification runs to recover the product from impure side fractions) to increase yield while maintaining target purity. Advances in chromatography separation have mostly relied on developing better chromatography stationary phases and finding the optimal combination of stationary phases, mobile phase (solvent) and load of feed material in order to improve resolution between product and impurities. However, single-column batch chromatography faces problems even with advanced stationary phases when it comes to separating product and impurities having very similar adsorptive properties. The general trade-off between yield and purity is an intrinsic feature of single-column batch chromatography with the consequence of losing yield at target purity. The yield-purity trade-off is accentuated when too much feed is loaded; thus, an optimal load is also needed to obtain sufficient resolution. Rechromatography as a means to improve yield leads to an accumulation of feed impurities and does not alleviate the yield-purity trade-off of obtaining a better product yield without compromising target purity. Although rechromatography can be automated [1–4], the overall purification time, including rechromatography, is prolonged by repetitive analysis of the side fractions confirming target purity prior to proceeding to the next rechromatography sequence. The feed of each rechromatography run, being composed of various side fractions, has a different composition than the original load material, caused by the accumulation of different impurities from each rechromatography sequence.

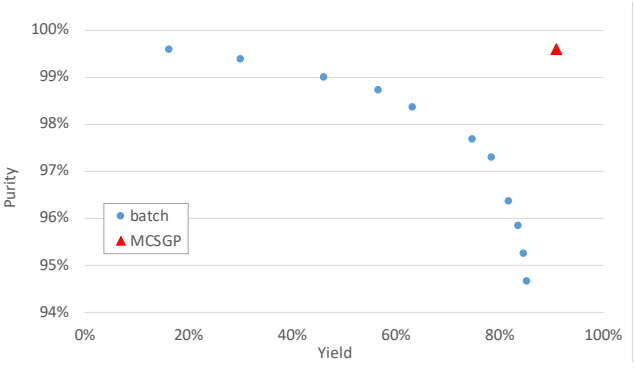
Improving the product separation from impurities by prolonging elution time, reducing feed load, and/or increasing column length will decrease productivity. With the intrinsic batch process constraints, good baseline separation of product and impurities

remains a significant challenge for the preparative-scale single-column batch process. A way to overcome the yield-purity trade-off and to desensitize loading constraints is to use a continuous process that operates outside the yield-purity constraint and combines the separation power of advanced stationary phases with enhanced process capacities, accentuating the separation power of the stationary phase. Figure 1 shows the yield-purity trade-off relationship of conventional batch chromatography.

The MCSGP process is a unique ternary continuous separation process that can unlock the yield-purity trade-off by providing high yield at target purity, at up to 10-fold higher productivity. MCSGP, being a continuous process, also minimizes scale-up constraints and is suitable for large-volume processing applications. The process eliminates the need for rechromatography and the associated time and resources for sampling and testing. MCSGP has been used successfully in many applications, including purification of therapeutic proteins and peptides, protein isoforms, conjugated proteins, small molecules, macrocycles, and fatty acids.

This paper focuses on the applications and process economics of MCSGP in peptide purification. It summarizes the MCSGP process principle and design, outlines process advantages and productivity gains, shows case studies, describes the power of MCSGP for scale-up, and concludes on process economics.

Figure 1: Yield-Purity Trade-off of Batch Chromatography. Circles represent conventional batch chromatography. The triangle shows yield-purity efficiency typically achieved with MCSGP chromatography.



MCSGP Process Principle and Design

The MCSGP process is a cyclic process applying internal recycling of impure side fractions to improve the yield [5–9], enabling high yield at target purity.

MCSGP design starts with a single-column batch process, which does not need to be optimized and is designed as an isocratic or gradient run. Obtaining a reasonable separation between product and impurity peaks in the batch run used as basis for MCSGP design is sufficient. Impurities that co-elute exactly under the product peak cannot be satisfactorily separated by MCSGP either. Therefore, it is important to ensure that some separation between product and impurities occurs in the batch run. The batch process is automatically transformed into an MCSGP process using an MCSGP process design tool embedded in the operating software of the continuous chromatography system, as explained further next.

The MCSGP process operates with two or more identical columns with the same stationary phase. MCSGP processes have been operated with up to eight column configurations [7,9]. MCSGP technology evolution reduced the required column configuration number to two, greatly reducing hardware and process complexity [5] without loss in performance.

