Drug Development & Delivery

March 2017 Vol 17 No 2

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The science & business of drug development in specialty pharma, biotechnology, and drug delivery

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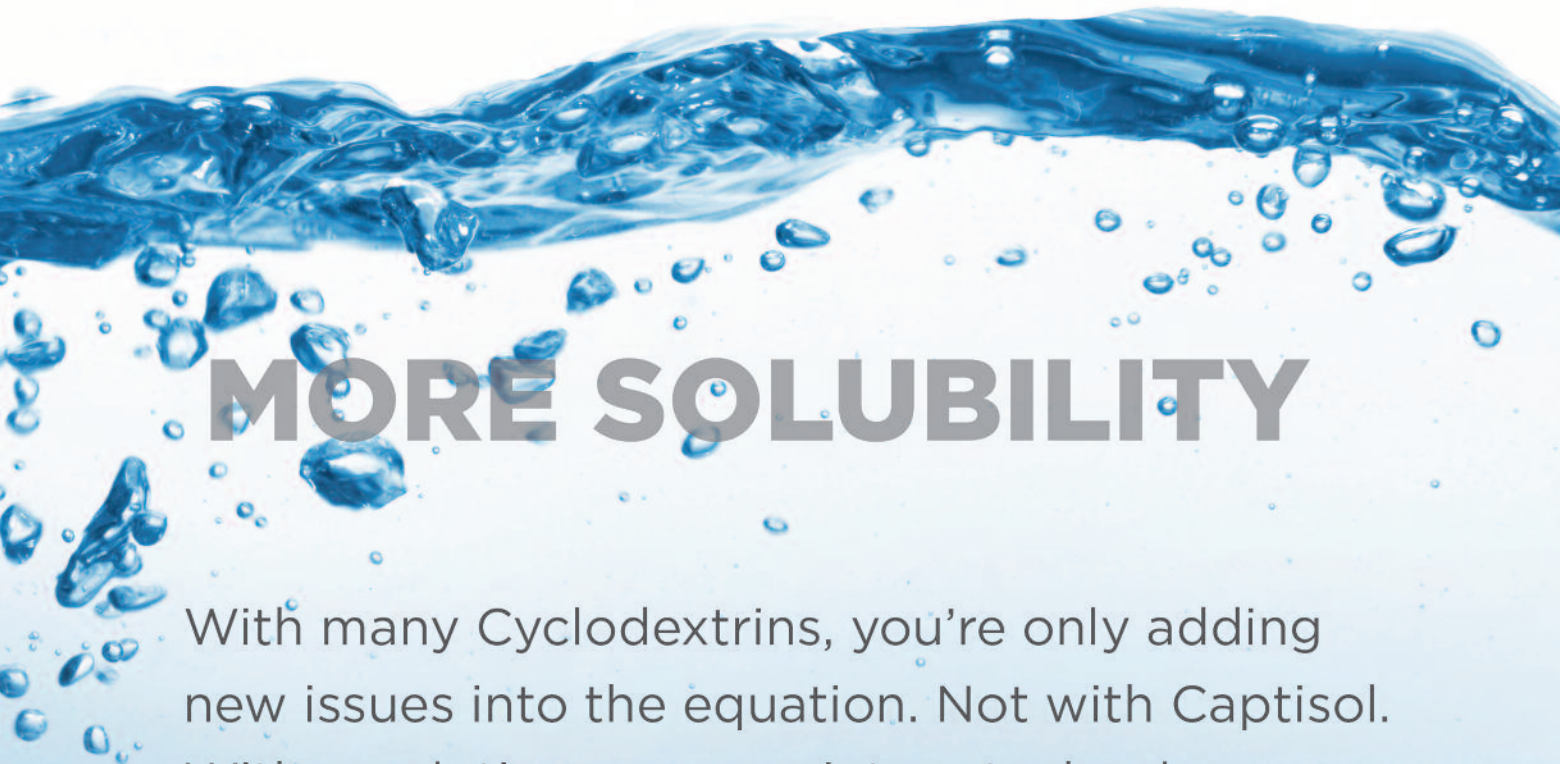

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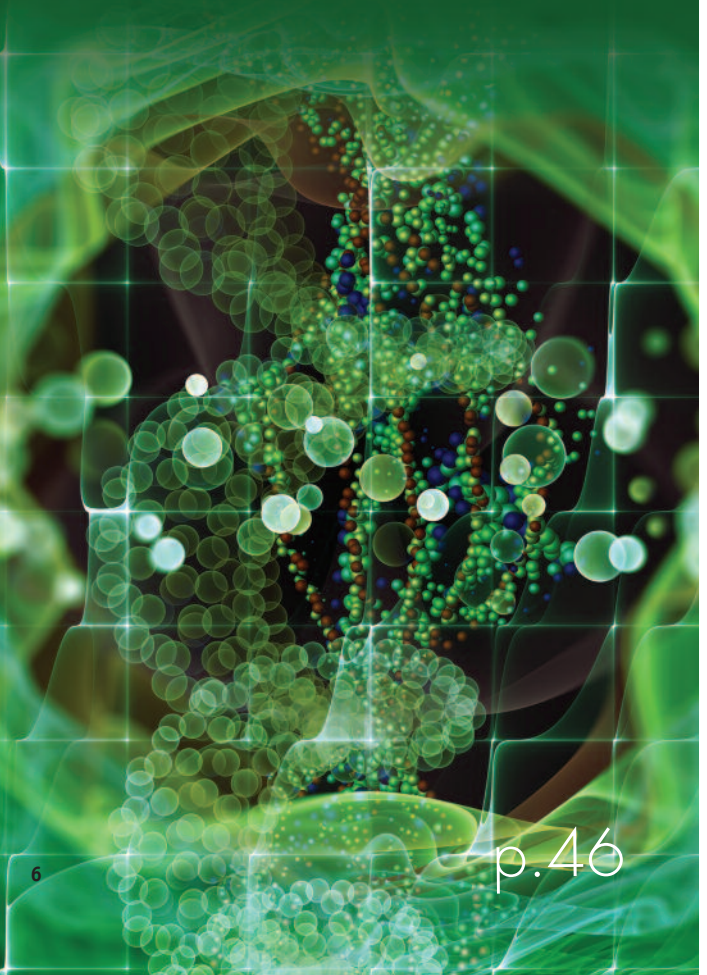

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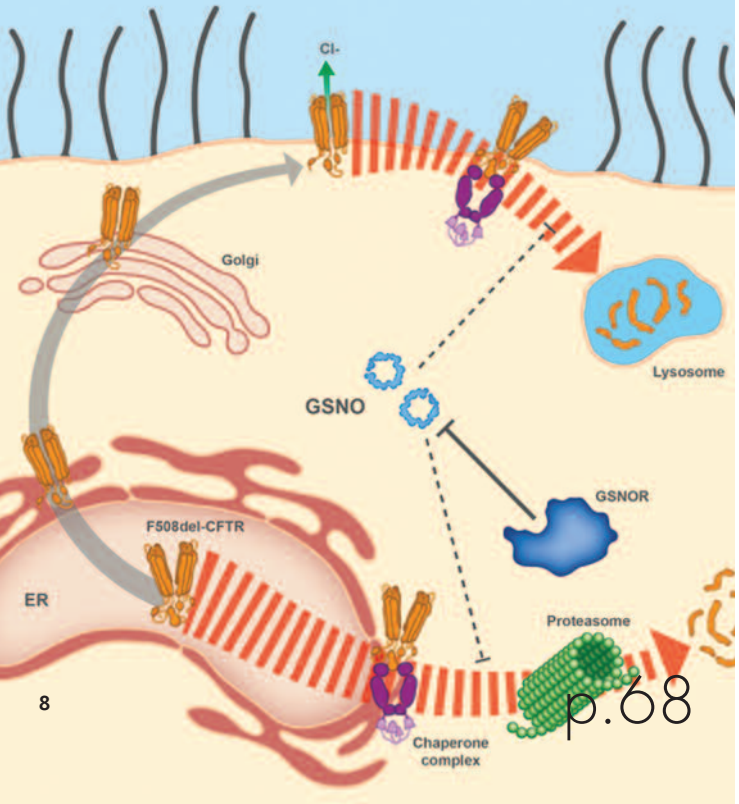

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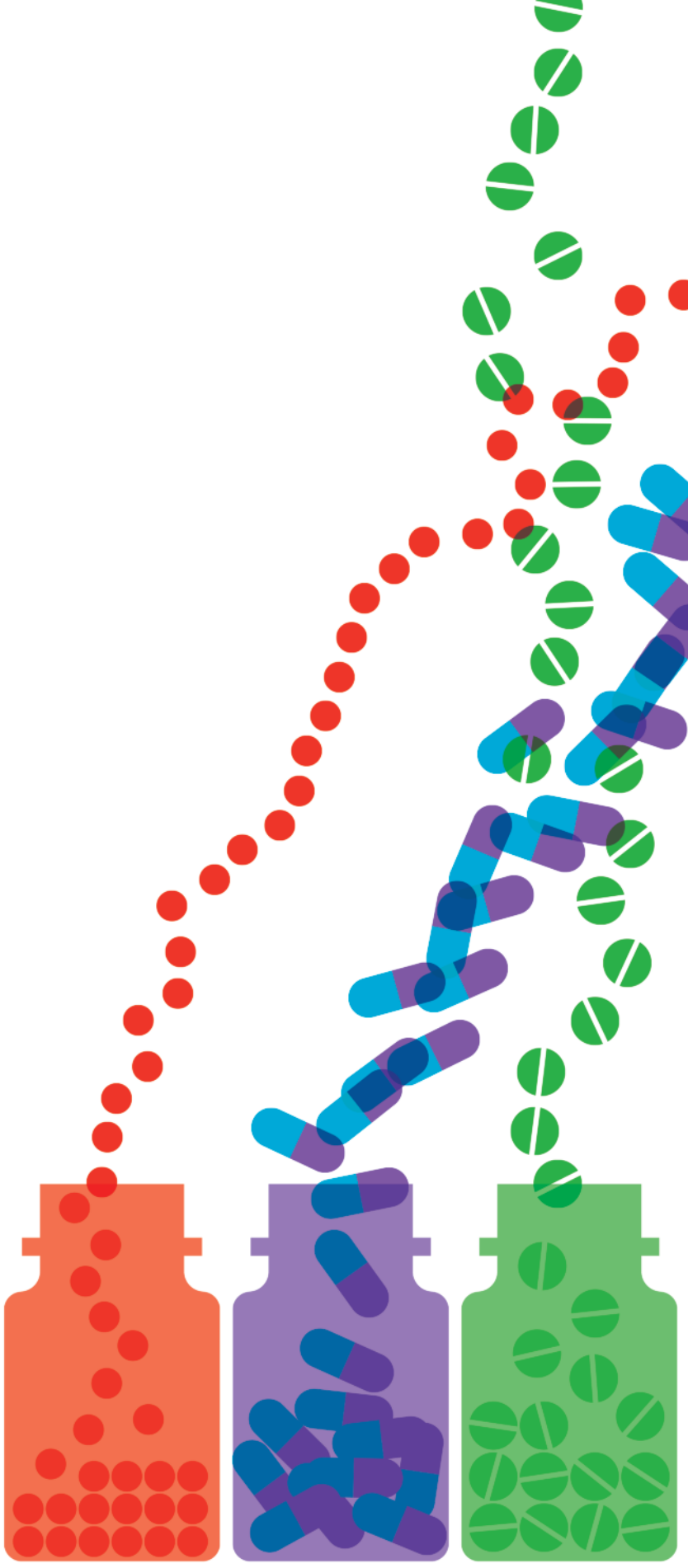

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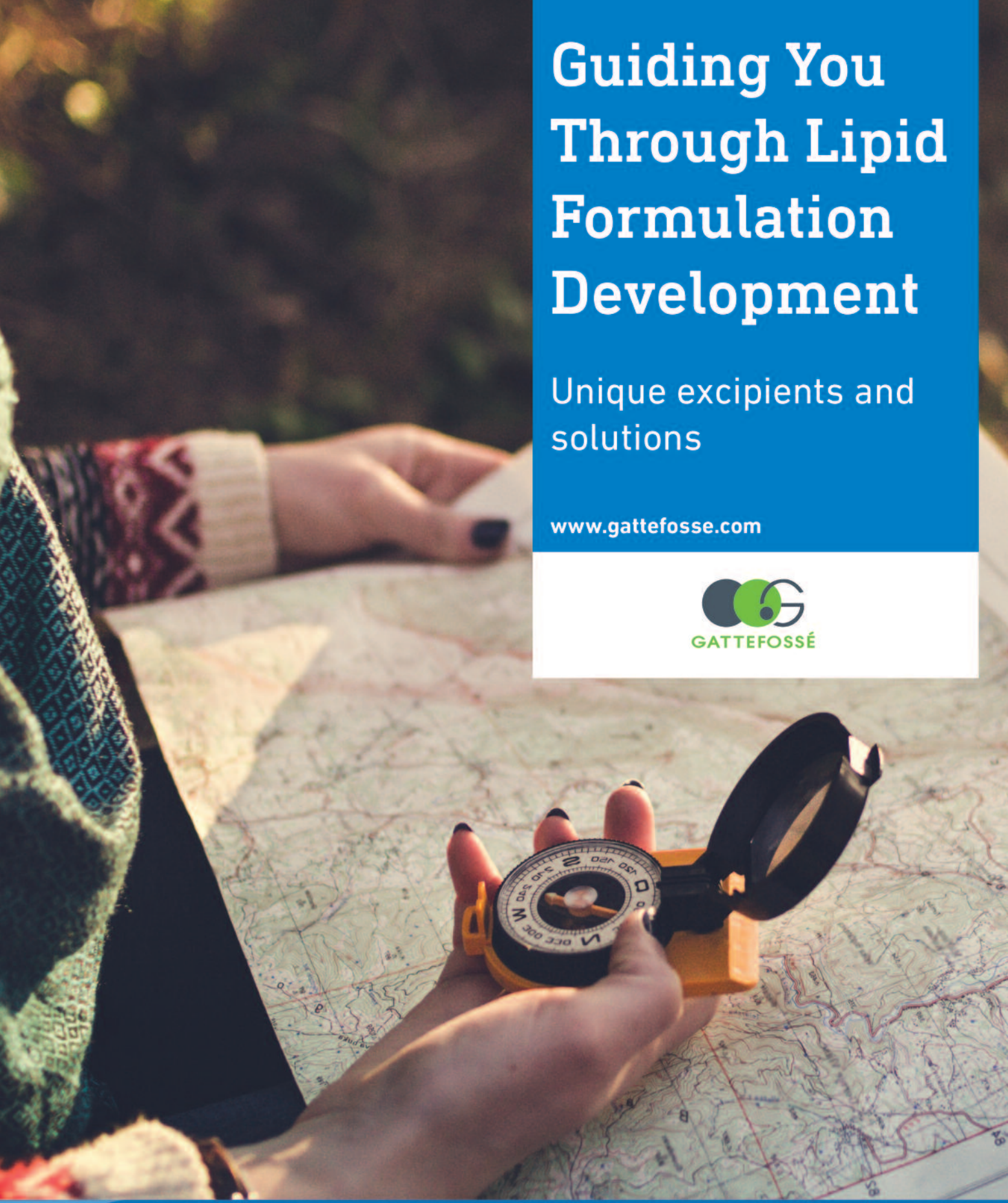

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COMBINATION CORNER

Keys to Avoiding Common Pitfalls in the Development of Product Requirements for Drug Combination Products

By: Jerzy Wojcik

INTRODUCTION

In combination product development, creating a Product Requirements Document (PRD) that serves FDA Design Control (DC) regulatory needs is more complex than traditional medical device development. The increased complexity stems from the need to account for the interdependencies between the drug and device. The pitfalls commonly observed within PRD's at Combination Product organizations are:

Poor Use Case Modeling: Teams do not use systematic approaches when defining the diverse use cases applicable for the combination product.

Incomplete User Needs: Teams do not involve a complete array of perspectives that support a full set of user needs.

Lack of Cross-Functional Team Input: Inadequate identification and integration of requirements from both drug and device development teams.

The aforementioned pitfalls can have significant ramifications on combination product programs and are usually uncovered late in the development timeline, ie, during validation or commercialization. It goes without saying that a delayed market launch or a slow commercial adoption rate due to unsuccessful market fit are costly penalties. Tips on how to build a robust combination product PRD from the beginning of a project are further explored.

WHAT IS A PRD, USE CASE & USER NEED, & HOW DO THEY CONNECT TO EACH OTHER?

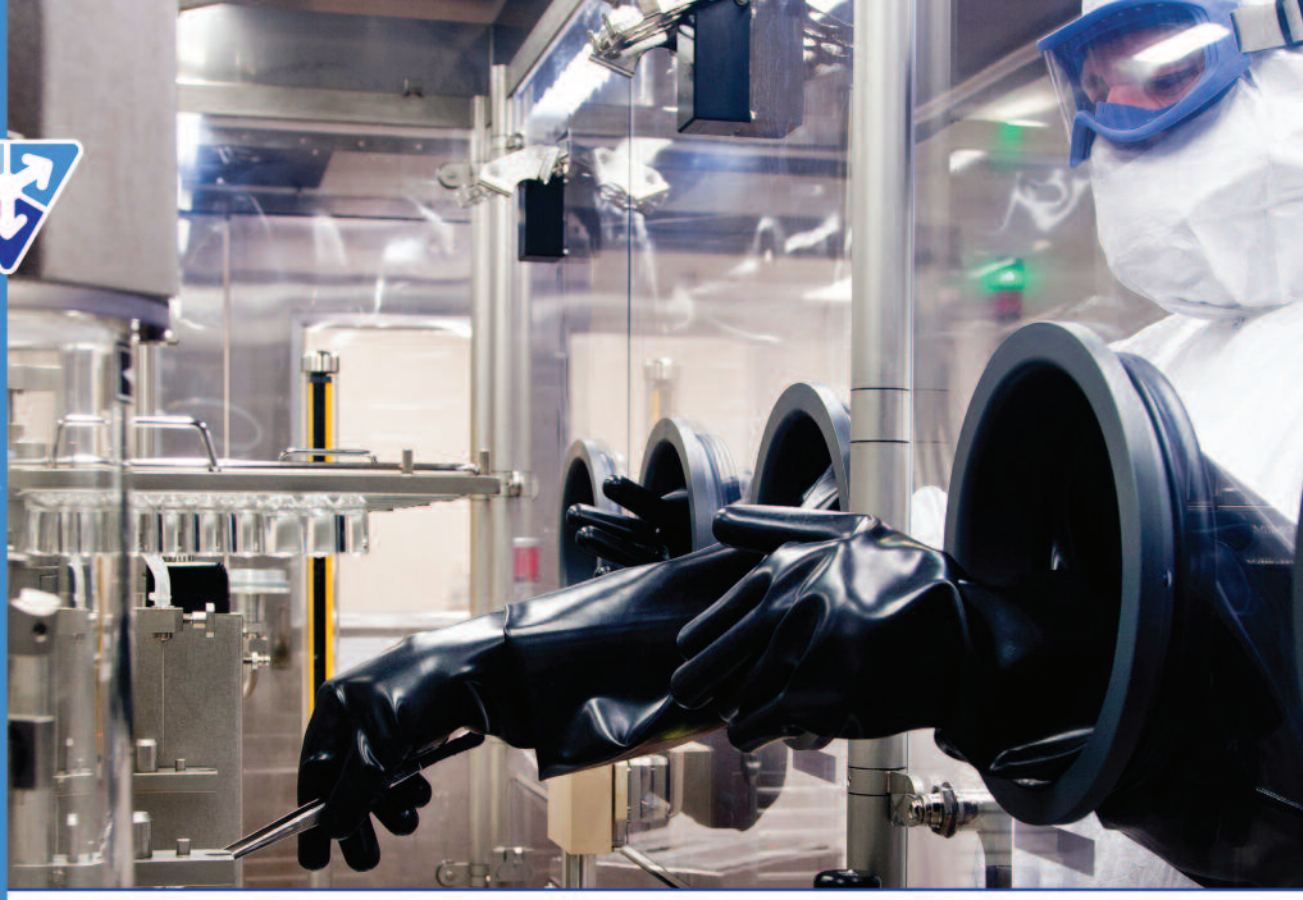
In order to understand how to build a robust PRD, one needs to understand the key terminology being utilized throughout the document. Figure 1 provides definitions and visualization of how the terms are connected to each other.