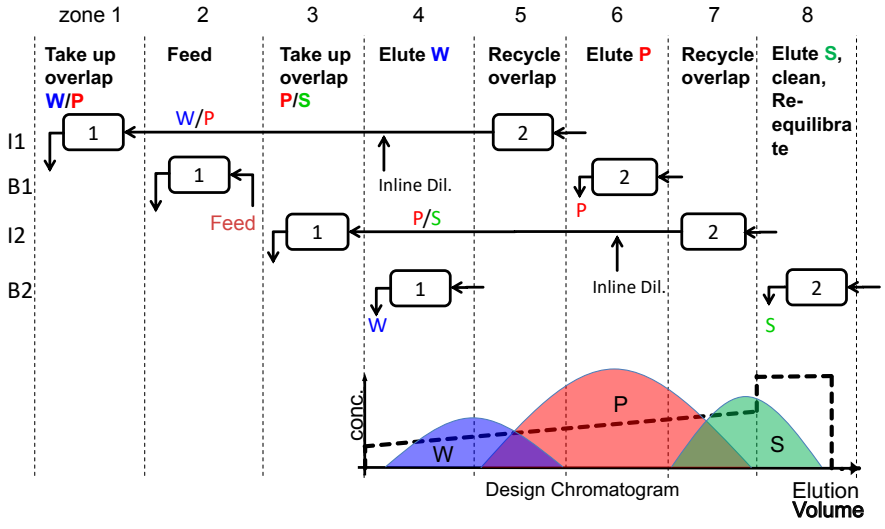
The process uses a minimum of two columns to operate several subprocesses continuously: feed containing the complex mixture with product and impurities is loaded on a first column and separation occurs as in single-column batch chromatography. While pure product is eluted for collection and impurities are discarded, both in a cyclically continuous manner, product-containing side fractions are kept in the process and are loaded on the columns followed by fresh feed until the most pure product is extracted. The columns are also cleaned and reconditioned as part of the process, thereby avoiding any accumulation of impurities or fouling of the stationary phase. Product elution is done by isocratic mode or linear gradient.

The process sequence of two-column MCSGP is shown in Figure 2. The MCSGP process is designed by starting with single-column batch chromatography (design chromatogram) using a linear gradient or isocratic conditions to identify and visualize the positions of the product at target purity, impurities, and overlapping sections of product and impurity. The MCSGP process design software executes the process flowsheet by dividing subprocesses into zones according to the presence of product and impurities. Each section of the design chromatogram corresponds to a specific task (zone) of the MCSGP process. I1, B1, I2, and B2 are subprocesses showing the tasks of the two columns (depicted as numbered barrels) in the different zones. Lines between columns show when columns are connected and arrows indicate the direction of flow. After having completed all sequential tasks (I1, B1, I2, and B2 shown in Figure 2), the columns switch positions and the formerly upstream column now becomes the downstream column of a new sequence (I1, B1, I2 and B2). Once the new sequence has been completed with the columns in the opposite order, one cycle is complete, and the first sequence is initiated again (note that Figure 2 only shows the first part of a single MCSGP cycle).

The required product purity can be adjusted by defining the width of the product elution window where predominantly pure product is found and collected. The average residence time of product in the system depends on the ratio of product being eluted and internally recycled. Typically, the average residence time of the product in the MCSGP process is three times larger than the residence time in batch chromatography.

The design of any MCSGP process requires one to initially run a

Figure 2: The Process Sequence of Two-Column MCSGP. Showing positions of product at target purity, impurities, and overlapping sections of product and impurity. P (red) = pure product; W (blue) = weakly adsorbing impurities; S (green) = strongly adsorbing impurities; W/P = weakly adsorbing impurities overlapping with product; P/S = product is overlapping with strongly adsorbing impurities. Subprocesses are divided into zones (vertical dotted lines) according to presence of product and impurities. The different MCSGP subprocesses are as follows. Row I1: W/P is desorbed from column 2 (zone 5), inline diluted, and taken up in zone 1 by column 1. Row B1: Column 2 desorbs pure product P (zone 6). Simultaneously feed is taken up by column 1 preloaded with W/P (zone 2). Row I2: P/S is desorbed from column 2 (zone 7), inline diluted and taken up in zone 3 by column 1 preloaded with W/P + feed. Row B2: Column 1 (zone 4) loaded in steps before is now eluted. Simultaneously, column 2 (zone 8) is cleaned and reconditioned.



single-column conventional batch chromatography under linear gradient or isocratic conditions to visualize and identify offline the positions of product at target purity and of impurities [5]. This initial chromatogram is called the design chromatogram. Using the MCSGP process design software, the design chromatogram is divided into sections according to the presence of product and impurities (Figure 2). The segmentation typically yields one section where only weakly adsorbing impurities (W) are present, followed by a section of weakly adsorbing impurities overlapping with the product (W/P), then followed by a section of pure product (P), and then by a section where the product is overlapping with strongly adsorbing impurities (P/S), and finally a section of only strongly adsorbing impurities (S). All MCSGP process parameters including inline dilution, feed flow rates, and volumes are calculated based on the design chromatogram by the MCSGP design software. The required feed volume is calculated based on replacement of the amount of peptide in the pure product section, which ensures that the overall peptide mass adsorbing onto the columns in each cycle remains constant and the process rapidly reaches a cyclic steady state.

MCSGP Advantages and Productivity Gains

The MCSGP process has significant advantages compared to single-column batch chromatography, including the following.

- Higher yield: Depending on feed purity, product purity specification, and the extent of overlap of product and impurities, a 40%–90% higher yield can be obtained without compromising target purity.
- Higher productivity: Yield improvement and product overloading without process performance decline leads to higher productivity. The process principle allows running steep gradients and applying higher flow rates. Productivity increase can be up to 10-fold higher than with conventional batch processes (Figure 3).
- Lower solvent consumption: The increased yield leads to reduced solvent consumption (the solvent consumption is expressed as liters of solvent consumed per gram of peptide produced). Solvent consumption is typically reduced by 70%, and solvent savings are even more accentuated under conditions of feed material overloading.