The PRD sets the stage for the entire development program and serves as a foundation for all activities and documentation that need to be generated to show support for satisfying the requirements. A well-structured PRD sets clear guard rails for what the device needs to be, what it needs to do, and describes what the intended use for the device is. The importance of this document reinforces the need for all functional roles to invest an appropriate amount of time on this critical activity.

DEVELOPING DIFFERENT USER CASES STARTS BY DEFINING USER POPULATIONS

When developing a combination product, it is useful to distinguish two populations of users: the "direct user" and the "indirect user" (also referred to as stakeholder).

The direct user includes the patient, the person using the product (eg, nurse, caregiver, and/or patient), the person preparing the product for use, and sometimes, the person(s) transporting or storing the device prior to use (eg, a drug that is shipped in frozen state). It is critical to recognize that a single device may have multiple direct users, especially as you start looking at what the user may say they need. For example, most users will say that a device should be easy to use, safe to use, and not take too much time to use. But considering an elderly patient and a 20-year old patient, what constitutes "easy to use" for doing something as sim-



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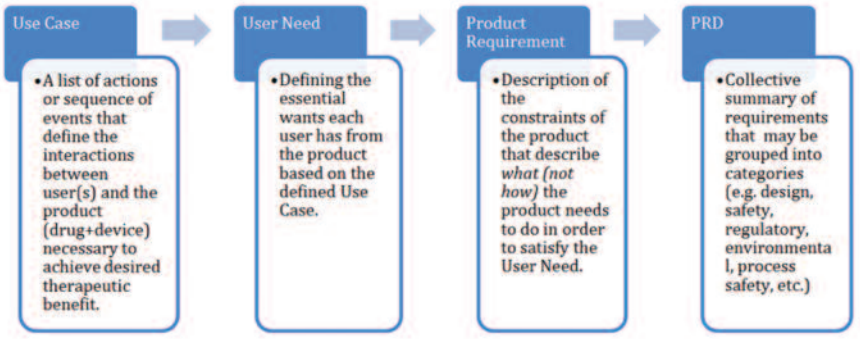

Definition & Interdependency of Key Terms

ple as opening a pill bottle for the 20-year-old may be significantly different for the elderly patient. Similarly, a high-school educated patient and a physician may have very different assumptions and methods on how to interface with a product containing a software interface, and it is important to consider both users throughout the design. If the team misses identifying the right users up front, it is very likely that there will be costly redesigns at a later point in time.

Indirect users, or Stakeholders, are those individuals whose work focuses on different aspects of developing or commercializing the product. These include but are not limited to distributor, marketing, sales, regulatory, finance, etc. Typically, drug development scientists have had minimal consideration for device development, as their primary focus is on the drug therapy. However, the new FDA combination product regulations require the consideration of the interaction between the drug and device. Therefore, the scientists are indirect users (stakeholders) and they will define key needs for the successful delivery of the therapy via the delivery system.

Traditional device development emphasizes researching the needs of the direct user(s) when defining product requirements. However, from a project management perspective, by researching stakeholder needs at the same time as user needs, a combination product project team can potentially reduce the total cost of development by avoiding problems of re-work or other delay-inducing steps. For example, by accounting for input from individuals who manage different aspects of commercializing a medical device product, the project can avoid a situation in which design inputs steer product development to a device that is ultimately too costly for the company to distribute at competitive prices.

DEFINE USER NEEDS BY ASKING HOW THE USERS WILL ACTUALLY USE THE PRODUCT

Once the users and stakeholders have been defined, the next critical step for the team is to "walk the path" of each user by deploying use-case modeling tools early in the requirements building process. Use-case modeling tools enable you to systematically look at each step of how a product is used across each user type, and ask the question, at a very basic level: "A this step, what does the user need the device to do, and what does the user need the drug to do?" That leads to two follow-on questions: "If the user needs the drug to do "X," then how is the device going to allow or enable the drug do that? If the user needs the device to do "Y," then how can the drug support that, or at minimum, not impede that from happening?"

These questions about the interconnections between the drug and the device will help with the identification of needs that will ultimately translate into detailed requirements. Going through this exercise will also help the project team reach a consensus on whether the drug or device is the primary mode of action from a development perspective.

If a project team does not deploy use-case modeling tools in developing a PRD, they could miss a step in the process, or miss a particular user or stakeholder need, which may appear minor, but leaves a gap in product requirements. This missing requirement gap carries over into missing a performance evaluation or a safety test, or a specific human factor consideration. The impact of gaps in requirements will also occur in subsequent phases of the project when the team conducts risk analysis, as the risk analysis will be based on an incomplete set of use case steps and requirements. While a product development team cannot expect to identify every requirement early in the project definition phase, using these tools will help capture and document many requirement details that the team may otherwise not uncover until validation testing, during submission, or during an audit. Better to find these missed requirements late in development than after the product is launched into the market and customer complaints or adverse event start coming in.

An example of missing user needs when performing a use-case map is for a drug delivery device that requires both left- and right-hand usage based on who will be administering the medication. The requirement to allow the device to be used in either hand is one that could easily be

missed by teams not digging deep into who the user will be and how they use the product. If this type of requirement is missed, the rework and remediation to accommodate both handed users will likely lead to significant design changes, additional costs, and project delays.

INVOLVE THE CROSS-FUNCTIONAL TEAM MEMBERS FROM BOTH DRUG & DEVICE TEAMS

Historically, drug development, device engineering, and R&D professionals specialized in either drug or device development, but not both. This caused an "over-the-wall" approach to development and often resulted in re-do design cycles, missed design features, and in some instances, a "not my problem" attitude when issues would arise. At the onset of a project, bringing in a broad cross-functional team when user needs and product requirements are being developed results in a much stronger and comprehensive PRD.

A well-designed cross-functional working group must involve representatives from both device and drug development teams and should include participation from R&D, engineering, marketing, manufacturing, regulatory, clinical, quality, supply chain, software development and IT (assuming the device has software components), legal, and other commercialization functions. Having someone with clinical experience who also understands and knows the patient will add valuable perspective, while having input from actual patients or users can add significantly to the dialogue while also reducing the time and effort necessary for summative or formative studies. With patient (ie, end-user) input, the development team can better understand the answers to questions such as: "in order for therapy to work better for you, what does the product need to do?" or "how does the device work for you if this or that feature or step was eliminated?" The discussions among the various cross-functional team participants in response to this user input will determine what requirements are ultimately captured in the PRD.

While it may seem excessive to pull such a large group into the discussions on users and use cases so early in a program, the cost of missing key needs and translating these into requirements becomes so much higher than the up-front time investment. While the input of some functions will be less than others, the likelihood of getting design inputs "right the first time" increases substantially through such a cross-functional approach. In the absence of cross-functional input, captured in an effective manner, a project team might find themselves having designed a novel device. For example, a team can develop a drug delivery drug pump that works perfectly to administer the therapy, but only realize after the pump has been launched into the market how negatively customers react to the loudness of the pump notifications and brightness of the user interface screen when using the pump at night and trying to sleep.

It is also important to note that as a development program continues through subsequent phases, issues will arise that will require a requirement to be revisited, renegotiated, and/or a new requirement be created. In these instances, a cross-functional team will more effectively deal with these situations if they also collectively worked together early in the project to create the PRD. More importantly, they will also be able to understand the background/origin of the product requirement to understand why it was identified in the first place.

SUMMARY

Product users not only demand the product to do what it is meant to do, but they also demand it meet their expectations for ease of use. Businesses, on the other hand, focus on minimizing project costs and develop products faster. With this divergent focus, it is more important than ever to bring the right team together early in a project to capture product requirements correctly. The cost of missing needs or requirements goes up exponentially as development proceeds, and many of these requirements can be identified early in the project if the right individuals are at the table.

As previously summarized, the three key steps to capturing the right product requirements include the following: 1) define the users and stakeholders and understand the product use case, 2) identify the user needs by "walking the path" of each use case for each user and ask what the user will need from the product, and 3) have the right cross-functional team members from the start of the project to leverage their broad perspective. ◆

Jerzy Wojcik is Senior Director of Regulatory Affairs & Quality Assurance at EdgeOne Medical Inc, an ISO 13485-certified medical device testing firm and consultancy focused on supporting combination products through the device development (design control) process. Prior to EdgeOne Medical, he was responsible for the regulatory oversight of combination and Class III devices at Baxter's BioScience division (now Baxalta, part of Shire plc). He earned his triple BA in Biology, Medical Technology, and Cytotechnology from Augustana College and is currently an Adjunct Professor in the School of Law at Northwestern University.

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AAV VECTOR MANUFACTURING

Challenges & Opportunities in the Manufacturing of AAV Vectors Used in the Delivery of Gene Therapy Treatments

By: Daniel C. Smith, PhD

INTRODUCTION

Significant advances in the specific targeting of delivery vectors and the increased therapeutic efficacy of such vectors for gene delivery have been made, stimulating major interest in the development and commercialization of therapeutic products focused on gene therapy indications. In the past few years, there have been a large number of positive clinical outputs for gene therapy-based products spanning broad therapeutic areas, including CAR T-cell immunotherapy, oncology, and regenerative medicine based on monogenetic diseases. In terms of gene delivery, viral vectors have emerged as the preferred vehicles of choice, used in 48% of the 483 current on-going gene therapy trials.[1]

Of the gene therapy products in development, recombinant Adeno-Associated Virus (AAV)-based vectors are currently the most widely used and show the greatest potential for delivery in gene therapy indications.[1-3] The first rAAV-vector-based clinical trial was performed 20 years ago; a Phase I study delivering a CTFR transgene via an rAAV vector to adult cystic fibrosis patients with mid lung disease.[4] In 2015, there were 103 rAAV vector-based products reported to be in development, a number that is expected to increase further in the next few years.1 The preferred use of rAAV vector systems is due, in part, to the lack of disease associated with the wild-type virus, the ability of AAV to transduce non-dividing as well as dividing cells, and the resulting long-term robust transgene expression observed in several Phase I/II trials.[5] Furthermore, different rAAV vector serotypes, either naturally occurring or hybrid/synthetically derived, can be exploited to specifically target different tissues, organs, and cells, and help evade any pre-existing immunity to the vector, thus expanding the therapeutic application and commercial potential of AAV-based gene therapies.[6]

Whilst the majority (74%) of AAV-based therapeutic products are in early to mid-phase clinical development, a number of promising clinical outputs have helped progress the pipeline of possible AAV-based products. In 2012, the Dutch-based company UniQure was granted marketing authorization in Europe for Glybera®, an AAV1-based gene therapy for the treatment of adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD). The recent clinical successes of AAV-, and other viral vector-based gene therapies has fueled significant investments into the sector; as such, there is growing demand for clinical-grade good manufacturing practice (GMP) production solutions for these viral vector products.

THE NATURE OF THE CHALLENGE

The development of manufacturing processes for novel biotherapeutics is time consuming and expensive. Recombinant viral vector production is seen as complex, with the production scale-up regarded as a major challenge technically, and a large barrier for commercialization.

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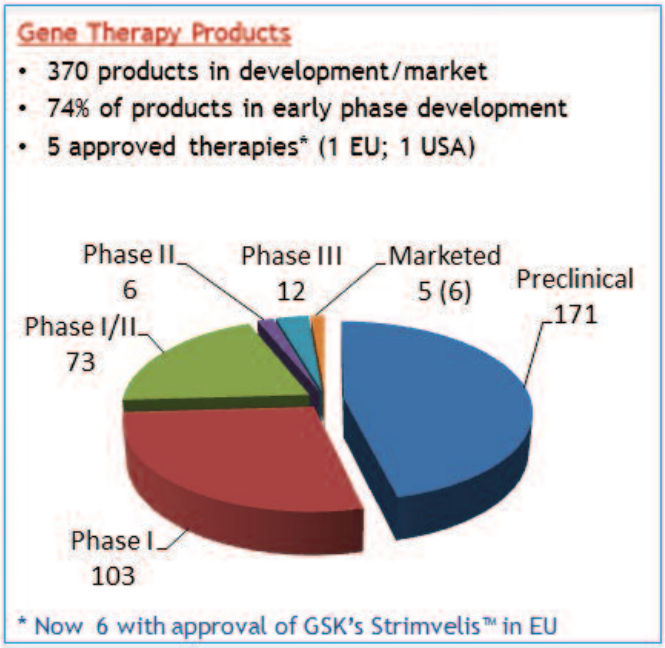
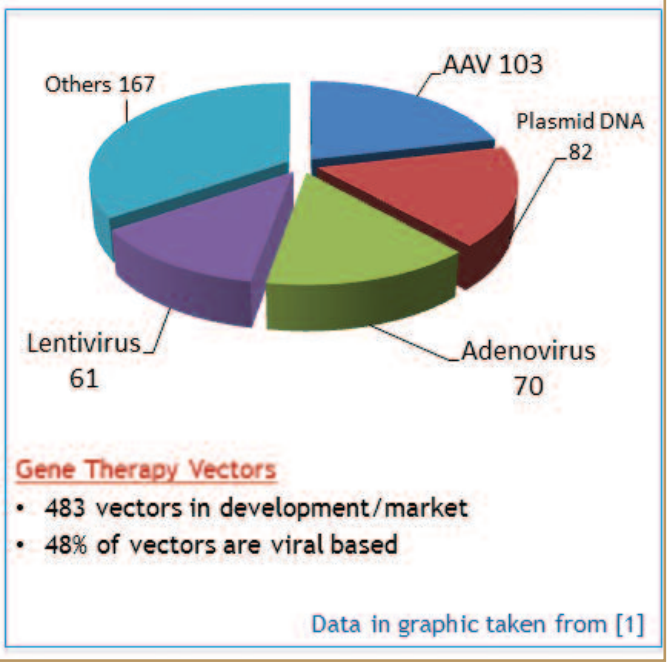
FIGURE 1





Reported clinical doses for AAV-based viral vectors range from 1011 to 1014 genomic particles (vector genomes; vg) per patient dependent on therapeutic area.[1,3,6] From a wider gene therapy development perspective, current scale-out approaches fall short of supplying the required number of doses to allow later Phase (II/III) trails to progress, thus retarding the development of gene therapy products. This is supported by the fact that the majority of clinical studies have been very small, performed on <100 patients (and in some cases <10), using adherent cell transfection processes that generate very modest amounts of product. When predicted amounts of virus required for later phase development are compared to current productivities (ca. 5x 1011 vg from single 10 layer cell factory), there is real concern that this approach will fall short of the material requirements for late phase and in-market needs for even ultra-orphan diseases, which have high dose and small patient cohorts, let alone more "standard" gene therapy indications.

In the case of AAV, a number of production strategies exist to generate viral vectors; as with all different strategies a number of advantages and disadvantages are associated with each.

STABLE CELL LINES FOR PRODUCTION

Generation of stable engineered cell lines, through the introduction of both regulatory (Rep) and structural capsid (Cap) genes and/or the rAAV genome, give rise to packaging or producer cell lines, respectively. AAV viral vectors are produced from packaging cell lines following transfection of the AAV construct and the co-infection with a helper virus, such as adenovirus (Ad) or Herpes Simplex Virus (HSV) or via a single infection with a recombinant helper viral vector containing the rAAV genome. For producer cell lines, AAV is generated following a single-step infection with an Ad or HSV helper virus. Stable cell lines have been reported to produce relatively high AAV vector genome (vg) particles per cell (up to 10,000 vg per producing cell). Packaging and producer cell lines have been generated using cell lines capable of both adherent and suspension growth, allowing for processes to be developed that utilize traditional tissue culture systems for small scale, combined with larger-scale manufacturing performed in suspension bioreactors. This scalable approach has been used in the production of an AAV1 product for heart failure; here the viral vector has been generated at a 2000-L scale from a HeLaS3 producer cell line, following co-infection with helper viruses.[7]

Despite the relatively high yield and scalability reported, a number of disadvantages have limited the use of the producer and packaging cell lines in clinical development. The generation of stable lines is technically demanding, extremely time consuming, and needs to be performed for every vector and AAV

FIGURE 2

Production Strategy	Advantages	Technical Disadvantages	Commercial Disadvantages
Helper Virus	• Scalable suspension system. • Serum free media can be used for production.	• Helper virus contamination • Long lead time for cell line and virus seed generation. • Increased purification & analytics required.	• Expensive cell line licensing. • Large Cost investment. • Long clinical production time.
Baculovirus	• Scalable suspension system. • Serum free media can be used for production.	• Baculovirus contamination • Long lead time for cell line and virus seed generation. • Increased purification & analytics required.	• Expensive licensing for cell line. • Large Cost investment • Long clinical production time.
Helper-Free Transfection	• No helper virus contamination. • Rapidly transient production. • No/low licensing required.	• Scale out rather than Scale up. • Requires serum containing media. • Low Productivity	• High costs for scale out (labour, materials, facility)

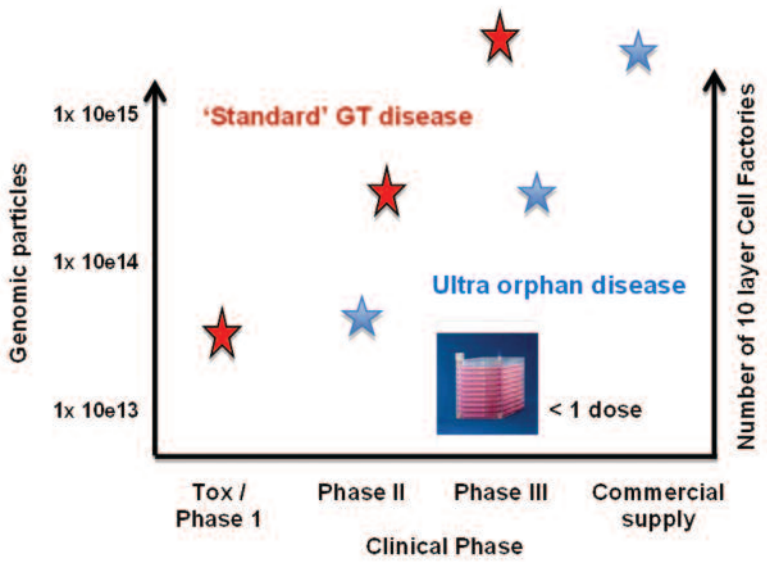
serotype combination. Clonal characterization and cell line stability is very time consuming and expensive, and furthermore carries potential risk based around cell passage history and the relationship between growth kinetics and vector production. A major concern is the use of helper Ad and hybrid variants in these systems. The production of the helper virus can itself be extremely costly and lengthy, with the need to carefully assess the quality of this critical starting material ahead of use in AAV production. Furthermore, establishing effective removal and clearance procedures to separate the helper virus away from the AAV vector product is not trivial, resulting in complex and costly downstream process development and a potentially high cost of goods.