MCSGP Peptide Purification Case Studies

In an early case study, MCSGP was used successfully for the purification of calcitonin produced by chemical synthesis using a six-column MCSGP process [7,9]. Because of its reduced equipment complexity and its increased operational flexibility, the two-column MCSGP process design has completely replaced six-column MCSGP.

In another case study, MCSGP was used for the purification of a therapeutic peptide from a starting material with a product purity of 66.1% [10], achieving a target purity of 98.7%. MCSGP displayed a yield improvement from 19% (batch) to 94% (MCSGP); a 10-fold

Figure 3: Yield-Purity-Productivity Relationship of MCSGP vs. Conventional Batch Chromatography. Single-column batch processes (blue) operate on a low productivity level without the potential for productivity gains when high yield and purity are required. MCSGP (red) operates at a much higher productivity level, maintaining high yield and purity.

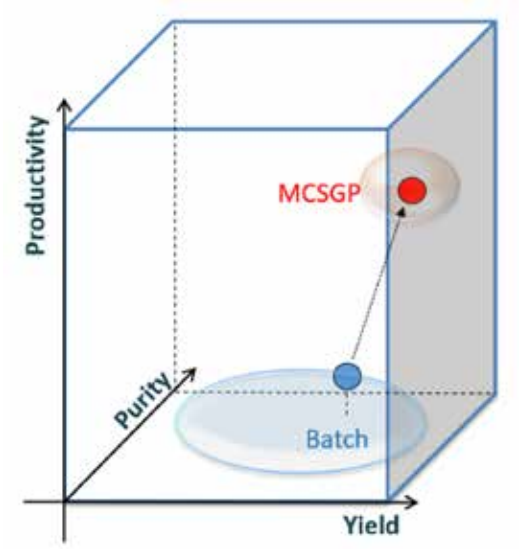
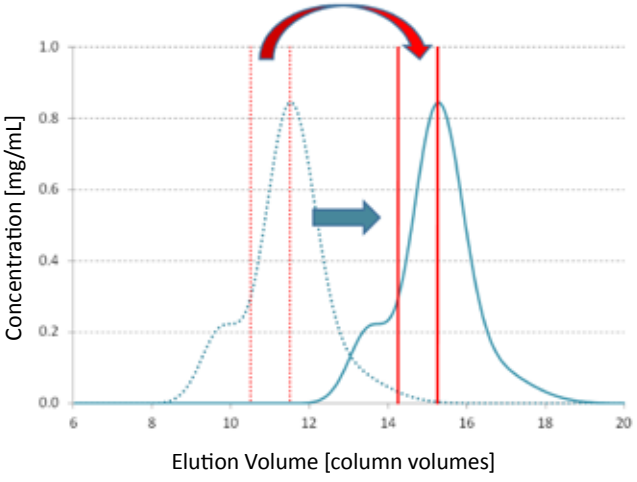


Figure 4: Effect of Dynamic Process Control MControl in MCSGP. A temperature drop causes the original chromatogram (dashed blue curve) to gradually shift (solid blue curve) to a later retention time also shifting the elution window (red vertical lines). MControl autocorrects for the new collection window, based on UV threshold value collection. Simultaneously, the elution gradient is prolonged with the same slope (not shown).



increase in productivity, from 3 g/L/h (batch) to 30 g/L/h (MCSGP); and a decrease of the solvent consumption by 70%, from 3.5 L/g (batch) to 1.0 L/g (MCSGP). These improvements had a significant impact on the operating cost and capital expenditure, as will be described in the forthcoming paragraphs.

Recently, MCSGP has been used for the purification of liraglutide, an acylated glucagon-like peptide-1 (GLP-1) agonist having a fatty acid moiety attached to the peptide chain. The study is not publicly available, yet positive results have been reported in the published study abstract [11]. The abstract states that, "The implemented twin-column MCSGP process has shown to be able to achieve very high yield (99.6 %), high purity (97.3 %), and very good performance in terms of productivity (0.24 g/L solvent or 5.8 kg/hr·m³ column)." This case study concluded that "the higher the required purity, the more favorable the MCSGP process is with respect to a conventional batch process." MCSGP has also been used successfully for insulin purification, obtaining a 3-fold higher productivity and 60% reduction in solvent consumption compared to a standard industrial batch insulin purification process (unpublished data).

CONSIDERATIONS FOR SCALE-UP

Equipment

MCSGP for peptide purification is best operated with HPLC systems having a flowsheet configuration that supports an MCSGP process. Entry-stage systems (Contichrom HPLC by ChromaCon) and scale-up systems (Ecoprime Twin HPLC by YMC) use the optimized twin-column system configuration. For scale-up, the quality of pump performance (being able to perform smooth gradients) is very important.