BACULOVIRUS PRODUCTION SYSTEM

Production of AAV vectors using a Baculovirus (BV) expression system emerged as a consequence of the BV system's ability to produce complex glycosylated recombinant proteins at high levels in SF9 insect cells at high cell densities. Building on AAV production via a stable cell line system, the BV system was developed to produce viral vector without the need to co-infect with a human helper virus. AAV2 was produced in Sf9 insect cells following co-infection with three recombinant BV vectors, encoding the transgenes for Rep, Cap, and rAAV genome, respectively. Since then, the BV system has been modified and improved, with systems now developed that use a two- vector approach, reducing the complexity of the process. Scalable solutions have also been employed; one approach used cryopreserved BV-infected insect cells that separately carry the required AAV components (rAAV genome, Rep, and Cap genes). The infected cell were used to inoculate a 200-L scale bioreactor containing unmodified insect cells, and released infectious rBV (rAAV, rCAP, rRep) in a continuous manner that subsequently infected the uninfected cells, thus driving a sustained production phase.[8]

Currently, the AAV1-based drug Glybera is produced using the BV system; however, several drawbacks have limited the use of the BV system to produce AAV vectors in the clinical setting. Overcoming the molecular cell biology aspects needed to produce a mammalian viral vector in an insect cell system using insect virus has major challenges; instability of AAV genes within BV has been reported, along with the inability to assemble AAV particles with the correct stoichiometry of capsid proteins, affecting the infectivity of the produced AAV viral vector. Similar to the stable cell line production systems, there are challenges in clearing and removing the starting and propagated BV from the AAV viral vectors during the downstream purification operation. However, several biopharmaceutical companies are currently using variations of the BV platform, and are actively working on improvements to mitigate the limitations of the BV system, moving toward large-scale clinical rAAV manufacture.

FIGURE 3



HELPER-FREE TRANSIENT TRANSFECTION

Transient transfection of plasmid DNA into mammalian cells for the production of AAV viral vectors is the strategy most commonly used in clinical grade manufacturing of these viral vectors. rAAV vectors are usually produced in human embryonic kidney 293 cells (HEK293), or HEK293 cell variants following introduction (transfection) of typically three DNA plasmids carrying the regulatory (Rep) and structural capsid (Cap) genes, the rAAV transgene, and the specific genes that provide helper Ad function. If all three plasmids are successfully transfected into a cell, the cell will produce an rAAV vector without the need to co-infect with wild type helper virus. The transfection approach is fairly rapid and versatile and has been used to produce different serotypes of rAAV, as only the gene sequence of the Cap genes has to be altered to produce the various serotypes. Furthermore, modification of the transgene plasmid allows for both single- and double-stranded (self-complementary) forms of the vector to be generated.

Again, the main challenge to this approach is the inherent lack of scalability due to the use of adherent HEK293 cells. As such, adherent cell systems require a scale-out approach based on the linear expansion of 2D surface area, rather than the volumetric 3D scale-up approach usually employed in the production of biopharmaceuticals. In order to produce and purify the required vector genome (vg) particle numbers of >1x1016 vg to support mid- to later-stage clinical trials, over 500 Hyperstacks™ (a Hyperstack has 36 layers and total surface area of 18,000 cm^2) would be needed. Whilst possible, this approach is not a viable option for most manufacturing facilities due to facility footprint, cost, and man power limitations. Work is underway to develop truly scalable, regulatory compliant, production solutions for rAAV vector generation. HEK293 cells have been adapted to suspension growth in animal component-, serum-free, and antibiotic-free media systems, with optimization of transfection conditions evaluated in shake flask, rocking, and stirred-tank bioreactor systems.

DOWNSTREAM VIRAL VECTOR PURIFICATION

Irrespective of vector production processes and scales, the ultimate goal of for AAV vector manufacturing is to have robust downstream purification that generates final clinical material that has high titre, high potency, and high purity. Due to the emerging nature of the viral vector field, most downstream approaches are based around traditional laboratory processes that are not scalable or suitable for clinical-grade manufacture. Limitations exist throughout the downstream purification of viral vectors; these include: the harvesting of the producer cells, cell lysis procedures to release AAV vector, the clarification and removal of cellular impurities, vector separation and purification, and vector formulation and sterile filtration.

The challenge can be exemplified by the way that genomic-containing vector particles have been traditionally separated from empty particles using gradient ultra-centrifugation. Whilst the resulting material obtained from such a step is of high purity and high potency, the time-consuming nature and complexity of scale up significantly limits the use of ultra-centrifugation within the downstream process. For therapeutic indications, other than those focused at ultra-orphan diseases that require small volumes of material to be purified, the need for processing large volumes requires an alternative method of purification. As such, chromatography-based approaches are being developed using affinity

"There remains a clear need for improved process productivities, and the need to develop manufacturing processes that can be applied to a wide number of AAV-based viral vector therapeutic candidates. Simplistically, the AAV vector is a delivery vehicle for a therapeutic gene, and the manufacturing process is not linked to that gene. Logic therefore dictates that it should be possible to generate platform processes specific for AAV serotypes and even possible to generate processes that can be applied to multiple serotypes."

binding and/or ion-exchange steps that provide efficiency, flexibility, and scalability to the purification of AAV vectors. As high- purity, high-potency vectors can be generated using ultra-centrifugation approaches, the challenge for a chromatographic purification approach is to generate vectors with the same degree of purity and potency. Regulatory consideration must therefore be given to any process change during the clinical development program. Also, due to the chemical and biological variances observed between the various AAV serotypes, the development of a single downstream platform for all AAV vectors may be unlikely; rather a number of potential solutions are likely to be employed.

ANALYTICAL SYSTEMS FOR THE CHARACTERIZATION OF PRODUCTS & PROCESSES

Developments are underway to improve clinical manufacturing processes and to move into scalable and controllable production and purification systems. However, these are stymied by the lack of processing knowledge of critical parameters at all stages of the manufacturing process, driven by the lack of suitable analytical systems to support development studies, and to interrogate and control production processes, as well as characterize final materials.[9] Linked to the manufacturing challenge is the regulatory requirement for the identification, characterization, and batch-to-batch control of the process- and product-related impurities present in highly purified material. Especially challenging are impurities related to the AAV vector products,which closely resemble the vector itself.

AAV vector particles can co-package non-specific plasmid material into the capsid. It has been reported that between 1% and 8% of purified AAV particles contain an incorrect nucleic acid sequence.[7] As reported clinical dose ranges vary from 1011 to 1014 genomic particles, there could be as many as 109 co-packaged impurities per dose. These process-related impurities require detailed characterization, along with an evaluation of the potential for the incorrectly packaged DNA to be active in transduced cells.[10]

Interestingly, most plasmids currently used for transient transfection carry an antibiotic resistance gene to enable plasmid selection and maintenance during their own production. Therefore, removal of antibiotic resistance genes would be desirable for the production of AAV in Helper-free systems. Technology exists, such as Cobra's patented Operator Repressor Titration (ORT™) plasmid maintenance system, to generate plasmid DNA lacking antibiotic resistance genes.[11] These systems eliminate the chance of co-packaging a functional antibiotic-resistance gene into the viral capsid, thus increasing the safety of the product and reducing the burden of characterization of AAV-related impurities.

VISION FOR A KNOWLEDGE-BASED SCALABLE PRODUCTION PLATFORM

There remains a clear need for improved process productivities, and the need to develop manufacturing processes that can be applied to a wide number of AAV-based viral vector therapeutic candidates. Simplistically, the AAV vector is a delivery vehicle for a therapeutic gene, and the manufacturing process is not linked to that gene. Logic therefore dictates that it should be possible to generate platform processes specific for AAV serotypes and even possible to generate processes that can be applied to multiple serotypes. This approach is not unprecedented; the development of platform-based development and manufacturing processes that disconnects production from specific products has had an enormous impact in other biologic areas (ie, monoclonal antibodies), reducing development cost, timelines, and cost of goods, and has also allowed drug developers to significantly expand clinical pipelines in multiple therapeutic areas.

To achieve this for AAV vectors, the underpinning scientific knowledge surrounding critical operational parameters in the manufacturing process needs to be generated and optimized, along with a suite of standard analytical methods. Any platform developed will need to be sufficiently flexible to accommodate multiple AAV vector types. Such development will have long- term benefits to the generation of materials for first-in-man studies, and onward for late-stage clinical studies and ultimately in-market supply. ◆

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BIOGRAPHY

Dr. Daniel C. Smith is Chief Scientific Officer of Cobra Biologics with the responsibility for developing the highest level of scientific excellence across the Group and enhancing Cobra's DNA, virus, microbial, and mammalian proteins research and development platforms. Prior to joining Cobra, he spent 4 years with the bioProcessUK team at the HealthTech & Medicines Knowledge Transfer Network (KTN), driving the innovation agenda for biologics bioprocessing in the UK as a Knowledge Transfer Manager. Dr. Smith gained his industrial experience at Cobra in a variety of roles progressing from Senior Scientist to Commercial Scientific Development Manager, responsible for developing the strategy for customer's projects, alongside maintaining scientific oversight of Cobra's R&D projects. He earned his BSc (Hons) in Biochemistry and his PhD in Molecular Cell Biology. He has more than 20 research publications to his credit; has worked with a number of academic groups across the UK, Europe, and the US; and has extensive academic research experience in cell biology, molecular biology, immunology, and protein biochemistry, with a particular expertise in protein-based toxins and cellular delivery vectors.

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BIOMARKERS

FDA's Design Control Requirements for Biomarkers in Drug Development

By: Kaiser J. Aziz, PhD

INTRODUCTION

The availability of validated biomarker-drug companion products will enable the molecular diagnostics and pharmaceutical industries to develop and rely on new genomic biomarkers in order to elucidate disease pathways, stratify patient populations, and monitor safe and effective use of these products for personalized therapeutic use. The use of companion biomarker with a particular drug application is stipulated in the instructions for use in the labeling of the product.

BIOMARKER CLASSIFICATION & QUALITY SYSTEM REGULATIONS

Biomarkers are in vitro diagnostic devices (IVDs) regulated under the FDA's Medical Device Law. A biomarker IVD provides measurable features or performance characteristics that are objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention. Biomarkers measure disease presence or progression that defines unique disease pathogenesis or responses to therapy. Biomarker tests are intended to perform a clinical assessment, such as blood analyte levels used to monitor and predict health status in individuals or across populations so that appropriate therapeutic intervention can be applied. Biomarkers may be used alone or in combination to assess or monitor the health or disease state of an individual. From a molecular perspective, biomarker IVDs are developed using genomics/proteomics technologies. It is imperative to distinguish between disease-related and drug- related biomarkers. Disease-related biomarkers give an indication of the probable diagnosis in cancer patients. Drug-related biomarkers indicate whether a drug will be effective in a specific patient or how the patient's body will process it. Biomarkers are also considered as the key to personalized medicine treatments that are individually tailored to specific patients for highly efficient intervention in disease processes. Biomarkers play a key role in design, discovery, and drug development. The availability of validated biomarkers will enable the pharmaceutical industry to bring revolutionary new medicines to market more quickly, safely, and less expensively.

BIOMARKER DESIGN CONTROLS

Design controls are a mechanism for bringing the design of certain class I and all class II and class III investigational devices under the umbrella of the good manufacturing practices (GMPs) of a corporate quality system. In 1996, the GMP requirements were revised to include the area of design control and have become a part of the Quality System Regulations (QSR) with which all medical device manufacturers must comply. It is incumbent on the manufacturer to demonstrate compliance with the QSR and,

Commercializing an orphan drug requires designing solutions to improve the treatment journey. In-home inventory management solutions combined with sophisticated logistics expertise makes participating in a clinical trial more convenient, easing recruitment and reducing withdrawal rates. Increasing patients' access to treatment, improving adherence, reducing costly emergency visits, and enhancing the quality of life for both patients and caregivers takes high-tech solutions and high-touch patient support. It takes a committed commercialization partner. It takes AmerisourceBergen.

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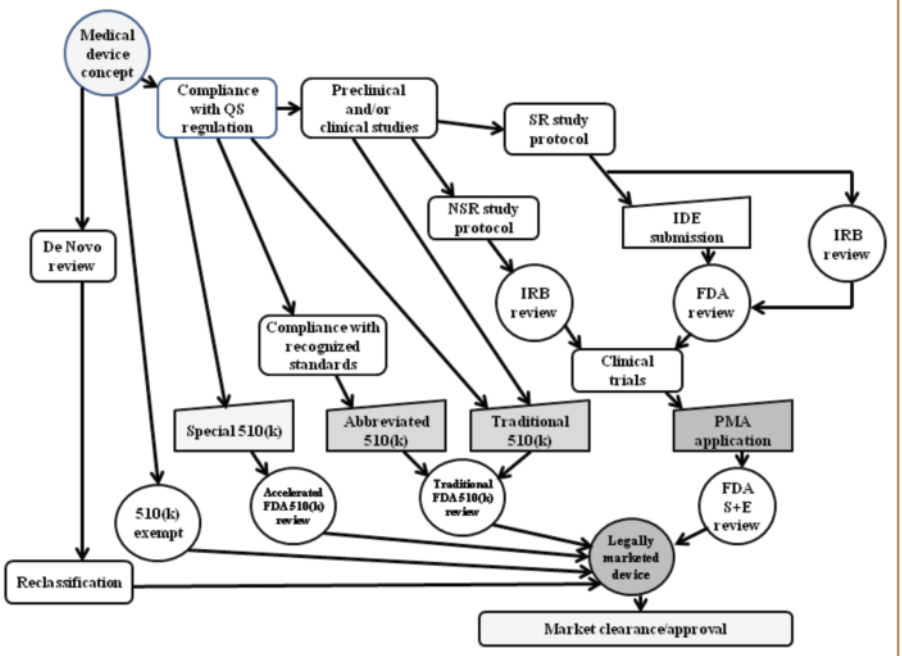
as of 1996, with design control requirements as well. Once the product definition and regulatory strategy have been prepared, IVD medical device developers must work to comply with the design control provisions of the QSR as the device development process moves forward. The QSR is the medical device equivalent of the pharmaceutical current good manufacturing practices (cGMPs). The QSR, unlike cGMPs, also regulates the IVD device development process via its design control provisions (21 CFR 820.30), which describes the IVD device developer's requirements under the design control provisions of the QSR. Design controls are an integrated set of management practices (policies, processes, and procedures), which are applied to control design activities while assessing quality and correcting errors through a reiterative device process control. Once management has determined that the device is feasible and the decision has been made to transition from research to clinical applications, the design control process begins. As such, the device application becomes part of a corporate quality system (Figure 1).

FIGURE 1



PATHWAYS FOR MARKETING DEVICES IN THE US

DESIGN CHARACTERISTICS OF BIOMARKERS

The FDA requires the consideration of human factors during the development of medical devices. In 1996, the FDA issued guidance, "Do It By Design-An Introduction to Human Factors in Medical Devices," which established design requirements to avoid so-called user errors.[1] Most recently, the agency introduced those concepts of human reliability to drug and biotechnology manufacturers. To elaborate this concept by frequency and by significance, one must differentiate between error (mistakes) and defects (also known as nonconformance). It is difficult for regulated firms to recall products because there were human errors during the manufacturing process. In some situations, the firm's quality system is unable to detect the human error and the non-conformed device distribution becomes an adulterated item. Human error can be defined as a departure from acceptable or desirable practices on the part of an individual, which results in unacceptable or undesirable outcome. Human factors include designing machines, operations, and work environments to match human capabilities, limitations, and needs. In those situations in which an operator does not properly execute a manufacturing step, human error can be avoided by using risk management tools described in ISO 14971-Application of Risk Management to Medical Devices [Hazard and Operability Study (HAZOP) and Hazard Analysis and Critical Control Point (HACCP)]. HACCP for medical devices is designed to prevent and/or control device safety and performance (Figure 2). A trained HACCP team is helpful for monitoring the IVD device production processes from raw materials, components receiving, manufacturing controls, distribution, and use by the customer. Since HACCP focuses primarily on the production process, it is also assumed that the design is complete, and the manufacturing system is already in place; however, HACCP, and/or the corrective and preventive action plan, may indicate the need to revise the design and/or the manufacturing process, subject to compliance with change control provisions of the QSR.[2,3]

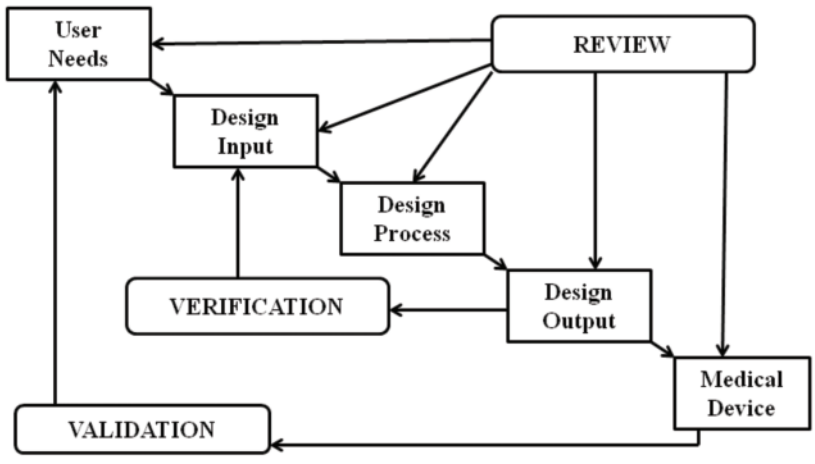
QUALITY SYSTEMS & GMPS FOR BIOMARKER APPLICATIONS

The QSR regulates both the IVD device development and the manufacturing process for all class II and class III devices from the beginning of the design engineering development phase until commercial use and post-marketing surveillance. The

"The sensitivity and specificity of recently developed biomarkers have the ability to greatly enhance cancer detection and the drug development process. Additionally, biomarkers will enable clinicians to develop individualized treatment plans for their cancer patients; thus making it possible to tailor drugs specific to their patient's specific tumor type. This will improve individual drug response rate with limited drug toxicity and costs associated with testing and related therapies."

IVD Biomarker Total Product Life Cycle (TPLC) interconnects all developmental aspects, manufacturing, and commercial use of products along with quality monitoring via design control requirements (Figure 3). The QSR also covers the manufacturing process for many class I devices. The goal of the QSR is to create a self-correcting system that reliably produces robust IVD device designs and production methods, ensuring these devices perform in a manner consistent with their intended use. Much of the information that is included in a 510(k) or PMA is taken from the Design History File (DHF), prepared as a result of the design control requirements of the QSR. Once a device is marketed, the corrective and preventive action (CAPA) provisions of the QSR are closely related to compliance with the MDR regulation. An additional feature of the QSR is that it follows the basic principles of the international medical device standard, ISO 13485, which is advantageous to enable device firms to sell their devices internationally to maintain quality system commonalities for most design and production-related activities. In most cases, the QSR system requires more extensive documentation than ISO 13485. The system requires documentation of specific activities of the development process, and documentation of specific evaluations and procedures of the manufacturing and quality processes. Frequently, the FDA investigators will follow the quality system inspection technique (QSIT) when inspecting a medical device facility (Figure 4). This process breaks the QSR compliance into four main modules and four satellite modules, some of which may not be applicable to all device firms. Generally, the FDA investigator will choose a subset of those modules and determine the device-specific compliance with QSR. This means that not every system's modules are reviewed during a QSIT inspection; however, this approach does yield a general assessment of the QSR compliance. Many IVD device firms rely on various customer-oriented feedback loops and accountability of the process. This approach can be useful by reducing time to market and by reducing the number of field corrections and recalls contributing to increasing customer satisfaction and IVD device's safety and effectiveness. The FDA's guide to Inspections of quality systems provides instructions for conducting IVD device QSIT/GMP inspections.[4-7]

FIGURE 2



APPLICATION OF DESIGN CONTROLS PROCESS

BIOMARKER DESIGN CONTROL COMPONENTS

The essential components of design controls stretch from planning through design transfer (from development, manufacturing to end user). Also, it is essential to maintain existing designs. These controls apply to all class II and class III medical devices and a small number of class I devices. The main purpose of the design control components are to establish and maintain procedures to control the design of the IVD device and maintain the intrinsic quality of the device in order to ensure that specified design requirements will meet user needs, the device's intended uses, its specifications, safety and effectiveness, and reduction in recalls. These design components are developed in a reasonable manner in compliance with the firm's existing design control standard operating procedures (SOPs). Design controls are closely linked to many other QSR components, and the entire quality system must work together to build and maintain the intrinsic quality of the IVD device. The device firms must prepare and follow SOPs that comply with the regulations and that fully describe how the firm will meet all relevant regulatory requirements. All the relevant activities must be fully documented in the firm's design history file (DHF).