Dynamic Process Control for MCSGP

A dynamic process control tool, MControl, has been developed for the MCSGP process. MControl is very important for robust MCSGP operation on both benchtop and GMP scale. MControl is capable of adjusting the MCSGP process in response to changes in temperature, solvent composition, and, to some extent, column performance—assuming that changes in these parameters lead to a shift in the chromatogram, yet do not have a significant impact on the resolution of product and impurities.

MControl is capable of adjusting the position of the product elution window (i.e., the start of phases B1, see Figure 2) based on UV thresholds that are reached during the interconnected and batch phases of the MCSGP process. Any peak shift is recognized and the product is collected by UV threshold, ensuring a robust autocorrection, rather than based on a fixed volume or time. For peptide purification, MCSGP is operated with RP chromatography. RP chromatography is very sensitive to temperature change, leading to a shift in the chromatographic elution profile with the risk of collecting incorrect elution fractions. As an example, lowering the temperature of solvents by just a few degrees will lead to a later product elution. MControl will autocorrect this deviation by recognizing the peak shift and thereby simultaneously shifting the product elution window, helping collect the right product

Table A: Assumptions for Economic Modeling Batch vs. MCSGP Process

		Batch	MCSGP
Column bed height	[cm]	25	10
Replacement of stationary phase	[%/year]	30	30
Stat. phase cost	[US$kg]	7,000	7,000
Synthesis batch size	[kg]	1	1
Synthesis costs / g	[US$/g]	200	200
Synthesis costs / batch	[$ USD]	200,000	200,000
Solvent costs	[$ USD/L]	6	6
Chrom. system costs	[$ USD]	500,000	1,500,000
Depreciation period	[a]	10	10
Number of samples to be analyzed per cycle	[-]	10	1
QA/QC costs per sample	[$ USD]	200	200
Plant operating costs	[$ USD/day]	8,000	5,000
Max. time permitted for chromatography	[hrs]	16	16

fractions. MControl can be also operated with specified delay periods by ignoring an initial elution profile prior to operating with a threshold collection. Figure 4 provides an overview of the principle of MControl use to operate the MCSGP processes in a robust manner with minimal supervision.

MControl is the simplest and fastest type of feedback control presented for MCSGP, as it provides a direct feedback affecting an ongoing peak elution. Other feedback control methods include control based on elution peak retention times [12], feedback control based on at-line HPLC analysis [13], and model predictive control (MPC) [12,14].

Process Modeling

Although chromatographic process modeling is not required to design an MCSGP process, it can be used to speed up process development. A chromatographic process model consists of equations describing mass balances, isotherm, and mass transfer that are solved numerically. The model parameters can be determined by fitting tools that automatically calibrate the model parameters based on a number of linear gradient experiments.

The chromatographic model can then be utilized to simulate single and multicolumn runs, without actually having to carry out the runs experimentally, and predicts their performance in terms of yield, purity, productivity, solvent consumption, and product concentration. Moreover, the model can be used to optimize the MCSGP process within user-specified design space borders.

Process Validation

Process validation concepts have been developed for twin-column countercurrent processes. Similarly, as in single-column chromatography, a risk-based approach is used, testing process parameters and multiple sets of operating conditions, corresponding to different steady states to characterize the process and identify critical process parameters. Simulation and optimization software based on a chromatographic model helps reduce the number of design of experiments (DoE) needed to define the operating space, as indicated in the previous section. A summary of these process validation approaches for a twin-column capture process has been presented and could be adapted to twin-column MCSGP to a large extent [15]. Simulated moving bed (SMB) chromatography processes using four to eight columns and countercurrent principles are in use for production of chiral molecules and comply with FDA requirements. Thus, the validation for MCSGP using only two columns is considered a feasible task.

MCSGP ECONOMIC ANALYSIS

Based on our own case studies, published data, and user feedback, an economic analysis for twin-column MCSGP chromatography of therapeutic peptides has been carried out, including a comparison with existing single-column chromatography. The assumptions are listed next.

Modeling Assumptions

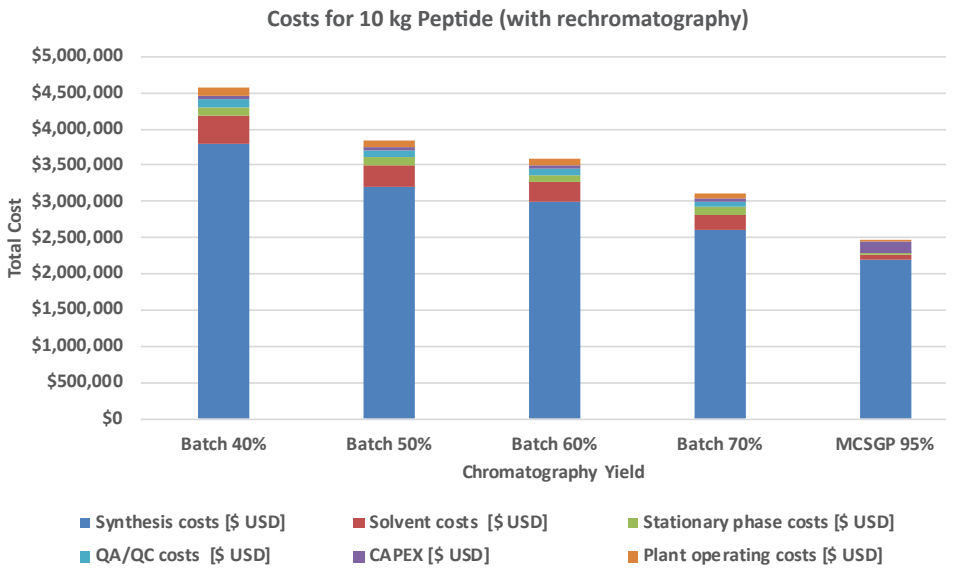
Single-column batch reference processes with an assumed achievable yield of 40%, 50%, 60%, and 70% were modeled and compared to a two-column MCSGP process with an assumed achievable yield of 95%. The different achievable yield in batch chromatography reflects the degree of difficulty in the separation.