ELEMENTS OF DESIGN CONTROL REQUIREMENTS

The design control regulations require each manufacturer to establish and maintain procedures for the following:

- Design and development planning
- Design input
- Design output
- Design review
- Design verification and validation
- Design transfer
- Design changes
- Design history file

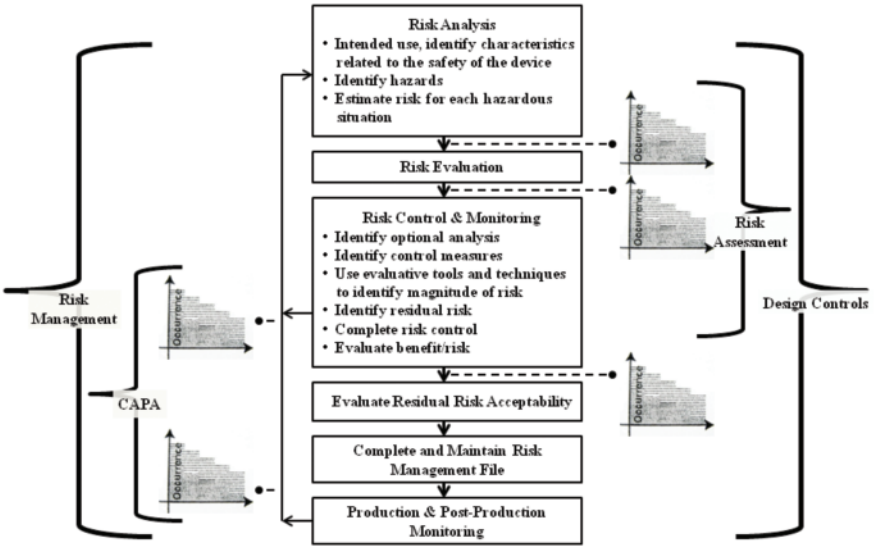
Medical devices, including IVD biomarkers that are intended for clinical use, are required to be cleared through the FDA's premarket notification 510(k) or premarket approval (PMA) processes. Biomarkers, in comparison with other types of medical devices, are unique in the area of device regulation because they can be reviewed under specific labeling requirements (21 CFR 809.10). This regulation delineates the format and content of the information that the manufacturer of biomarkers must provide to the user

TABLE 1

HER 2/neu measurement for Herceptin therapy	K-RAS Mutation Test for Cetuximab
Hercept Test and HER2 Fish for Herceptin therapy Hercept Test is currently used as a clinical diagnostic and predictive biomarker for cancer treatments	Biomarker tests that have developed after a drug has come to market.
FDA approved HER 2 tests determine whether a patient may be a candidate for Herceptin (trastuzumab) therapy, which is indicated for treatment of metastatic breast cancer and gastric cancer	FDA cleared K-RAS test as a predictive marker for Cetuximab for the treatment of epidermal growth factor receptor (EGFR) expressing colorectal cancer patients bearing the wild type K-RAS gene.
Herceptin lacks effectiveness in the HER 2 marker negative population, and also has possibility of causing severe adverse effects. Therefore it is important to use a companion biomarker test to identify only those patients who could benefit from the therapy	Compared to patients with the K-RAS mutation, patients of EGFR-expressing metastic colorectal cancer with wild type K-RAS respond well to Cetuximab, in terms both of overall survival and of progression-free survival.
The Hercept test represents an early success of a test for personalized oncology threatment. FDA approved IHC test followed by chromogenic in situ hybridization (CISH) approved in 2011. Currently, clinicians use the Hercept test as the first-line screen for patients with the over-expressing HER 2 proteins.	FDA cleared the biomarker test in 2012 and changed the Cetuximab label to include the K-RAS test as a requirement for treatment of metastatic colorectal cancer patients.

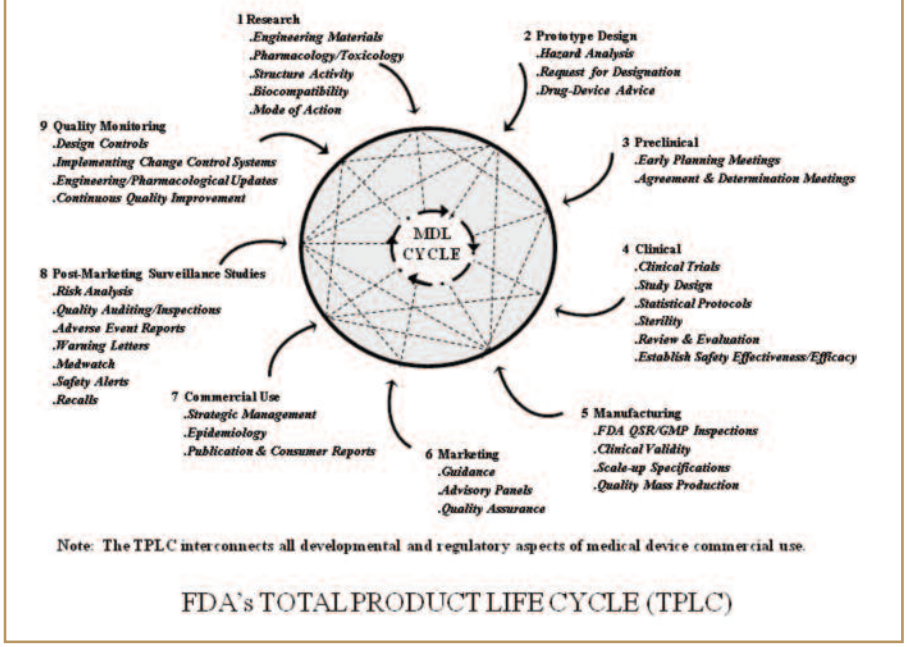
EXAMPLES OF FDA APPROVED COMBINATION PRODUCTS

FIGURE 3



MEDICAL PRODUCT RISK MANAGEMENT

FIGURE 4



FDA's TOTAL PRODUCT LIFE CYCLE (TPLC)

(information required to support biomarker test system's labeling in terms of product's use and expected performance).

The QSR requires manufacturers of biomarkers to establish and maintain procedures that control the design of the biomarker system in order to ensure specified design requirements are met. The intrinsic quality of devices, including their safety and effectiveness, is established during the design phase. Thus, appropriate design controls are observed and maintained during preproduction stages of development so that finished devices are safe and effective for their intended clinical uses (Table 1).

Risk analysis must be conducted for the majority of medical devices and IVDs subject to design control requirements. Design deficiency can be a major cause of quality problems. The main goal of establishing a design control plan is to address the impact of design concepts as they relate to clinical utility of biomarkers in order to enhance benefits while reducing risks. The key element of the design output is the preparation and transfer of all documentation that is required to manufacture the biomarker product with consistent built-in quality. The documents usually include evidence of manufacturing equipment qualification, process flow diagrams, protocol describing a set of manufacturing procedures, standard operating procedures for release specifications, and instructions. These documents are part of the Device Master Record (DMR), which provides the basis for GMP audits by the FDA.

FDA QUALITY SYSTEM INSPECTION TECHNIQUE (QSIT)

The FDA's QSIT approach to inspection is derived from seven sub-systems described in the QSR (21 CFR, Part 820). Four primary areas are the main focus of inspection: management controls, design controls, corrective and preventive actions (CAPA), and production and process controls. The remaining three subsystems are covered via "linkages" within the QSIT inspection subsystems. The QSIT review includes both a broad review of whether the firm has procedures in place that meet the general QSR requirements and a closer detailed review of specific device technology applications and records to verify that the requirements have been implemented in actual production, design, and daily quality assurance situations described in the premarket applications (510(k) or PMA).

MOLECULAR BIOMARKERS

Molecular biomarkers have been cleared by the FDA using acceptable platforms based on applied genomics and proteomics principles. Molecular biomarkers incorporate useful techniques that are complementary to routine testing within clinical lab disciplines (clinical chemistry, hematology, microbiology, virology, and immunology). The development of molecular diagnostic tests are based on the type of application for which the test is designed and intended for particular use. The development can be based on analysis of the genetic material or its' products (ie, an examination or detection of DNA, of DNA adducts, or of RNA or the proteins produced). These IVD tests are generally based on an analyte, such as DNA, chromosome, protein, or other gene products, to detect mutations, karyotypes, disease-related genotypes, and phenotypes intended for clinical uses. Such uses include diagnosis, monitoring, prognosis, identification of carriers, or prediction of disease risks.[3,5,6] Recently, there has been heightened interest and development in the application of biomarkers in oncology, including the role of KRAS in CRC and other EGFR-associated cancers (Table 1). In patients whose tumors express the mutated KRAS gene, the KRAS protein, which forms part of the EGFR signaling pathway, is always "turned-on." This overactive EGFR signal-

ing means that signaling continues downstream even when the upstream signaling is blocked by an EGFR inhibitor, such as cetuximab (Erbitux), which results in continued cancer cell growth and proliferation. Testing a tumor for its KRAS status (wild-type vs mutant) helps to identify those patients who will benefit most from treatment with cetuximab.

The sensitivity and specificity of recently developed biomarkers have the ability to greatly enhance cancer detection and the drug development process. Additionally, biomarkers will enable clinicians to develop individualized treatment plans for their cancer patients; thus making it possible to tailor drugs specific to their patient's specific tumor type. This will improve individual drug response rate with limited drug toxicity and costs associated with testing and related therapies.

SUMMARY

- Risk and hazard analysis activities are required as part of total product life cycle (TPLC).
- The standard for the application of risk management (ISO 14971) for medical products is part of TPLC.
- The risk management process covers risk analysis, risk evaluation, and risk controls through CAPA and design control requirements.
- Design control requirements described in this publication play a key role from biomarker design prototype, manufacturing process controls, and the finished product for user needs.
- The extent of testing and evaluation is proportional to the level of risks associated with the biomarker technology and intended clinical use.
- FDA reviews the "safety and effectiveness" of the biomarkers, and it is essential that any risks and hazards are mitigated to "acceptable" levels.

CONCLUSION

The FDA reviewers and field investigators evaluate the design control requirements and processes and make recommendations based on whether the manufacturer has the required checks and balances in place, and whether the manufacturer verifies and validates the implementation of the design control requirements in support of the sponsor's 510(k) or PMA. ◆

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BIOGRAPHY

Dr. Kaiser J. Aziz completed a 30-year career with the FDA, where he was Director of Mechanics and Materials Science and Associate Director of Clinical Lab Devices. He worked with individual and industry organizations in both design and total product life cycle (TPLC) approaches to pre-market applications for medical devices, pharmaceuticals, and combination products. He has designed, developed, and presented numerous training programs for medical devices and drug development industries (FDA's QSIT and HACCP Programs). His expertise includes the FDA's Quality System Compliance, Clinical Research Assessment, Product Development, Guidance for Protocols for Pre-Clinical and Clinical Studies for US Premarket Approval Process. Dr. Aziz earned his MS from Michigan State University, his PhD from American University, and a Post-Doctorate in Health Services from the University of Southern California.

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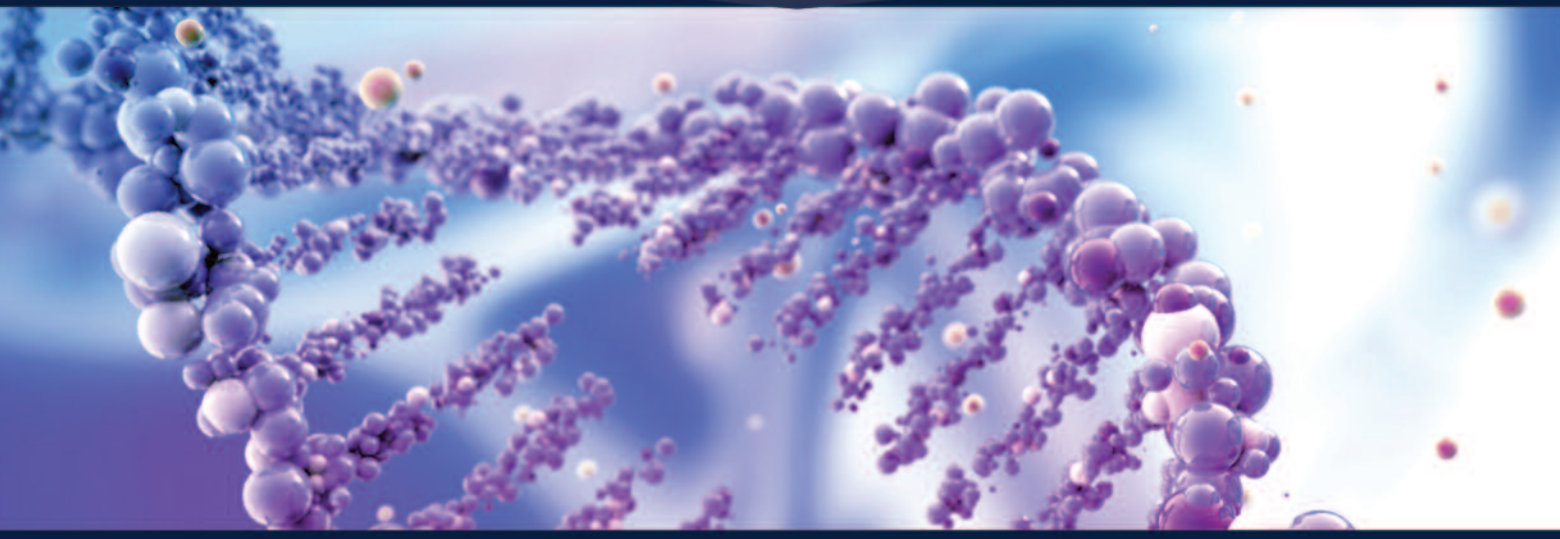

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CELL THERAPY

PLX-R18: Cell Therapy for Treatment of Acute Radiation Syndrome & Bone Marrow Failure Diseases

By: Racheli Ofir, PhD, and Noa Sher, PhD

INTRODUCTION

PLacental eXpanded (PLX) cells are placenta-derived, ex vivo, expanded, mesenchymal-like, adherent, stromal cells that are designed to be administered to patients without the need for tissue or genetic matching. These cells, expanded on the world's first GMP-approved 3D bioreactor cell growth platform, release soluble biomolecules that act in a paracrine or endocrine manner to facilitate healing of damaged tissue by stimulating the body's own regenerative mechanisms.

PLX-R18 cells, Pluristem's second PLX product, release a combination of therapeutic proteins in response to a damaged or poorly functioning hematopoietic system, the system that creates the blood cells that protect us from infection, uncontrolled bleeding and anemia. The product is currently in development to treat Acute Radiation Syndrome (ARS) and incomplete engraftment of transplanted hematopoietic cells.

ARS is a syndrome caused by exposure to a high dose of ionizing radiation over a short period of time; even low doses of radiation damage the radiosensitive hematopoietic system (causing H-ARS). To date, FDA-approved therapies for treatment of H-ARS include single proteins, such as G-CSF and GM-CSF.[1] Cell therapies have the potential to rescue hematopoietic failure based on a complex mechanism of action, involving numerous secreted proteins released from cells that react to their in vivo environment. Pluristem has tested the ability of a 3D-expanded placenta-derived stromal cell product, PLX-R18, designated for the treatment of hematological disorders, to alleviate symptoms in the H-ARS mouse model. Studies support the conclusion that PLX-R18 is a strong candidate for the treatment of H-ARS as well as a plethora of bone marrow failures with similar symptomatology.

PLX-R18 ACTIVITY IN VITRO

In vitro, PLX-R18 cells were shown to secrete hematopoietic proteins, proteins involved in maintenance, renewal, differentiation, and mobilization of hematopoietic cells, such as GCSF, MCP-1, IL-6, and IL-8. In addition, the secretions from PLX-R18 cells have been demonstrated to induce bone marrow migration through transwell inserts and to stimulate colony formation. Therefore, their ability to secrete regenerative proteins that positively impact the hematopoietic process supports their potential as therapeutics for indications involving failure of the hematopoietic process.

PLX-R18 RESCUE OF HEMATOPOIESIS IN VIVO

PLX-R18 efficacy in rescuing hematopoiesis was tested in a well-characterized model of lethal irradiation in collaboration with NIAID and with Hadassa Medical Center. Administration of PLX-R18 intramuscularly to mice 1 and 5 days after total body irradiation (LD70/30) significantly increased survival and rescued


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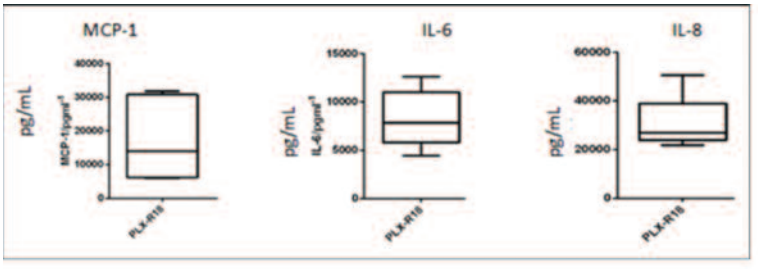
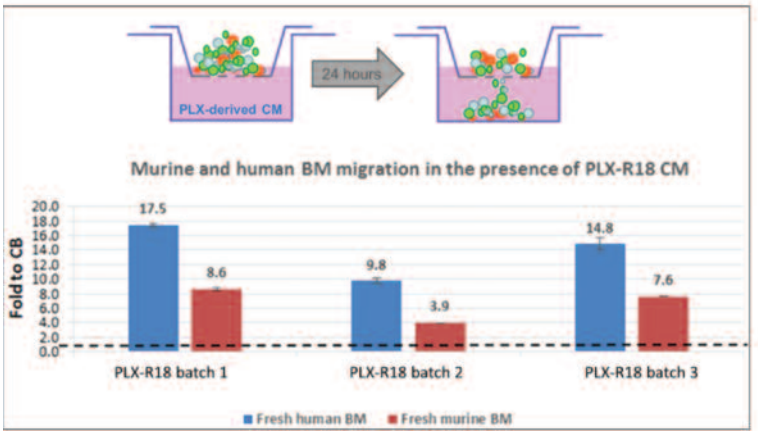
"Cell therapies have the potential to rescue hematopoietic failure based on a complex mechanism of action, involving numerous secreted proteins released from cells that react to their in vivo environment. Pluristem has tested the ability of a 3D-expanded placenta-derived stromal cell product, PLX-R18, designated for the treatment of hematological disorders, to alleviate symptoms in the H-ARS mouse model."

radio-induced weight loss relative to vehicle-injected controls. Similar results were seen when cells were injected on days 2 and 5 after irradiation, indicating that a window of time exists during which therapy can still be effective in case of lethal irradiation.[2] In addition, cell treatment significantly increased the number of colony-forming hematopoietic progenitors in the bone marrow and raised peripheral blood cellularity to values near those of un-irradiated control values.

In vivo secretion studies indicate that PLX-R18 cells responded to radiation-induced hematopoietic failure by transiently secreting haematopoiesis-related proteins to enhance reconstitution of the hematopoietic system. The PLX-R18 cells secreted factors that induced the early secretion of endogenous (mouse-derived) hematopoietic factors (such as KC, IL-6, and G-CSF) in irradiated mice. These factors were secreted on days 2-14 after irradiation in treated mice (peaking on day 4-9), whereas in untreated animals they peaked much later (at around day 16) in those animals which survived to this time point. Secretion of exogenous (PLX-R18-derived) and endogenous (mouse derived) factors enables an earlier increase in the number

FIGURE 1





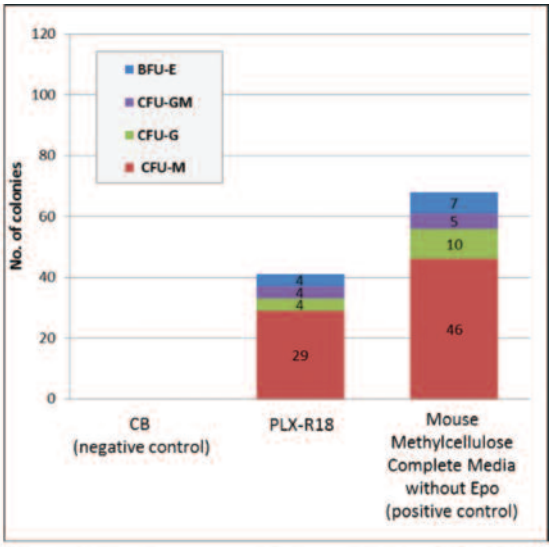


Figure 1. *In vitro* assays indicating potential of PLX-R18 in supporting hematopoiesis. A, Luminex-based measurement of cytokine secretion levels in PLX-R18 conditioned medium. **B,** *In vitro* migration of human and murine bone marrow cells through transwells towards PLX-R18 derived conditioned medium (fold relative to negative control, CB). **C,** PLX-R18 induces formation of various types of colonies from bone marrow.

of multi-lineage hematopoietic precursor cells (HPCs) in the bone marrow and enables the migration of bone marrow cells. Higher levels of cellularity in the bone marrow can be seen on days 4-9 following PLX-R18 treatment, allowing earlier hematopoietic rescue after irradiation. Proliferation, differentiation, and migration of HPCs ultimately leads to an elevation in the levels of multiple blood lineages in the peripheral blood (with significant differences visible on day 23 after treatment). The end result of this regenerated hematopoietic system is a higher survival rate in PLX-R18-treated irradiated mice.

PLX-R18 SAFETY

In vitro studies have indicated that PLX-R18 lacks the ability to differentiate into osteocytes or adipocytes, supporting their proposed mechanism of action of endocrine protein secretion. PLX-R18 cells were proven to have a stable karyotype and to reach senescence, supporting their

FIGURE 2

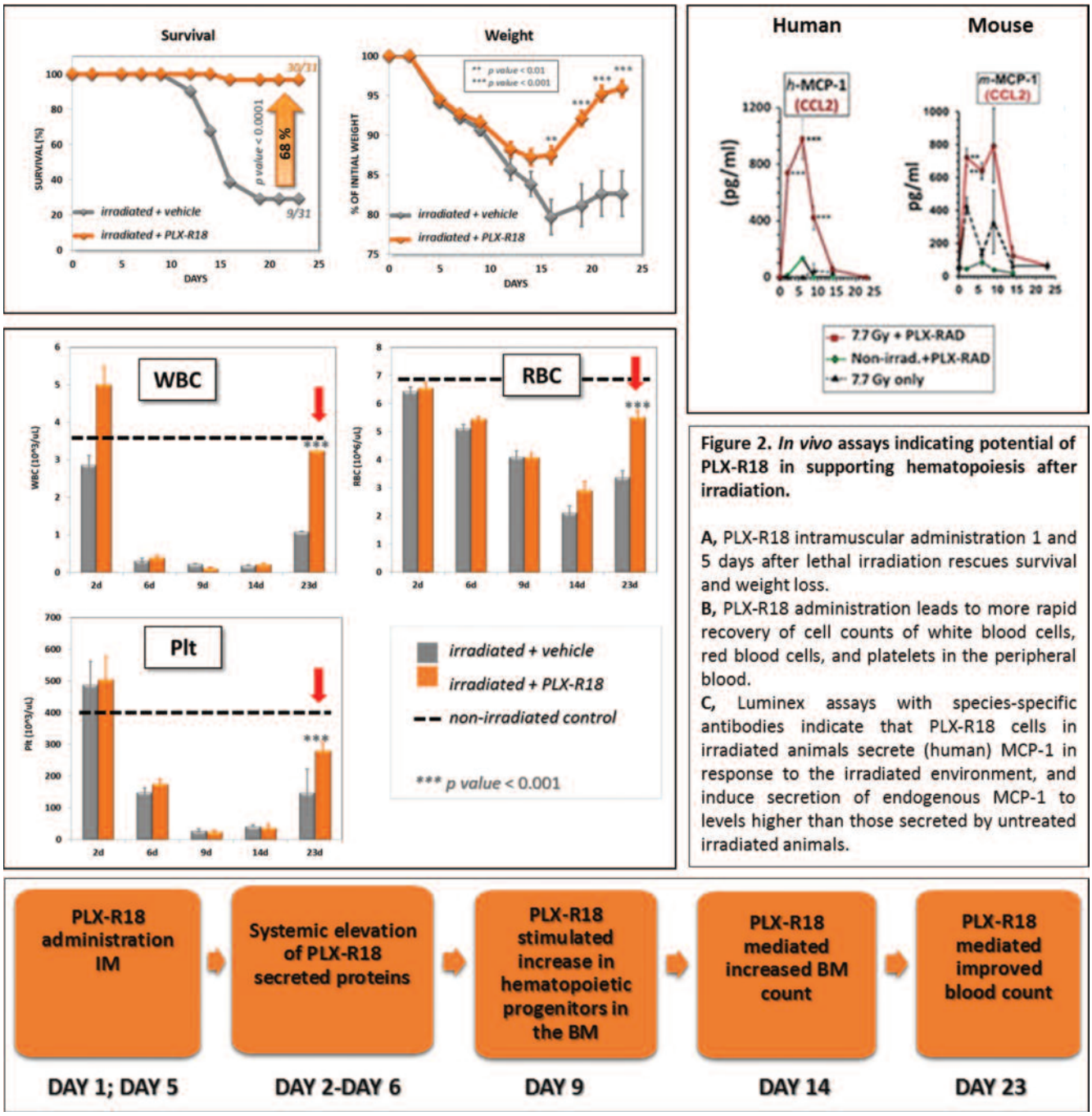


Figure 2. ***In vivo*** **assays indicating potential of PLX-R18 in supporting hematopoiesis after irradiation.**

A, PLX-R18 intramuscular administration 1 and 5 days after lethal irradiation rescues survival and weight loss.

B, PLX-R18 administration leads to more rapid recovery of cell counts of white blood cells, red blood cells, and platelets in the peripheral blood.

C, Luminex assays with species-specific antibodies indicate that PLX-R18 cells in irradiated animals secrete (human) MCP-1 in response to the irradiated environment, and induce secretion of endogenous MCP-1 to levels higher than those secreted by untreated irradiated animals.

safety for clinical use. PLX-R18 cells do not express HLA class II molecules or co-stimulatory molecules, supporting their use as an off-the-shelf allogeneic product. Safety studies in vivo have indicated no treatment-induced toxicity or pathologies, and biodistribution studies indicate that the PLX-R18 cells remain localized to the site of injection within the muscle. Therefore, clinical use of PLX-R18 by intramuscular administration is not expected to have any associated safety concerns.

CONCLUSIONS

Taken together, placenta-derived stromal cells have the capacity to alleviate bone marrow failure symptoms arising from acute radiation by systemic secretion of proteins. PLX-R18 can be safely used as an off-the-shelf allogeneic treatment, enabling Pluristem to harness the power of cell therapy to provide next-generation treatment options for ARS. This new generation of therapies secretes multiple proteins with hematopoietic potential and naturally responds to the in vivo environment in real-time. The US National Institutes of Health's NIAID is initiating dose evaluation studies of PLX-R18 in ARS as a basis for a potential pre-marketing trial in a large animal model. ◆

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BIOGRAPHIES

Dr. Racheli Ofir joined Pluristem in 2007, serving as Vice President of Research and Intellectual Property. She is responsible for leading projects involving the characterization of PLX cells, Pluristem's leading placenta-derived cell product candidate, including evaluating the biological activity of the cells in in vitro and animal studies. She is also responsible for the studies that determine the safety profile and pharmacokinetics of PLX cells and is in charge of all preclinical aspects of the PLX regulatory process and for the communications with the relevant regulatory authorities. She has applied and prosecuted over 10 patent families filed worldwide, is co-inventor on five patent applications, and is co-author of numerous peer-reviewed articles. Dr. Ofir earned her PhD from the Technion, Israel Institute of Technology, where she investigated Telomeric position effects on gene expression and DNA replication in Human cells. She completed her post-doctoral fellowship at the Technion in Molecular Embryology, investigating genes involved in early development of vertebrates' nervous system.

Dr. Noa Sher is the Product Profile Research Manager at Pluristem Therapeutics, responsible for all in vitro and in vivo studies involving mechanism of action, safety, and efficacy of Pluristem's two lead products, which are currently in clinical trials. She previously headed the University of Haifa Bioinformatics Service Unit, and served as Deloitte's Incentives Department Life Sciences expert. She completed her post-doctoral training at the prestigious Whitehead Institute for Biomedical Research and at the Technion – Israel Institute of Technology, where she led several multidisciplinary research efforts to address long-standing problems in developmental biology and to develop a single cell transcriptomics assay, which is widely used and cited in the field. She earned her PhD in Biochemistry and BSc (summa cum laude) from the Hebrew University, Jerusalem, Israel. She has received many excellence scholarships and prizes throughout her career and has published numerous works in high- impact journals.

PATIENT-CENTRIC TECHNOLOGY

How Technology Can Impact Patient Adherence: Increasing Patient Engagement & Education to Save the Healthcare Industry Billions

By: Andrew W. Dunning

INTRODUCTION

Poor patient compliance and adherence cost the healthcare system more than $564 billion annually. It is important that pharmaceutical brands and healthcare providers (HCPs) leverage technology to help reduce primary non-adherence, also known as Rx abandonmentt and improve adherence to treatment at a patient's initial diagnosis. To accomplish this, more brands are embracing patient-centric technology as a marketing strategy. An influx of new biologic and biosimilar medications are about to hit the market, making patient-centric technology programs an impactful marketing strategy for brands looking to stand out from the competition. Brands are leveraging these technologies to streamline patient access to complex drug therapies, correctly train patients on how to administer treatment, and engage with patients through mobile applications.

As healthcare costs continue to rise and adherence rates fall, the resource strain on the healthcare system has led to more scrutiny of specialty and highly managed drugs. Some of the challenges associated with these issues can be overcome by simplifying the prescribing process and enrollment into appropriate patient support services. This has become increasingly important as HCPs experience tighter time constraints and higher volumes of patients, resulting in decreased interaction between patients and HCPs.

Technological advancements are rapidly changing the way HCPs practice, drug companies market, and patients engage with the healthcare system. While there is a wide variety of technologies available to healthcare stakeholders, below are several examples of technologies that specifically cater to pharmaceutical brands that want to leverage a patient-centric marketing strategy to increase their market share and boost patient adherence rates.

PATIENT-FOCUSED PRESCRIBING WORKFLOWS

Specialty and highly managed medications that utilize efficient prescribing workflows, either in a portal or within their EHR, offer HCPs, patients, payers, and pharmacists a more seamless and transparent experience. In fact, according to an American Society for Quality (ASQ) survey, 69% of respondents noted that efficient EHR technology has the ability to eliminate time-consuming tasks and reduce costs for healthcare organizations, allowing HCPs to focus on patient care. Traditional patient access models and tools available to prescribers of these drugs have been the pen, paper enrollment forms, and fax machines. Some of the primary pain points associated with this traditional model include, but are not limited to, incomplete Patient Enrollment Forms (PEFs), communication gaps, and timeliness revolving around the transition of care, and locating appropriate injection center locations.

Unlike the linear paper-based process, technology like iThis has become increasingly allow these services to happen in tandem and has been shown to accelerate time-to-therapy and reduce Rx adandonment. Leveraging technology to replace

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paper-based processes relieves administrative burden and shifts valuable healthcare resources to direct patient care. Also, converting paper-based processes to technology-based workflows and integrating them within the HCPs EHR creates an opportunity to generate valuable real-world evidence (RWE) that can be used to improve patient compliance, adherence, and health outcomes.

Features That Impact Patient Adherence

Brands should select technology solutions that multi-task to simplify patient access and improve patient adherence. Specialty and highly managed medications often require additional steps during the prescribing process that can result in patients waiting extended periods of time before beginning therapy. It is important that technology is capable of more than simply reducing the time it takes for patients to initiate treatment; it should reduce the burden on HCPs prescribing medications and facilitate enrollment of patients in various patient support services.

Selecting the right portal or EHR-integrated workflow that efficiently streamlines the entire prescribing process is a key to success of new specialty and highly managed drugs. These workflows need to automate the majority of the PEF and ePrescribing process. Modules, such as eEligibility to verify patient pharmacy and medical benefits, payer and therapy-specific ePrior Authorization completion, eConsent for HCPs and patients, and digital enrollment in other patient services, all contribute to a smooth and seamless prescribing process.

Using Technology to Improve Care While Complying With Regulations

In addition to simplifying the prescribing process, technology can be leveraged to ensures HCPs are compliant with Meaningful Use and ePA regulations. With the advent of biosimilars and the forecasted growth of the cost of specialty medications to 50% of total spend of the Rx market, it's imperative that pharmaceutical brands utilize the most efficient technologies available to them — and that HCPs become familiar with these processes, including ePA in anticipation of such increased demand.

ePA transforms the paper-based PA workflow into an electronic process that minimizes prescription abandonment and administrative waste. With enhanced accuracy and efficiency, easy-to-use workflows streamline the process for ePA and affords HCPs more time to focus on direct patient care. For HCPs, using ePA allows them to make the best decision for the patient without the hassle of calling in or faxing the prescription. If implemented properly, the ePA process provides real-time decision support by submitting the PA to the patient's payer during the e-prescribing process and proactively asks the HCP for the required information. As a result, patients avoid a delay in receiving medication and are less likely to abandon therapy. Using a workflow with a built-in ePA feature also enables pharmacists to fill prescriptions quicker. This means that patients begin therapy sooner, understand their payer coverage, and therefore are potentially moreadherent throughout treatment.

Connecting All Stakeholders to Improve the Patient Journey

By leveraging the power of technology to connect all stakeholders involved in delivering specialty care and creating the most successful outcomes for patients, communication is streamlined throughout drug delivery. With enhanced accuracy and efficiency, EHR-integrated workflows have the ability to replace long paper process, ensuring patients receive their prescribed medication much quicker than they would through standard practices. Accelerating things like electronic prescribing, electronic patient consent, ePA, real-time patient benefit eligibility queries, digital enrollment into therapy support programs, and more, HCPs are able to focus on patient care, which results in happier patients, improved adherence, and potentially imporved patient outcomes.

TRAINING TECHNOLOGY FOR DRUG DELIVERY

Another common thread in the pharmaceutical drug market is the need for device training solutions that connect and resonate with patients, while effectively communicating brand values and benefits to HCPs. Traditionally, products fulfilling these needs have been restricted to rep-delivered or direct mail pieces that have struggled to improve patient behaviors and error reduction. The experts in training device technology at Noble have acquired a deep understanding of how patients learn, combined with knowledge of patients' emotional and behavior patterns that occur after the point of diagnosis and throughout their treatment. Integrating effective training solutions ensure that patients receive consistent and relevant information at onboarding and throughout their treatment.

Prioritizing the Onboarding Experience

The ultimate goal of using training devices is to ensure that patients are autonomous in their treatment, or have the ability to consistently and effectively administer a prescribed dose free of error. In order to achieve this goal, patients progress through a number of learning stages in which motor and muscle skills are acquired and confidence is built. The early stages of this learning process is known as onboarding, or the first 30 to 90 days of treatment. Errors experienced during the onboarding phase are frequent in nature, but are often avoidable by using the proper training tools and protocol. The use of smart and sensor technologies monitor patient behaviors and provide corrective feedback when a step is out of sequence or self-administration is insufficient. Such an approach provides patients the support needed to efficiently learn how to use their drug delivery device and autonomously manage treatment.

Considering Emotions & Human Factors

After much success in these areas, companies are focusing their attention on improving the patient experience within this delivery market. This requires a patient-centric approach to drug delivery, which begins with understanding of the stages patients pass through during treatment. This begins with the initial diagnosis and extends through the total lifecycle of a patient's treatment. A number of human factors must be considered when applying a patient-centric approach. The emotions experienced during these processes are unique to each stage and often require specific educational approaches to fully address. Emotional stressors, such as fear and anxiety associated with self-administration, lack of experience with drug delivery devices, and poor muscle memory impact the safety and effectiveness of administering the medication. If factors such as these are not taken into consideration prior to the onboarding process, patients may show avoidance behaviors that may lead to low adherence rates.

Impactful Value

In today's market, a growing number of patients are being prescribed self-administered drug treatments. In order to ensure high levels of adherence, brands should prioritize the onboarding experience and ensure that everything is done to set patients up for the most successful drug treatment process possible. By utilizing training technology to educate patients prior to treatment, they have the opportunity to become familiar with the drug delivery device so that they learn and anticipate the steps necessary for proper drug administration. A study conducted by Noble found that 64% of users reported having a training device to practice with at home, prior to beginning treatment, would help decrease anxiety, and therefore improve adherence. Pharmaceutical companies that prioritize the patient experience by using training technology to help these patients properly onboard to therapy will continue to benefit from competitive advantages and the value they create.

LEVERAGING MOBILE TECHNOLOGY TO INCREASE PATIENT ADHERENCE

In today's connected world, pharmaceutical brands can also look to mobile applications in order to increase patient adherence throughout the drug therapy treatment process. Applications, such as Mango Health, use software rooted in game design to inspire patients with chronic conditions to think differently about how they manage their health and drug therapy programs. Focused on medication management and adherence first, because this is the most critical step toward better health for millions who suffer from illnesses, the technology enables pharmaceutical brands to build relationships with patients through daily support as they navigate the management of their drug therapies.

Using adherence applications during the onboarding process, patients are able to create healthy habits that follow them throughout the treatment process in order to ensure successful outcomes. Some functions within this technology include routine scheduling, setting reminders, receiving important information, and earning incentives for staying on track with therapy.

Scheduling and reminders allow patients to create a map of their healthy habits by recording health data, such as weight and blood pressure, and setting alerts for when it is time to take medications. Patients also have access to all the information they need to understand medications, including drug interactions and side effects. Lastly, patients are motivated to maintain their health habits by earning points to unlock incentives, such as gift cards and charitable donations. By leveraging mobile applications that help patients establish healthy habits during the onboarding process, pharmaceutical brands have the ability to boost adherence throughout the duration of treatment.