We assumed that the longer the peptide, the more impurities accumulate and the lower achievable yield is obtained under constant load due to narrower peak pooling (Table B). MCSGP has been shown to achieve substantially higher yields than batch processes under given purity constraints. We did not model iterative synthesis optimization steps to deplete individual impurities resulting in

Table B: Assumptions for Economic Modeling of Different Achievable Batch Process Yields Depending on Peptide Lengths/Impurity Content vs. Achievable MCSGP Process Yield at the Same Purity

Parameter	Unit	Batch 1	Batch 2	Batch 3	Batch 4	MCSGP
Yield	[%]	40	50	60	70	95
Flow Rate	[cm/h]	181	181	181	181	271
Load	[g/L]	10	10	10	10	10
Cycle Time	[min]	233	233	233	233	80

Figure 5: Total Costs for Production of 10 Kg Peptide per Year Shown as a Function of the Yield in Batch and MCSGP Chromatography.



improved yield. It was assumed that rechromatography was used to recover 25% of the yield loss in batch chromatography. Because of its internal recycling principle, the achievable yield of MCSGP was assumed to be 95% and independent of peptide impurity content or size.

Additional assumptions of the batch reference run and the MCSGP run are reported in Table A. Additional assumptions of the chromatographic process are summarized in Table B. The processes are operated at different linear flow rates of 181 cm/h (batch process) and 271 cm/h (MCSGP process), respectively. A larger flow rate in MCSGP is assumed because the process, due to its internal recycling capabilities, can achieve high product yield at high flow rates without compromising yield and purity. For batch processes, lower flow rates have to be used to obtain better mass transfer and a reasonable product yield. The loads and cycle times are also summarized in Table B.

RESULTS

Total Costs Comparison

Using the abovementioned assumptions, the total costs for the production of 10 kg peptide annually was calculated. The results are shown in Figure 5, where total peptide production costs are shown as a function of the yield in batch and MCSGP chromatography. The overall costs, including synthesis and purification, are dominated by the synthesis costs, which represent 80% to 90% of the total costs.

As for batch processes, the chromatography yield increases (40%–70%) and the synthesis costs decrease because fewer synthesis batches have to be produced to obtain the targeted production output of 10 kg per year. Because the MCSGP process provides consistently higher yields (95%) independent of peptide length and impurity content, no additional synthesis batches are necessary to obtain the target production amounts.

Table C: Additional Assumptions for Chromatography

Parameter	Unit	Batch 1	Batch 2	Batch 3	Batch 4	MCSGP
Yield	[%]	40	50	60	70	95
Flow Rate	[cm]	60	60	60	60	30
Load	[L]	70.7	70.7	70.7	70.7	2x7.1
Cycle Time	[L/min]	8.5	8.5	8.5	8.5	3.2

Figure 6: Chromatography Costs for Production of 10 Kg Peptide per Year for Batch Chromatography. Costs are shown for varying product yield and for MCSGP. The capital expenditure (CAPEX) is per year for a 10-year depreciation.