Collecting Data to Improve Adherence

One challenge commonly seen in the pharmaceutical industry is the inability to track patient data throughout the drug therapy process. Mobile adherence applications enable pharmaceutical brands and HCPs to gather this valuable data. The technology utilizes commercial programs that involve data integrations with industry partners to create better experiences for patients. This often includes functions to deliver pre-populated medication lists, in-app refills, and targeted content to on-therapy patients. By offering applications that patients use on a daily basis, pharmaceutical brands can access unique patient data that triggers earlier, more effective patient interventions. These interventions can be based on any combination of daily activity in the application. For example, when a patient misses consecutive doses of medication or receives poor lab results, HCPs are notified so that they can connect with patients to ensure treatment adherence.

Data collected through the Mango Health app shows that the technology does, in fact, boost patient adherence and engagement. The application has a 1-year return rate of 34%, meaning that one-third of patients who sign up still utilize it after 1 year. As a reference, typical mobile game applications see 1-month return rates of approximately 30%; this data reveals that the application is able to keep a significant number of users engaged with the drug therapy treatment. The application also sees an average of 17.1 sessions a week per user, which indicates that these patients are utilizing the application's features at least twice each day. Additionally, more than three-fourths of monthly patients that use the application, interact with it at least once per day. These data points reveal that technology has the ability to encourage greater patient engagement while collecting valuable information about patient habits that enable HCPs and pharmaceutical brands to stay up-to-date on patient adherence and compliance.

LOOKING TO THE FUTURE

Many long-standing biologics are facing biosimilar competition in at least one or more of their indications, resulting in significant the need to simplify access programs and differentiate based on patient support. As patient access and treatment choices expand, the importance and value of patient onboarding will continue to grow as a competitive differentiator and key driver of patient outcomes and effective disease management. Prescribing and patient onboarding are critical stages that shapes users perceptions and attitudes toward treatments. Technology offers the best hope of simplifying patient access, improving adherence rates, and improving healthcare outcomes. ◆

BIOGRAPHY

Andrew W. Dunning is Vice President, Strategic Development for AssistRx with more than 20 years of experience in the biopharmaceutical industry, including the access and reimbursement of specialty drugs, domestic and international strategic marketing, and most recently, health information technology (HIT). Mr. Dunning started his career with Merck as a Managed Care Analyst and eventually "carried the bag" as a sales representative. Following Merck, he held various positions with advertising and strategic agencies, where he partnered with brand teams to develop brand strategy and execute marketing plans. In his career, he has launched several specialty oncology and immunology products, including the largest oral oncolytic distributed through the specialty channel. Prior to joining AssistRx, Mr. Dunning was the Senior Director of Strategic Development for Practice Fusion, the largest cloud-based EHR in the US. He made the jump from traditional marketing to HIT to help brands understand how to leverage HIT for marketing and translate the value of data into actionable insights. Mr. Dunning earned his BA in Communication Studies from Bloomsburg University of Pennsylvania and attended the University of Central Florida for graduate studies in healthcare administration.

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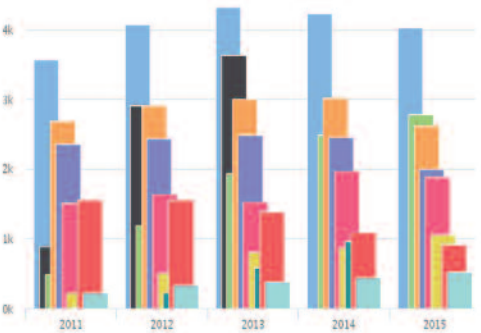
- Find and compare contract manufacturers and other outsourced services
- Assess competitive landscapes around an indication and research competitor pipelines
- Track generics and biosimilars, and identify Rx to OTC switch opportunities



Dynamic, customizable data display

Easy to Use Apps

Prospector
Search on industry sector, indication, route, most advanced phase and molecule/API type. Find companies within the search criteria in any region of the world by drawing a circle around the location of interest. Click for detailed information on companies within the selected search parameters and geographic area.

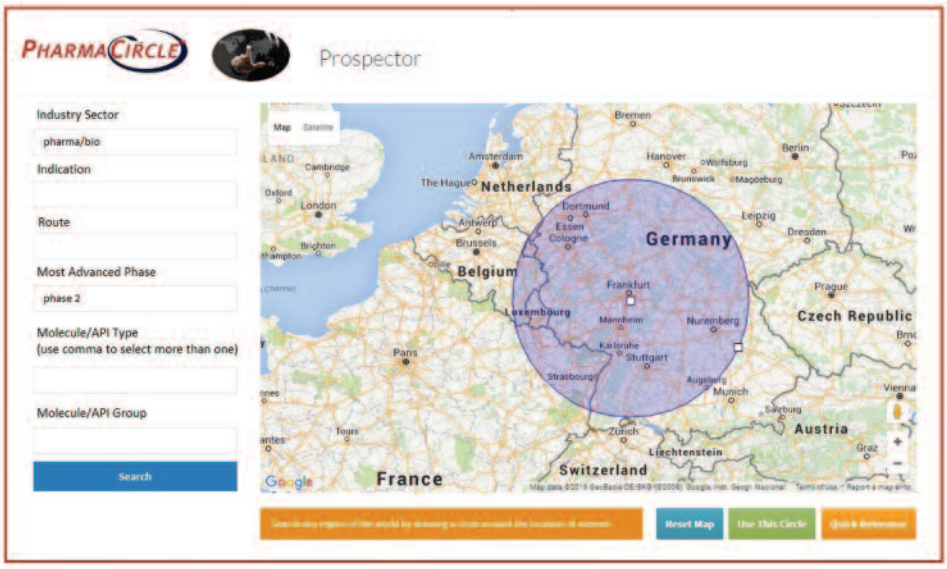
Spyglass
Create your personal watch list and track up to 30 indications, companies and products. Receive latest industry news with daily updates on your selections.

Timescape
View development timeline. Chart phase dates by region/country. Export chart as an image file and underlying data to an Excel spreadsheet.

Label Comparison
Compare current and previous versions of the label for the same product with changes highlighted, and view labels for different products side-by-side. Export comparisons to Excel and PDF.

Reconnaissance
Quick view and instant analytics on the competitive landscape around an indication, competitive intensity within an indication, and competitor pipelines across indications. Chart drugs and biologics by owner companies, highest development status within the indication, mechanism type, NME/ Generic/OTC, route, and dosage form. Programs/products are linked to development summaries.

Merge Simulator
Create a virtual company incorporating global assets of two business entities. Overlay and analyze pipeline/product, technology, operations, financial, deals and investments details to assist with initial due diligence on prospective acquisitions and mergers.



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SPECIAL FEATURE

Bioavailability & Solubility: New Approaches to Enhance Drug Performance

By: Cindy H. Dubin, Contributor

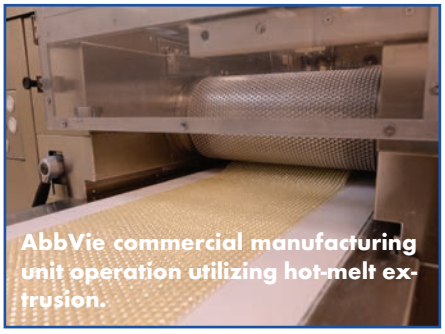
Among all newly discovered chemical entities, about 40% are lipophilic and fail to reach the market due to their poor water solubility.[1] And the future pipeline is estimated to comprise 90% poorly soluble compounds, according to Bryan Wiesner, Director, External Development and Outsourcing, AbbVie.

Solubility issues complicate drug delivery but there is an array of techniques available to enhance solubility and improve the bioavailability of these drugs. This annual *Drug Development & Delivery* report highlights many of those techniques, how to determine the right technique for your compound, and how some pharmaceutical companies are realizing faster time to market as a result.

AbbVie: Hot-Melt Extrusion is a Viable Solution for Poorly Soluble Compounds

Hot-melt extrusion (HME) is a proven, enabling technology for enhancing the bioavailability and solubility of solid oral doses, including potents. AbbVie was an early adopter of HME technology for formulation development and dosage form for several reasons:

- As a solvent-free technology, it is environmentally friendly;
- Once developed, it is an extremely robust and reliable process;
- Continuous processing makes it a more economical method of manufacturing;
- It is accepted by regulators globally; and
- It has applications for abuse deterrence and taste masking.



AbbVie commercial manufacturing unit operation utilizing hot-melt extrusion.

"HME, an amorphous dispersion technology, uses pharmaceutical-grade polymers to formulate insoluble or poorly soluble drug molecules," says Mr. Wiesner. "This dissolves and distributes the API through a specialized matrix, using heat and shear energy, to form a solid solution of known potency and uniformity. This improves efficacy and drug delivery efficiency. The extrudate can be subsequently formed into tablets, multilayer tablets, and capsules, even with advanced profiles like dual API in a single dose or API coatings on a core."

HME has been used to improve drug performance and patient compliance by reformulating drugs as controlled or modified release to reduce daily dose requirements, or, for example, to avoid the need for refrigeration or substantially reduce daily pill burden rates, says Mr. Wiesner.

ABITEC: Lipid Excipients Enhance Permeation & Increase Bioavailability

The challenges facing the successful formulation of poorly soluble, lipophilic active pharmaceutical ingredients (APIs) can be complex and multifactorial. Perhaps the most critical barriers to overcome in a successful formulation are enhanced drug

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- **Pharmaceutical Impurities**
- **Legal and Policy Strategies for Drug Companies in Today's Global Market**
- **Accelerating Your Product's Development: Practical Considerations from Pre-Clinical through Commercial** Sponsored By: Catalent
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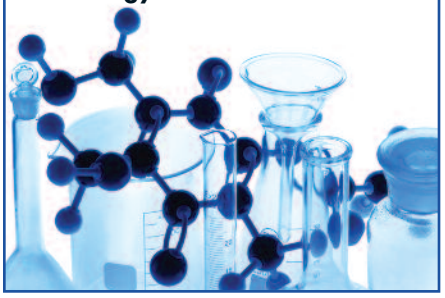
ABITEC is enhancing bioavailability and solubility through lipid technology.



permeation and increased bioavailability of the active. While there are approaches capable of improving drug dissolution, there are relatively few that can improve drug permeability, claims Dr. Donald Kelemen, Head of Corporate Business Development, ABITEC Corp. Rarer still are excipients that improve dissolution and permeability, are part of normal human physiology, and are capable of negating the food effect and protecting the Active Pharmaceutical Ingredient from degradation in the GI tract. "Functional lipid excipients can provide for all of these benefits," says John K. Tillotson, RPh, PhD, Pharmaceutical Technical Business Director, ABITEC Corp. "By dissolving the API in a lipid-based preconcentrate, an oil-in-water emulsion can be generated in the GI tract with the active ingredient molecularly dissolved or dispersed in the lipid phase of a micellar system." Depending upon composition, these micelles can offer several functional advantages, including serving as a protective environment for the API, instilling permeation enhancement for polar actives through reversible tight junction modulation, and as a substrate for mitigating the impact of P-glycoprotein efflux.

ABITEC develops lipid-based excipients to enhance bioavailability of poorly water soluble and poorly permeable molecules for the pharmaceutical industry. The excipients are manufactured in accordance with strict cGMP and applicable IPEC (International Pharmaceutical Excipient Council) guidelines in ISO-certified facilities. Recently, ABITEC has expanded its manufacturing capabilities to provide greater flexibility to serve our customers throughout development from preclinical to commercialization.

"ABITEC supports the needs of the formulators by developing and providing applications research, investing in manufacturing agility, and innovating to develop new product lines that meet the changing demands of our customers," says Dr. Tillotson. "Through research partnerships with major universities, we develop new applications papers and guidance on solubility, phase behavior, and permeability of functional lipid formulations that are available to formulators and provide a starting point for formulation development."

AMRI: A Systematic Approach to Formulation

With the increasing number of new chemical entities that may belong to BCS Class II and IV, a formulator rarely gets the opportunity to develop a simple oral solution. The high number of poorly soluble compounds in the industry is leading to the growing need for developing enabling technologies. Understanding the chemical and preformulation property of the API is the first step toward identifying a suitable enabling technique to enhance solubility or bioavailability. Underlying variables and their relationship to product performance and manufacturing needs are also important considerations. A systematic approach for handling formulation issues is required.

A primary driving factor for determining the best formulation approach is to assess the dose/solubility ratio, explains Amol Matharu, PhD, Senior Director, Pharmaceutical Development, AMRI. The maximum absorbable dose is directly related to the solubility, absorption rate, GI volume, and GI transit time. Physiology of the GI tract also plays an important role. For example, the pH change during GI transit can induce precipitation of weakly basic compounds (pKa > 6) and increase solubility for acidic ones (pKa < 5). An experienced and qualified lab should be used to design the biorelevant tests, such as dissolution conditions, to better estimate *in vivo* product performance.

Identifying the conditions limiting oral absorption is critical to elaborate the mitigating strategies. For a dissolution rate-

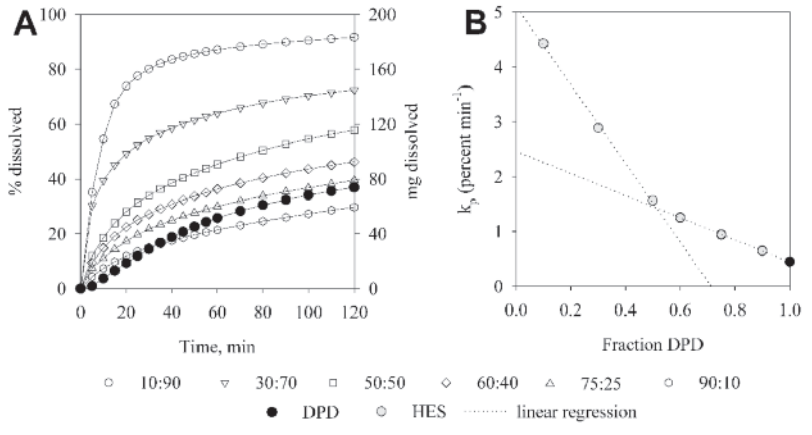


Table 1: (A) Dissolution of API formulated as High energy solids (HES) can be modified by modulating drug:polymer ratio, which can (B) be used to understand and adapt its release mechanism (kp is the dissolution rate constant).

limited system, where the compound is not fully dissolved in the absorption window (dissolution time is greater than transit time), mitigation strategies include salts, a polymorphic form, particle size reduction, surfactants, polymers, amorphous API, and complexation. In a solubility-limited absorption, where there is incomplete exposure of the drug (absorbed dose is less than total dose), the problems can be mitigated using lipids, a prodrug, solid dispersion, and solid state forms. Finally, for permeability-limited absorption, where there is poor absorption, the main strategies involve using prodrugs or permeability enhancers.

Based on needs and the API properties, some of the enabling techniques utilized include lipid-based drug delivery systems, solid dispersions, nanoparticles, long-acting injectables, and solid oral controlled release formulations. Several examples from AMRI's experience: A poorly soluble API at preclinical development was formulated as an oral solution in Capmul/Labrasol for a tox study and a PK study; and a micronized API in capsule was developed for a Phase I clinical study. In another case, to improve bioavailability of a poorly soluble drug, a high-energy solid was evaluated in which API was dispersed in polymers through spray drying. As illustrated in Table 1, dissolution of API was modified by modulating drug:polymer ratio. A blend-in-capsule formulation was developed using the high-energy solid for a Phase I clinical study. In the third case, when cosolvents, lipids, surfactants, and complexation techniques alone failed to improve the solubility of an API, a combination approach was used to improve the solubility 80,000 fold, giving an oral solution drug product using a measured balance of various excipients serving defined roles — for example, a mix of dimethylacetamide, Labrasol, and Tween 20 or Tween 80. The formulation was physically and chemically stable and ready for dosing in the preclinical study. In another project, suitable drug exposure was maintained by formulating a long-acting injectable suspension. Careful modulation of the zeta potential and mixing parameters yielded an elegant flocculated drug product utilizing a rugged, reproducible, and scaleable manufacturing process.

Not all solubility problems necessarily involve BCS class II and IV compounds. For instance, one project involved developing a controlled-release tablet for an API that is highly unstable and water soluble. While various matrix-forming agents were evaluated, none were effective to achieve a target release period of 24 hours. "Exploiting the chemical properties of the API, acid-derivatized complexing agents were utilized to slow the release and achieve a stable product with a desirable dissolution profile," says Dr. Matharu.

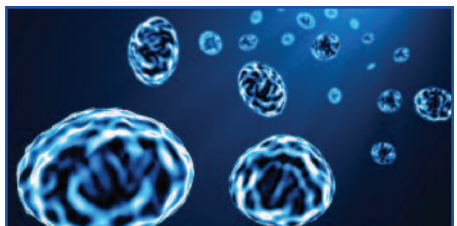
Ascendia: Nanoparticles Hold Promise for New Compounds

As a specialty CDMO, Ascendia focuses on creating formulation solutions for poorly water-soluble molecules. Some of the newer approaches the company offers include nanoemulsions and solid-lipid nanoparticles. "The goal with nano-emulsions is to dissolve and stabilize the drug in a suitable oil vehicle, and then produce oil-in-water nanoemulsions using either a high-shear homogenization or a micro-fluidization process," explains Jingjun "Jim" Huang, CEO of Ascendia.

Minimizing the amount of co-surfactants and co-solvents required for long-term physical stability is a key strategy. With solid-lipid nanoparticles, the surface area advantage of nanoparticles is extended by having the drug homogeneously dispersed in a lipid carrier before nanonization. An alternative is to coat a drug nanocrystal with a lipidic material prior to final dosage form preparation. Both nanoemulsions and nanoparticles can be administered orally or via injection. Solid-lipid nanoparticles are especially useful for long-acting injectable formulations of poorly soluble drugs, he says.

"Many emerging pharmaceutical companies have promising compounds that require novel delivery science to achieve their bioavailability targets," says Dr. Huang. "Ascendia helps clients determine the best formulation approach by investigating multiple options. While we have capabilities in spray-drying, hot-melt extrusion, ball-milling, micro-fluidics, and homogenization, it is not always obvious which technical approach will optimize a drug's performance. Ascendia accelerates development time by conducting formulation comparisons and selection in parallel."

Combinations of excipients and approaches can lead to new intellectual property for a drug's formulation. For example, for one client, Ascendia developed a nanoemulsion formulation of a drug that has only 3ng/ml water solubility. This drug exhibited significant dose proportionality and food-effect issues. Ascendia experimented with a matrix of oils and surfactants to develop several prototype formulations. In the oil phase of the na-



Ascendia's NanoSol nanoparticle technology.

"Excipients play an important role in formulation and drug delivery, but their role is sometimes limited in certain dosage forms because of regulatory restrictions." Shaukat Ali, PhD, Technical Support Manager, BASF

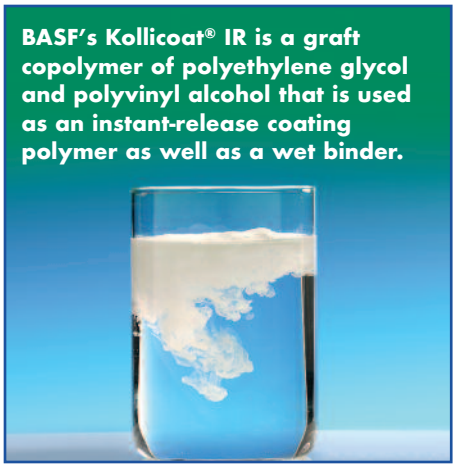
noemulsion, drug solubility was achieved in the 30-100mg/ml range—a 1 million-fold improvement. Multiple formulations achieved good chemical stability, physical stability, and water dispersibility. All of the formulations produced nano-emulsions with droplets sizes less than 1μm, and ranged from as small as 20nm to ~ 700nm. "This feasibility study yielded a viable oral formulation for the client that is now being tested clinically to determine the improvement in dosing kinetics and the elimination of the food-effect," Dr. Huang says.