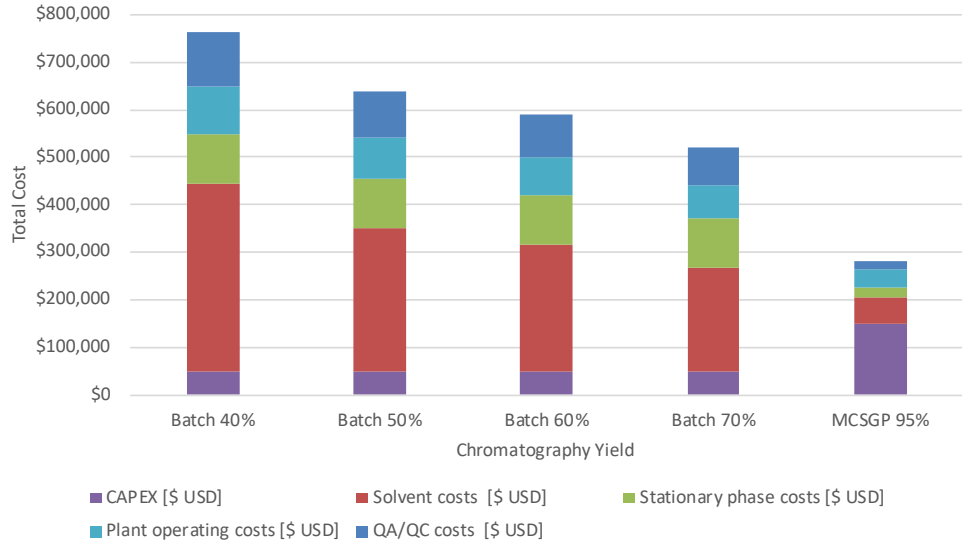


Figure 7: Payback Period for Investment in MCSGP Compared to Batch Processes with Different Yields. Example readout: For a batch yield of 40%, the payback period for a system with MCSGP function will be 6 months based on total cost savings. For a batch yield of 70%, the payback period will be 19 months assuming a production quantity of 10 kg peptide at target purity. When doubling the production amount to 20 kg, the payback period will be halved.

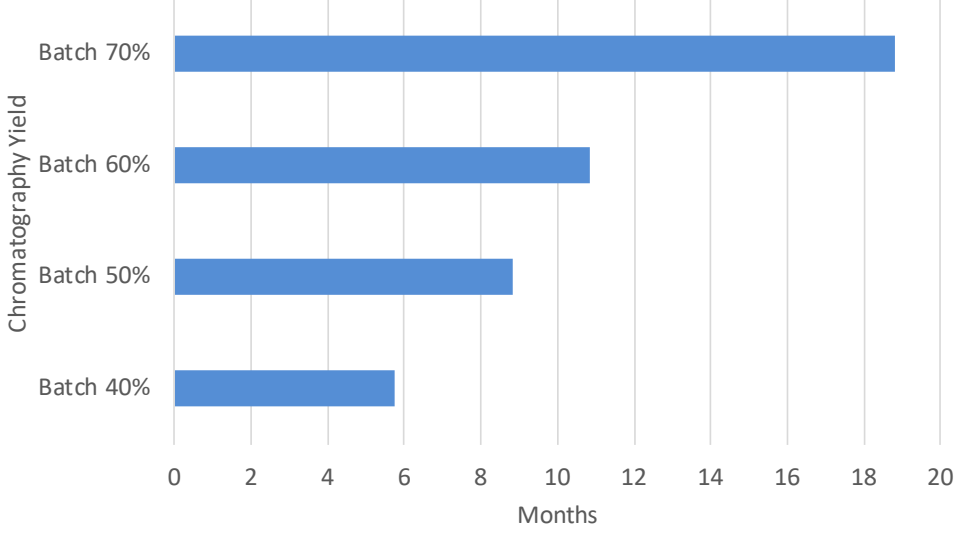


Figure 8: Relative Solvent Consumption of MCSGP Compared to Batch Processes with Different Yields. MCSGP saves up to 85% of solvents.

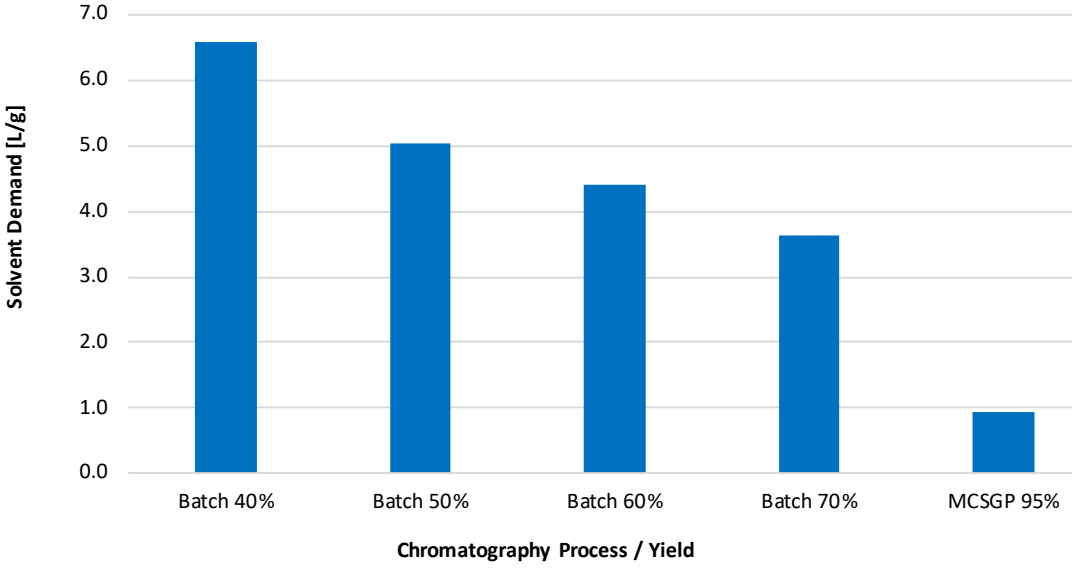
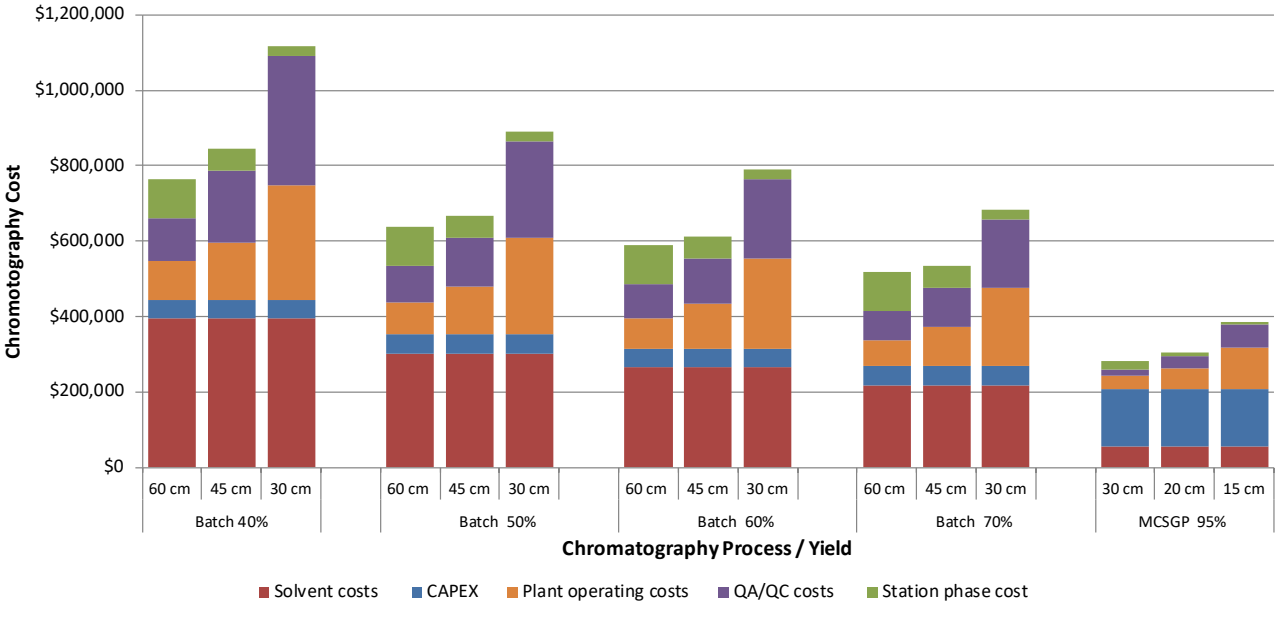


Figure 9: Downstream Processing Costs Assuming Different Column Sizes. The downstream operating times are shown on top of the data bars.



Although for a chromatography yield of 40% the overall costs are $4.5 million USD, costs decrease with increasing yield, reaching $3.1 million USD for 70% yield. The overall costs for MCSGP are $2.5 million USD, indicating a savings potential of $2.1 million USD with respect to the batch process with 40% yield and $0.6 million USD annually with respect to the batch process with 70% yield.

Downstream Cost Comparison

The downstream processing costs for batch chromatography, excluding the synthesis costs, are dominated by solvent costs and plant operating costs, followed by stationary phase costs and quality assurance/quality control (QA/QC) costs (Figure 6). Equipment costs (capital expenditure [CAPEX]/year with 10-year

depreciation) are the smallest cost contributor. The overall downstream processing costs decrease with increasing yield, due to the lower number of additional batches that need to be synthesized to reach the annual production target of 10 kg peptide. As the yield increases from 40% to 70%, the annual downstream processing costs decrease from $760,000 to $520,000 USD for batch purification.

The downstream processing costs for the MCSGP scenario are $280,000 USD, representing at least 40% cost savings compared to the batch chromatography scenarios. The costs of MCSGP-based downstream processing are dominated by the CAPEX, which accounts for 50%. Smaller contributions are from plant operating costs, QA/QC, and solvent costs. For the MCSGP case, stationary phase costs are negligible, contributing around 3% to the downstream processing costs because significantly smaller columns are used (70.7 L (batch) vs. 2x 7.1 L [MCSGP]). Columns are typically repacked annually with 30% stationary phase replacement. Thus, the cost of goods sold (COGS) elements for the batch are different than for MCSGP and the absolute COGS for MCSGP are significantly lower.

Payback Period

MCSGP total cost savings compared to batch chromatography scenarios are between $0.6 million to $2.1 million USD for 10 kg target production (Figure 5). The CAPEX cost difference of MCSGP HPLC systems vs. batch HPLC systems is estimated to be $1 million USD (Table A). Based on the preceding parameters, a payback period can be calculated as follows: Payback = (CAPEX difference batch vs. MCSGP)/(total cost savings by MCSGP). In comparison with batch processes with 40% or 70% yield, the payback period of MCSGP lies between 6 months and 19 months, respectively, as shown in Figure 6. The cost savings through MCSGP are dependent on the annual production amount and the batch yield. Higher target production quantities result in a corresponding shorter payback period, as equipment utilization is increased. See Figure 7 for payback period for investment in MCSGP compared to batch processes with different yields.