BASF: Excipient/API Combinations That Expedite Drug Development

Solubility of new chemical entities has been a key issue in drug molecule development. As discovery of more insoluble compounds continues, the industry is adopting more innovative formulation technologies to overcome the solubility and bioavailability challenges to make them commercially viable and FDA compliant. These new approaches are opening doors to more than 80% of NCEs in the pipeline that would otherwise have a modest chance of succeeding, says Shaukat Ali, PhD, Technical Support Manager, BASF. These include solid and liquid dispersion technologies for the development of tablets and soft gels, solvent-free temperature-controlled hot-melt extrusion and shear stress-driven Kinetisol® solvent-based spray drying and electro-spraying technologies. Lipid-based liquid dispersion formulation technology, such as self-emulsifying and micro-emulsifying drug delivery systems, is also employed for the more insoluble NCEs to speed up development cycles.

BASF offers a range of excipients for developing oral solid and liquid dosages. The basic screening of excipients is key to the selection of the appropriate formulation technologies or platforms. BASF also provides medium to high throughput API screening services for customers with a range of excipient choices that provides them the flexibility to design the appropriate solid or liquid formulation dosage.

"Excipients play an important role in formulation and drug delivery, but their role is sometimes limited in certain dosage forms because of regulatory restrictions," says Dr. Ali. However, many excipients are multifunctional and can give formulators options. For example, Kollidon® VA64 is a film former–a dry binder–used in both direct compression and roller compaction, and also acts as a solubilizer in the melt extrusion of poorly soluble compounds. Kollicoat® IR, a graft copolymer of polyethylene glycol and polyvinyl alcohol, is used as an instant-release coating polymer as well as a wet binder.



BASF's Kollicoat® IR is a graft copolymer of polyethylene glycol and polyvinyl alcohol that is used as an instant-release coating polymer as well as a wet binder.

"Excipients like Kollidon VA64 and Kollicoat IR are available commercially and have been used in oral solid, liquid, and topical formulations," says Dr. Ali. "Novel excipients, such as Soluplus®, address the specific requirements of APIs where standard excipients are not as effective."

He continues: "Our technical and processing know-how and the understanding of excipient chemistries and functionalities enable formulators to efficiently identify the optimal API/excipient combination that expedites drug development," says Dr. Ali. "For instance, to identify the appropriate polymers or solubilizers for solid or liquid dispersions, screening a broad range of excipients from our portfolio is important to select the ideal candidates for an optimal formulation."

Capsugel: A Vertical Approach to Avoid Risk During Scale-Up

Capsugel helps customers formulate and advance challenging compounds in many ways. Its core approach to product development accounts for three interconnected themes: Upfront rational formulation design that is based on science, the needs

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A customized pharmaceutical spray dryer at Capsugel's Bend, OR facility.

of the molecule, and the needs of the finished dosage form. "This approach translates to greater speed to clinic and market, while our focus on rational design is well suited to meet the market's demand for more specialized products for specific patient population groups," says Hywel Williams, PhD, Principal Scientist, Research and Development, Capsugel.

Capsugel's range of enabling technology addresses slow dissolution rate and/or low solubility (often linked to low oral bioavailability) or to modulate the pharmacokinetic profile of a compound. "We have strategically invested to support client programs from early development through clinical testing and into commercial manufacturing," says Dr. Williams. "Having a vertically integrated offering can also minimize program complexity and risk by avoiding potentially problematic technology transfers during scale-up."

Ensuring that a client's compound is sufficiently bioavailable via the oral route has many dimensions–and is sometimes not limited to addressing dissolution rate or low solubility–requiring that other biopharmaceutical aspects be considered. For example, achieving high bioavailability combined with low variability and minimal local toxicity may require one or more of the following approaches:

- Transient increases in intestinal permeability, e.g., for compounds that are large/ionizable/efflux transporter substrates;
- Recruitment of the bile salt/phospholipid conduit to boost absorption in the fasted-state to mitigate food-effects;
- Targeting of a specific gut segment to exploit a compound absorption window;
- Bypass a specific gut segment to minimize local irritation or compound degradation, or to maximize local compound effects in lower GI segments; and/or
- Access the lymphatic system to reduce first-pass metabolism.

"Our product development teams have encountered myriad combinations of compound characteristics and drug delivery challenges," he says. "This experience is proving crucial in addressing the obstacles associated with increasingly complex molecules and specialized applications."

In addition to broadening its understanding of formulation, biopharmaceutics, and processes, Capsugel is investing to expand the formulation and processing space of its core technologies to meet the wider requirements of customers. These include lipophilic salts for increased dose loading using lipid-based formulation approaches, and spray dried dispersion "Hot Process" technology for compounds with low organic solvent solubility.

Catalent: A Range of Enabling Technologies Reduce Risk, Improve Time to Market

As the cost of drug development rises, and as companies look to develop drugs for smaller populations, there is pressure to do more with less, to make decisions with the minimum of data and without delay, and to try to manage the inevitable risks. This often means relying on well-known and predictable approaches. But drug companies look to new technologies to provide patent protection, protect the value of their investment in the long term, or to widen the net where standard technologies have been tried and unsuccessful.

Catalent has assembled a range of enabling technologies to support these developments. Platform screening protocols help quickly and inexpensively collect data to determine which approaches are most suitable and which molecules have inherent issues that need to be resolved. "To enhance collaborative scientific development between Catalent, its customers, and partners, we have created a new Science and Technology function to accelerate the development of drug products through the use of advanced formulation and drug delivery technologies," explains Stephen Tindal, Director, Science and Technology at Catalent.

To help companies at the early stage of formulation development, a platform screening protocol called the OptiForm® Solution Suite combines preliminary for-

Catalent offers a range of solubility enhancing technologies, including controlled-release encapsulated granules.

mulation development with a molecule pre-formulation screen. This provides customers with a "toolkit" for improving the bioavailability of poorly soluble drugs using a range of bioavailability-enhancing technologies, including the OptiForm API salt form, particle engineering, lipid-based formulations, and amorphous dispersion.

At the pre-formulation stage, Catalent's OptiForm API solid form optimization includes salt form screening to optimize solubility and stability, as well as polymorph screening to optimize the crystalline form. Originally developed by GlaxoSmithKline, Catalent has refined OptiForm API screening to help more customers speed the development and optimization of their drug molecules. It offers a high throughput platform for salt, crystal-form, and co-crystal screening, and has been applied to more than 500 compounds, spanning from early-stage lead compounds through launched products.

"Our platform screening protocols use minimal amounts of API, are completed quickly, thus saving money," claims Mr. Tindal.

Using OptiForm Solution Suite, customers receive a summary of study results, recommendations, and risk assessment for each dose form option to yield better bioavailability. These include operational considerations, regulatory approval risks, and patient specific considerations. A dedicated scientific advisor works with the customer to review all the data and make recommendations for the customer's team. At the end, the customer receives materials for use in animal pharmacokinetic studies, which can include lipid solutions and/or suspensions, milled solid dispersions, and micronized/milled salt form.

As an example of how Catalent worked with a client to improve bioavailability, consider the case of Trio Medicines Ltd. The company was progressing a pro-

Solubility-enabling excipients turn "brick dust" APIs into therapeutic dosage forms (Dow).

drug API with poor bioavailability through Phase 1. The formulation was sub-optimal. The molecule was classified as BCS Class II. The challenges were limited molecule characterization, fast turnaround, and limited budget. Trio was looking to increase the Area Under Curve (AUC) by three to five times and improve the formulation's robustness. Catalent data revealed that the molecule should be classified as a Developability Classification System (DCS) IIa (i.e. limited by rate of dissolution rather than absolute solubility) with some stability issues (not uncommon for a prodrug). In this study, three of the four candidate formulations showed improved AUC potential. Trio would like to increase AUC further, and is considering its options before deciding on the best formulation with which to proceed.

Dow: Developing Amorphous Solid Dispersion & Manufacturing Technology for an API

In order to improve the performance of a poorly soluble API, it is imperative to formulate a dosage form in a way that enables the API to readily enter solution and be absorbed by the body. Excipients play vital roles in providing functionality to the final drug product to achieve this goal. "For example, through stabilizing the compound in a high energy state for an amorphous solid dispersion, imparting hydrophilicity to the dosage form to promote dissolution, and maintaining dissolved drug in solution to allow for absorption, the API performance can be enhanced," says Elizabeth J. Tocce, Associate Research Scientist, Dow.

Dow Food, Pharma and Medical has introduced a line of excipients to enable formulations of poorly soluble drugs to meet their end targets through not only final dosage form performance but also improved use in manufacturing technologies. The AFFINISOL™ polymers are cellulosic derivatives designed specifically for hot-melt extrusion and spray drying applications. "The AFFINISOL portfolio includes a novel grade of hypromellose, AFFINISOL HPMC HME, that has advantageous thermal properties for hot-melt extrusion and improved solubility in organic solvents for spray drying applications," explains Kevin P. O'Donnell, Associate Research Scientist, Dow.

In addition to the novel hypromellose, there is also AFFINISOL HPMCAS, which is offered in three standard acetate/succinate substitution grades. "HPMCAS, with custom acetate and succinate substitutions tailored to an API to ensure the optimal performance, is supported through a scalable cGMP market development plant," says William W. Porter III, Associate Research Scientist, Dow.

Additionally, Dow Food, Pharma and Medical has technology capabilities and expertise to further assist formulators in developing a robust drug product. In-house high throughput screening techniques can enable rapid identification of the ideal polymer(s) and drug loading to formulate a stable solid dispersion with optimum performance. Once identified, a formulation can be translated to the desired manufacturing technology. For example, a formulation selected for hot-melt extrusion can

Evonik's EUDRAGIT® polymers have been used to facilitate the delivery of the active ingredients to a predetermined area of the GI tract.

be further developed at the laboratory scale for process parameter selection, which is confirmed through scale up when needed.

Evonik: Aiming to Get Formulations Right the First Time

Evonik recently launched EUDRATEC® PEP technology, a versatile formulation toolbox where challenging actives (peptides, proteins, BCS II, III and IV compounds) and functional ingredients are combined in a modular way to meet targeted therapeutic needs. Dr. Firouz Asgarzadeh, Director of Technical Services, Formulation and Application Services, Health Care, Evonik Corp., says that Evonik's EUDRAGIT® polymers have been used to facilitate the delivery of the active ingredients to a predetermined area of the GI tract, as well as for all types of controlled drug release profiles.

"Functional excipients like EUDRAGIT polymers have revolutionized the concept of excipient use in the pharmaceutical Industry. They allow for the successful development of products with improved bioavailability, targeting, and/or patient compliance," says Dr. Asgarzadeh.

Additionally, to support customers in minimizing the number of screening experiments and in the selection of the appropriate combinations of pharmaceutically approved polymers with actives to form solid dispersions, Evonik has developed a sophisticated platform called MemFis® (Melt Extrusion Modeling and Formulation Information System). "MemFis uses solubility parameter calculations and hydrogen bond formation probabilities to screen approximately 30 different polymers in combination with the API to identify the best initial approach for formulating a solid dispersion."

When screening solid dispersion formulations, MemFis allows the selection of the most effective formulations with a minimal number of experiments (typically 3-5) instead of random mixing and matching of hundreds of polymer-drug combinations in an empirical approach.

Evonik has also invested in hot-melt extrusion and spray drying equipment in several of its technical centers to help clients with feasibility studies and formulation development based on MemFis results. "The objective is to offer clients a "first time right" approach to formulation development, enabling shortened development times as compared to conventional random screening methods with a myriad of trial experiments outside of the appropriate design space. This systematic approach saves money and significantly reduces time to market."

Evonik has applied MemFis to numerous customer projects. In one recent study, MemFis was used for a company developing a generic version of an existing commercial HME drug product. "The results from MemFis directed us to a polymer that was not utilized in the original brand product formulation," explains Dr. Asgarzadeh. "Both the initial *in vitro* dissolution and stability studies exhibited better performance of the "super generic" version relative to the branded product. The client is continuing further clinical studies with Evonik's new formulation proposal."

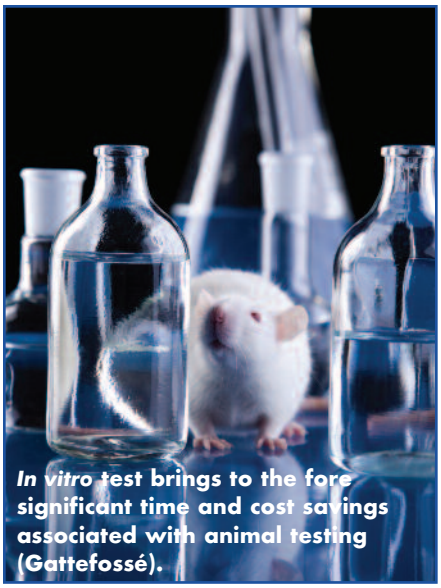
Under a recently formed collaboration with Medimetrics, Evonik offers a combination of controlled delivery options, *in vivo* delivery measurements via wireless communications, and data interpretation with a single-use capsule that is swallowed, called Intellicap®. This service conducts site absorption studies to precisely identify where the drug is best absorbed along the GI tract. Based on the results from these studies, the targeted development of oral controlled release formulations with increased bioavailability can proceed more rapidly, says Dr. Asgarzadeh.

Gattefossé: Taking a Lead on Lipid-Based Formulations

The indisputable fact before the pharmaceutical industry is that a majority of emerging APIs suffer from bioavailability issues attributed to poor solubility, dissolution rate, intestinal permeability, and food effect. A growing number of these compounds are peptides and macromolecules with upward inclination for molecular size, LogP value, and sensitivity to pH and ionization, which may also become substrates for intestinal transporters and enzymatic degradation in the GI tract, explains Jasmine Musakhanian, Scientific & Marketing Director, Gattefossé.

"Hydroalcoholic solvents may improve the drug solubility in the dose but are likely to fail in maintaining the drug in a solubilized state *in vivo*," she says. "Traditional approaches like drug micronization or salt formation may offer tangible but limited value for a small number of drugs. As each API presents its own unique set of challenges, early consideration to the science, timing, and choice of technology becomes critical."

Among the fully developed and in-



***In vitro* test brings to the fore significant time and cost savings associated with animal testing (Gattefossé).**

creasingly popular approaches to bioavailability enhancement is the lipid formulation approach, which is seconded by polymer-based solid dispersion technologies. "Lipid-based formulations are leading the way for bioavailability enhancement because of their unique ability to simultaneously improve intrinsic solubility, enhance solubilization and supersaturation of API *in vivo*, and to protect the API against precipitation or binding to enzymes in the GI tract," says Ms. Musakhanian. "Unlike solid dispersion approaches that require extensive kinetic stability studies, lipid formulations are much easier to develop in soft or hard gelatin capsules. Easy to manufacture and readily scalable, they offer significant savings in development time."

An important and often overlooked benefit of lipid formulations is mitigation of the food effects associated with more than 80% of poorly soluble drugs. Food effect can lead to significant issues during clinical development and post market safety and patient compliance, requiring drug label warnings of intake with meals or on an empty stomach.

Gattefossé specializes in lipid excipients and formulations for addressing drug solubility and bioavailability in oral, topical, and other routes of administration.

Gattefossé offers Preclinical Guidelines for early drug development stages, detailing the appropriate excipient dose per animal model. "Our customers can also tap into our Oral Bioavailability Guidelines where we provide step-by-step approaches to identifying and selecting the most promising combination of drug with excipient(s), how to determine stability and miscibility of excipient mixtures, their particle size dispersion, and *in vitro* lipolysis assays to help predict the *in vivo* performance of prototype formulations," says Ms. Musakhanian.

Gattefossé has worked with global organizations toward the development of predictive tools such as lipolysis (lipid digestion) testing that can help predict the potential *in vivo* behavior of the lipid formulation in humans. "This *in vitro* test brings to the fore significant time and cost savings associated with animal testing, which incidentally is not always predictive of bioavailability in humans," she says.

iCeutica: Accelerate Development of New Chemical Entities

Mechanical particle size reduction of the drug substance is a well-known method of increasing the surface area, thereby increasing the dissolution rate of a poorly soluble compound. Jet milling is the most common and widely available method of particle size reduction, but it is limited to reducing average particle size to 3-10 micron, and the powder is typically difficult to work with due to high static and low bulk density. Wet media milling can yield submicron drug particles, which are stabilized with excipients in an aqueous suspension. The drawback to this technique, says Dr. Maura Murphy, Senior Director of Pharmaeutical R&D, iCeutica, is that the water must be removed by a lengthy granulation process. There are some marketed compounds utilizing this technique, including sirolimus (Rapamune®) and aprepitant (Emend®).

It is also possible to produce submicron drug particles utilizing a dry media milling process, which removes the difficulties of the wet media milling process while achieving similar benefits. iCeutica's SoluMatrix Fine Particle Technology™ is an attritor milling process utilizing ball media and inert GRAS excipients to grind the active to a submicron particle size. Through this low-energy milling process, the excipients that help grind the drug substance remain at 2-10 micron, while the active is reduced to an average of 200-800nm. The excipients also serve to stabilize the drug substance particle size. "In contrast to high energy milling processes such as jet milling, the attritor milled powder has much less static and has moderate bulk density, allowing for much easier handling," she says. The attritor milling process does not typically alter the drug substance crystal structure, ensuring the product remains thermodynamically stable. This technology has been utilized to optimize absorption in marketed compounds such as diclofenac (Zorvolex®) and meloxicam (Vivlodex®).

iCeutica offers development services utilizing the SoluMatrix technology to improve the dissolution rate of compounds for partner companies. iCeutica can conduct rapid feasibility studies, as well as complete dosage form development, clinical study management, and GMP manufacturing up to 150kg scale.

"Improvement of the dissolution rate can enhance drug performance of poorly soluble compounds by improving oral bioavailability, reducing the pharmacokinetic variability, and reducing or removing

food effects," says Dr. Murphy. "A faster dissolution rate can also reduce the time to reach pharmacodynamics effects for compounds with extended Tmax."

Metrics Contract Services: Amorphous & Nanoparticulate Technologies Increase Absorption Rates

Nanoparticulate technology is transforming the industry's ability to successfully formulate poorly soluble APIs. Nanoparticulate formulations of poorly dissolving APIs can provide faster drug absorption and higher bioavailability by increasing the API's dissolution rate. Amorphous nanoparticle dispersions can increase the absorption rate of API while simultaneously stabilizing the amorphous state of the API and its higher solubility.

Metrics Contract Services offers the ability to manufacture spray-dried material or to micronize the API through jet milling, both of which improving solubility and bioavailability and augment Metrics scientists' knowledge of formulating amorphous materials and nanoparticles. The resulting material will be formulated as a capsule or a tablet.

When it comes to developing challenging compounds, it helps if the scientists know whether the client has performed preliminary solubility studies, any kind of simple animal PK studies, or even what the critical quality attributes are, such as modified release or the need to deliver the drug in the small intestine, explains Michael DeHart, PhD, Developmental Scientist II, Metrics Contract Services. "Such information allows us to move projects forward expeditiously without duplicating efforts."

Also challenging is the sheer number of excipients on the market, as well as the different grades available. "Scientists at Metrics Contract Services work closely with our vendors' sales teams and technical support personnel to ensure that we are choosing the optimal excipients from the beginning in order to expedite development," says Dr. DeHart.

One client brought Metrics a prodrug known to be susceptible to acid degradation and general hydrolysis, which meant it had to be protected from stomach acid. In addition, exposure time to fluid in the small intestine needed to be minimal. "We took a two-pronged approach to resolving these issues," explains Dr. DeHart. "First, we knew an enteric coat was essential to provide acid protection. Second, we incorporated muco-adhesive polymers into the core tablet, which helped it adhere to the walls of the small intestine. This allowed the prodrug to permeate across the small intestine, where it then was hydrolyzed to the API. Despite the daunting challenge of preventing hydrolysis throughout transit in the stomach and small intestine, animal studies confirmed that we were able to provide bioavailability of the molecule of interest."