Operational Aspects of MCSGP

Besides the capital expense and payback consideration shown previously, MCSGP has benefits with respect to operational aspects, including the following.

- Reduced equipment requirements for pumps, pressure rating
- Reduced column dimensions
- Reduced stationary phase costs
- Reduced solvent consumption
- Overloading with MCSGP possible without performance loss for overlapping product/impurity peaks
- Reduction in QC sampling and testing

In the simulated cases, batch chromatography requires a 60 cm inner diameter column and 25 cm bed height, leading to a total column volume of 70.7 L, whereas MCSGP operates with two columns of 30 cm inner diameter and 10 cm bed height, resulting in a total bed volume of 14.2 L, leading to lower stationary phase costs. The use of smaller columns and resin volumes in MCSGP is possible due to the increased yield of the chromatographic process and to the larger linear flow rates of MCSGP, which strongly reduce the cycle time compared to batch chromatography. A summary of the operational results is provided in Table C. Another factor contributing to cycle time reduction is that during the disconnected states of the process, the columns are operated at half the residence time. Lower column hardware costs and facilitated packing of the smaller columns were not included in the calculations but would be also in favor of MCSGP.

Smaller columns also reduce the required pump dimensions despite the larger linear flow rates that are used. Although an 8.5 L/min (= 510 L/h) pump is required on a batch skid, the MCSGP skid would only require 3.2 L/min (=190 L/h) pumps, resulting in smaller piping and components and a smaller equipment footprint despite using two columns. The higher load and yield of MCSGP leads to reduced solvent consumption in chromatography, measured in liters of solvent used per gram of peptide purified.

The solvent consumption decreases strongly with increasing yield: For MCSGP it is 0.9 L/g, whereas the consumption for a batch process with 40% yield is 6.6 L/g and the consumption for a batch process with 70% yield is 3.6 L/g (see Figure 8). Thus, MCSGP is capable of reducing solvent consumption by up to 85%, corresponding to up to a 56,000 L savings per year for 10 kg peptide produced. Although direct solvent cost savings have been quantified in the preceding cost calculation, indirect costs such as additional supporting infrastructure, solvent preparation, handling, and disposal have not be included. Because of the reduced solvent consumption of MCSGP, the latter factors would have numbers in favor of MCSGP.

MCSGP has a larger number of feed injections per run than batch chromatography but a lower number of QC samples than batch because for each cycle only a single pool is being sampled and analyzed. With batch chromatography, repetitive QC sampling and analysis is required because rechromatography results in more QC sampling. In this study, we assume that 10 analyses are required per single-column batch cycle and one analysis per MCSGP cycle. The smaller number of fractions in MCSGP leads to an overall reduction of QA/QC costs.

A sensitivity analysis was carried out to examine the impact of reduced column size on the downstream costs in dependence of the process/yield. For batch chromatography, the investigated column diameters were 60 cm, 45 cm, and 30 cm, whereas for MCSGP they were 30 cm, 20 cm, and 15 cm. The results are provided in Figure 9 and results show that for all cases (batch 40%–70% yield vs. MCSGP) stationary phase costs decrease as expected, but plant operating costs and QA/QC cost rise and surpass the cost savings obtained using smaller columns. Smaller columns require larger operating times, as indicated in the figure, because more cycles (injections) need to be performed.

CONCLUSION

The economic evaluation of twin-column countercurrent chromatography (MCSGP) for the purification of peptides produced by chemical synthesis shows significant cost advantages of MCSGP, with a payback period for MCSGP compared to different batch scenarios of between 6 and 19 months for an annual production of 10 kg of peptide. Different cases of MCSGP with 95% yield and single-column batch processes with 40%–70% yield were compared, simulating purifications of varying difficulty due to variable impurity content or peptide size. Rechromatography was included in the calculations for single-column chromatography. MCSGP does not require rechromatography due to its high yield and has a total cost advantage (mainly by reducing the number of upstream synthesis batches required to reach target production quantity). Other advantages include significant reduction in solvent consumption.

The cost savings through MCSGP vary between $0.6 million and $2.1 million USD, depending on the yield of the single-column reference process. Thereby, the annual downstream processing costs range from $760,000 to $520,000 USD for single-column batch chromatography purification, depending on the yield, and only $208,000 USD for MCSGP, showing a cost savings of at least 40%. The analysis revealed that the use of larger columns was favorable due to the reduction in plant operating time and number of injections, leading to smaller QA/QC effort, which offset the larger stationary phase costs of larger columns. Indirect solvent costs such as additional supporting infrastructure, solvent preparation, handling, and disposal have not been included in the comparison but the numbers would be in favor of MCSGP due to its reduced solvent consumption.

Regulatory authorities are supportive of continuous manufacturing for pharmaceuticals, which also covers continuous chromatography techniques such as MCSGP. Available simulation and optimization tools allow a reduction in the number of designed experiments for defining the operating space and facilitate process validation.

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