MilliporeSigma: Excipients That Smooth the Regulatory Pathway

Two major factors in determining the success of a drug are the delivery form and bioavailability. Both of these topics are addressed by MilliporeSigma's Actives and Formulation R&D activities.

"The interaction of new technologies and excipients, as well as new formulation approaches, create an increasingly complex scenario," says Andrew Bulpin, Head of Process Solutions Strategic Marketing & Innovation at MilliporeSigma. "A gap in support exists when working with customers to establish formulation techniques and excipients within their R&D platforms using their model APIs. Thus, MilliporeSigma offers pharmaceutical developers support through counseling, hands-on training, and formulation development at our "Formulation Center" at the Darmstadt site, and within our global service network and collaboration centers (M Lab™ Collaboration Centers)."

As a manufacturer of excipients, MilliporeSigma finds the right excipients to boost solubility of APIs, Mr. Bulpin explains. "Poor solubility of small molecules as well as biomolecules is multi-factorial and a one-size-fits-all approach is not applicable. Thus, providing a comprehensive toolbox of products and addressing different solubility technologies and solutions is a must."

However, many of MilliporeSigma's customers are reluctant to use novel excipients, given the regulatory implications. To this end, the company formulates these compounds with proven technologies and excipients, ensuring a smooth path through the registration and approval process, he says. "Our offering of more than 400 Emprove® excipients is focused on exactly that."

Excipients' impact on API bioavailability requires that scientists determine if the API can be formulated with standard formulation technologies or if nonconven-

Formulation development takes place at MilliporeSigma's Korean MLab™.

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tional formulation approaches need to be employed. "MilliporeSigma is working with advanced excipients (Parteck® product portfolio) and formulations that support oral or alternative administration routes that meet the innovator's desire and increase the patient's comfort," says Mr. Bulpin. "We do this by considering modified release approaches and the use of tablets, capsules, or patches instead."

Particle Sciences: A Range of Solubilization Approaches Ensures a Right Fit

As formulation scientists know, solubility is one of the key physicochemical parameters a formulator needs to understand and manipulate in order to develop viable formulations. Particle Sciences (PSI) has a number of solubilization approaches ranging from *in silico* design, to nanoparticulate suspensions, to solid solutions, to lipid-based systems such as LyoCells® (PSI proprietary reverse cubic and hexagonal phase nanoparticulate delivery system). API characteristics will determine which technology is best to use. For instance, a heat stable highly potent compound with a positive logP naturally drives towards hot-melt extrusion. "A relatively labile molecule with good lipid solubility may be a good candidate for LyoCells, and a classic BCS II molecule should always be evaluated for its amenability to be formulated as nanoparticulate suspensions," says Robert W. Lee, PhD, Vice President of Pharmaceutical Development Services, PSI.

Recently, one of PSI's clients had a need to deliver a BCS II API across the blood brain barrier (BBB). "The API was crystalline so we nanomilled it in order to increase its rate of dissolution," explains Mark Mitchnick, MD, CEO, Particle Sciences/CMO-Lubrizol LifeSciences. "We then developed a nasal dry powder dosage form to facilitate delivery across the BBB. To minimize potential delivery into the lungs, we spray dried the nanoparticulate suspension in the presence of a larger, inert carrier to produce a mean particle size on the order of 20μ and also eliminated fine particles. This approach worked very well and provided the highest *in vivo* API concentrations into the brain in a primate study."

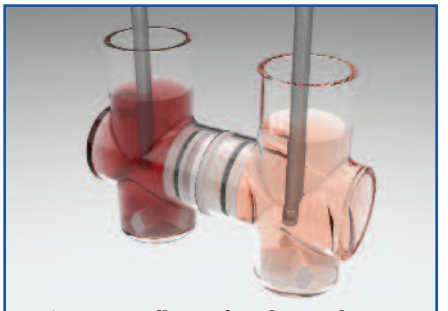
A well-informed formulation effort starts with preformulation data, including extensive solubility and excipient compatibility data. PSI uses DOSE™, a proprietary solubility evaluation approach based on Hansen Solubility Parameters. "This data helps guide our selection of excipients and matrix components in the case of emulsions, solid lipid nanoparticles, polymeric micro/nanoparticles, and solid solution approaches," says Joey Glassco, MBA, Global Market Manager, Drug-Eluting Devices & Pharmaceutical Services, Lubrizol LifeSciences – Particle Sciences. "This can also guide nanomilling when targeting vehicles with the lowest solubility. Based on the physicochemical characteristics of the API, we assess which drug delivery methods will provide the biological performance and match the desired target product profile."

In all of these methods, the excipients play a key role. To increase the range of materials at its disposal, PSI maintains strategic relationships with a variety of excipient suppliers, such as with PLGA for use in polymeric nano- and micro-particulate formulations. As part of Lubrizol LifeSciences, PSI has access to a variety of polymers that play a key role in the solubility of APIs such as thermoplastic polyurethane-based technologies. "These relationships help speed our development whether the polymer is used or not," says Dr. Lee. "Sometimes even knowing what raw material won't work in a particular application helps to point us in the right direction more quickly."

And with the backing of its parent company, Lubrizol, a Berkshire Hathaway Company, PSI is proceeding into commercial manufacturing by breaking ground on modular commercial clean room space. "The versatile design of our facility is conducive for the manufacturing of low-volume, high-value complex products, such as nanoemulsions, polymeric nanoparticles, solid lipid nanoparticles, and PLGA micro and nanoparticles," says Ms. Glassco. The facility will be commercial-ready in the third quarter of 2017 and the first product will follow shortly.

Pion Inc: Physicochemical Characterization Ensures More Effective Formulations

Increasing solubility is only one part of improving bioavailability of drugs. In order to increase flux of the drug through a biological membrane, the permeability of the API through the membrane has to be taken into account. Creating amorphous solid dispersions that increase kinetic solubility of low-soluble compounds without decreasing their effective permeability is one way to achieve higher bioavailability.



To increase flux of a drug, the permeability of the API through the biological membrane needs to be considered (Pion Inc).

Pion Inc. provides a comprehensive suite of physicochemical characterization services that help formulation scientists develop the most-effective formulation in terms of its ability to get absorbed through oral or other routes of administration. These include: ionization constants (pKa) measurements, lipophilicity (logD/logP), solubility and permeability in buffers and biorelevant media, *in situ* dissolution of pre-formulations in buffers and biorelevant media, and flux measurements. Additionally, Pion Inc. provides instruments and services that help pharmaceutical companies answer key questions about the absorption potential of their drugs from the early stages of formulation until the final stages of drug product development.

Excipients, formulations, and drug delivery platforms are often intended to modify the rate and extent of absorption with the goal of improving bioavailability. Understanding the effect of excipients and formulations on physicochemical properties of API is critical for developing a successful drug product.

In one example, a client provided five different formulations in an attempt to select the most promising one for further development, explains Konstantin Tsinman, Chief Scientific Officer, Pion Inc. "Two formulations showed similar improvements in solubility and dissolution while only one of these two demonstrated superior flux. It was later confirmed by the client that the formulation selected based on flux measurements performed the best in dogs."

Drug formulation optimization at Quotient.

Quotient Clinical: Rapid Formulation Development Optimizes Solubility

While industry has done a tremendous job of developing excipients, formulations, and drug delivery techniques to improve solubility, the question remains: Which is right for my program?

"There are many reasons as to why a particular technology might be selected, including molecule properties and therapeutic indication, but eventually a prototype formulation must be developed and tested in some way," says John McDermott, Executive Director, Drug Product Optimization, Quotient Clinical. "Initially, laboratory analysis and preclinical studies are used, but these methods are notoriously poor at predicting drug behavior in humans. Often, performance remains sub-optimal when the formulation is dosed to human subjects, and the development program is further disrupted while additional cycles of formulation development and clinical evaluation are performed."

Mr. McDermott says that Quotient Clinical has developed an innovative approach to identify and overcome these challenges, which enables formulations to be designed, manufactured, and clinically evaluated rapidly within a single organization. "Drug product can be manufactured within 7 days of dosing, removing stability package generation from the critical path to obtain clinical data on product performance," he says. Integrated GMP manufacturing with clinical testing allows clinical data from one study period to be used in order to select the product to be manufactured for evaluation in the next period. This rapid formulation development and clinical testing (RapidFACT®) approach permits biotech and pharma to select and optimize solubility enhancing formulation technology such as spray-dried dispersions, lipidic, and nano-crystalline systems in human subjects, quickly, he says.

In one example, a client completed a Phase 1 clinical trial using an oral suspension of a spray-dried dispersion, but transition to a solid oral dosage form was needed for further development. "In this case, the sponsor had observed a lack of correlation between the *in vitro* and preclinical models, so drug product selection was impossible without supporting clinical data," explains Mr. McDermott. "A RapidFACT program was designed to develop a range of tablet prototypes based around the core spray dried dispersion. Performance was compared in a rapid and flexible manner in human subjects.

This RapidFACT program evaluated a range of solid oral dose options in the absence of a predictive *in vitro* or preclinical model, and identified a suitable product for further clinical development in less than 8 months. Mr. McDermott adds: "RapidFACT therefore delivered significant time savings, with a total of 10 formulations evaluated on the basis of human PK data in a clinical phase lasting less than 10 weeks." ◆

Reference

1. Manikandan, P., et. al., Improving Solubility and Bioavailability of Poorly Water Soluble Drugs by Solid Dispersion Technique – A Review, Int. J. Pharm. Sci. Rev. Res., 23(1), Nov – Dec 2013; no 42, 220-227, http://globalresearchonline.net/journalcontents/v23-1/42.pdf.

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Contract Manufacturing

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Innovative Logisitcs Management

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Drug Development & Delivery

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The Grünenthal Group is an independent, international, research-based pharmaceutical company headquartered in Germany. Grünenthal has affiliates in 25 countries worldwide, and its products are sold in more than 155 countries. Grünenthal developed the INTAC® platform for solid oral dosage forms. The technology combines PEO-based formulations and a proprietary hot-melt extrusion process. Products based on INTAC show particular properties in regard to physical breaking strength. The technology is utilized in FDA-approved products to impede physical manipulation for misuse and abuse purposes. Grünenthal is currently developing immediate-release single-entity and fixed-dose combination opioids, modified-release prescription stimulants, and pseudoephedrine products. INTAC is a leading technology for abuse-deterrent products in the prescription and OTC space. For more information on how you can prevent abuse of your product, visit The Grünenthal Group at **www.intac.grunenthal.com.**

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Drug Development
EXECUTIVE

Amy Grogg, PharmD
Senior Vice President
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AmerisourceBergen: Partnering With Orphan Product Manufacturers to Drive Commercialization Success

Since the Orphan Drug Act (ODA) was passed in 1983, the FDA has approved more than 500 orphan drugs for the treatment of rare diseases, yet only 5% of rare diseases have therapies on the market. Incentives from the ODA, including clinical research grants, tax credits and waivers, and reductions and refunds associated with the Prescription Drug User Fee Act, have opened the doors for manufacturers, large and small, to pursue developing and marketing molecules for rare diseases. But, bringing an orphan drug to market has its own unique set of challenges and considerations that must be overcome. This is especially true for smaller manufacturers without the extensive commercial infrastructures that larger pharmaceutical companies often have. *Drug Development & Delivery* asked Amy Grogg, Senior Vice President of Strategy and Commercialization at AmerisourceBergen Specialty Group, for her perspective on the barriers orphan drug manufacturers face and the solutions available to them through strategic partnerships with distributors.

Q: Can you describe some of the work that AmerisourceBergen has done to help manufacturers launch and commercialize rare and orphan disease products?

A: AmerisourceBergen has provided commercialization services for more than 100 rare disease products – or nearly 20% of all orphan products on the market. We're the manufacturer's partner through the entire development, launch, and commercialization process. By focusing on the patient journey and guiding manufacturers toward decisions that benefit the patient first, we've created a model for aligned success. That means supporting the design of clinical trials and their execution in markets around the world. It means demonstrating the product's value story to payers, so all appropriate patients can benefit from accessing these life-changing products. It means providing the patient support and specialty pharmacy services that remove barriers to access and affordability and provide the high-touch approach that helps patients remain on therapy. And perhaps what is often overlooked, is guiding a manufacturer through the complex decisions inherent in designing a channel strategy that will help their product have the greatest impact for its patients.

This last piece is one of the most important roles a distributor plays in the success of rare and orphan disease products. Manufacturers need their products to fit as seamlessly as possible into a provider and patient's everyday pattern. AmerisourceBergen works directly with our manufacturer partners to help them gain a full picture of how their products might be used in the real world.

For example, will the product be accessible to physicians when they need to treat a patient in the hospital? Or, does the hospital have to break its standard workflow and order the product from a specialty pharmacy? In an era when all healthcare stakeholders are striving to maximize efficiency, any exception to the standard workflow creates an administrative burden that ultimately reduces the time available for patient care. Decisions that affect this workflow can make a difference in product availability. More importantly, it can make the difference of whether patients can receive vital medications as swiftly as possible.

Effective commercialization is a multi-dimensional puzzle. Manufacturers have to know what works well based on their products' attributes and their patient populations. They have to be aware of the potential impact of market trends from changes in policy, reimbursement, or the competitive environment. They have to consider how best to reach their target audiences — whether

that's health systems, specialty pharmacies, or community physicians. That's what AmerisourceBergen does alongside the manufacturer's launch team, figuring out that puzzle and designing strategies that lead to the best experience for patients and providers.

Q: What challenges do small and mid-sized orphan drug manufacturers face?

A: A record 566 therapies were reported in development for rare diseases in 2016. While the market opportunity is substantial for pharmaceutical companies, developing and commercializing orphan drugs is not without its challenges: high cost, special storage requirements, complex side effect profiles and high-touch patient support requirements.

The explosive growth of therapies for rare diseases has also

"Keep the patient first and foremost on your mind and in your plans…Collaboration is essential…Commercializing orphan drugs comes with a lot of challenges, but with so many rare diseases still needing treatments, not only is there opportunity in the orphan space but also the possibility of truly impacting patient lives for the better."

increased payer scrutiny. As market baskets become increasingly competitive, payers are looking more critically at the cost of therapies with indications for rare diseases. The high budget impact of orphan drugs contributes to restrictive utilization management via formularies and/or preferred pharmacy network design. While these behaviors may limit plan costs, they also shape the patient experience and manufacturers must consider how patient support services, such as hub models, can streamline that experience for patients and caregivers alike.

For example, the rise in competition has led to more aggressive step therapy practices. This is most prominently seen when an approved biomarker-related test is available for even part of the labeled indication. Through this practice, payers require patients to first undergo comparable, less-costly drug regimens, approving the use of the prescribed orphan drug only after other therapies have failed.

Access barriers are especially high for small to mid-sized orphan drug manufacturers that don't have the resources or existing relationships to reach a wide variety of customers. Also, the gap in guidance combined with pressures to manage budgets has many payers increasing prior authorization (PA) requirements. These barriers emphasize the need for manufacturers to communicate the product's clinical and economic value with a focus on the impact on the total cost of care.

With the volume of clinical development in the orphan space growing exponentially, pharmaceutical companies must design their commercialization strategies around the patients and providers who will use their products to ensure they create the best outcomes.

Q: What solutions are available to small and mid-sized orphan drug manufacturers to support commercialization and patient access?

A: Engaging with a qualified strategic partner as soon as 2 years pre-launch can help manufacturers know which hurdles to anticipate and give them the competencies to succeed. Small and mid-sized orphan drug manufacturers, in particular, should consider the support of an integrated partner in driving access to the products.

For example, Xcenda, a strategic consulting firm and part of AmerisourceBergen, can offer guidance on health economics and outcomes evidence that will support the value of the product with both payers and providers.

ICS, another part of AmerisourceBergen, has worked with

dozens of small and mid-sized manufacturers to create tailored offerings that address infrastructure, distribution, business process, and patient-engagement hurdles. A unique service model that combines third-party logistics, specialty pharmacy, and patient support solutions under a single point of contact has been especially valuable to manufacturers in the rare and orphan community. And given the specialty transport and handling requirements, we've seen a number of manufacturers work with World Courier, AmerisourceBergen's global logistics arm, as their products move from the clinical trial stage all the way through commercial logistics.

Ultimately, AmerisourceBergen creates a suite of solutions that work synergistically to the benefit of customers, patients and manufacturers.

Q: For manufacturers with products in clinical trials, what should they be considering as they look to the next phase of commercialization?

A: AmerisourceBergen's philosophy is that it is always key to begin with the patient. Every patient has a unique journey, but a rare disease patient's experience can be particularly long and fraught with uncertainty. Reports have shown a patient suffering from a rare disease typically visits up to eight physicians and receives two to three misdiagnoses before an accurate one is ultimately reached.

From a very early stage, manufacturers should connect with existing advocacy groups for rare disease patients. They can help smooth a treatment's path from research to approval, as well as advocate in matters of regulatory or payer restrictions. These groups also provide a means for manufacturers to develop deeper understandings of patients' needs and can help in the actual development of the product – providing information on which routes of administration and dosing schedules will be most effective and adhered to.

Similarly, investing in patient support programs can improve product access and reduce time to therapy, while optimizing outcomes. These programs support the uninsured and underinsured by providing financial assistance that combats the high cost of orphan therapies. Patient case managers also play a vital role not only as essential resources for patients but also as mediators for health outcomes data that manufactures can use to demonstrate real-world effectiveness and the value of their orphan products.

In some cases, the orphan drug is the only disease-modifying treatment available for patients with a specific rare condition. For some ultra-orphan diseases, a manufacturer may be required to spearhead advocacy efforts. A non-branded website before the launch of an orphan product can become a community hub for patients, housing educational materials and potentially serving as a patient registry that helps to facilitate direct communications post-launch. It also can be a platform for manufacturers to track adherence, progress and outcomes, which in turn could substantiate payer coverage and reimbursement strategies down the road.

As early engagement is important with patients, it is also paramount to engage with physicians. Manufacturers, staffed with teams of researchers and scientists, often develop the deepest understandings of the rare diseases – and the symptoms – that they seek to treat. Compiling and disseminating educational materials can ensure accurate diagnosis and ultimately help patient access. This might be in the form of formal protocols or algorithms for diagnosis, treatment guidelines or the creation of a diagnostic test.

Q: Is there anything you'd like to stress to manufacturers about commercializing orphan products?

A: Keep the patient first and foremost on your mind and in your plans. Always challenge yourself on how you can make the therapies more accessible to those that need them. That's what we've been privileged to do with our manufacturer partners, and it's allowed us to build a broad set of expertise from clinical trial logistics to patient support services, and everything in between. Collaboration is essential. Commercializing orphan drugs comes with a lot of challenges, but with so many rare diseases still needing treatments, not only is there opportunity in the orphan space, but also the possibility of truly impacting patient lives for the better. ◆

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THERAPEUTIC FOCUS

GSNOR Inhibition to Stabilize & Improve Mutant CFTR Processing

By: Steven Shoemaker, MD

INTRODUCTION

Cystic fibrosis (CF) is a life-shortening genetic disease that affects an estimated 70,000 people worldwide, including approximately 65,000 in the US and Europe.[1,2] CF is caused by mutations in the gene that encodes the cystic fibrosis transmembrane conductance regulator, or CFTR, a membrane protein channel that helps to regulate fluid and electrolyte balance in epithelial tissues throughout the body. Until recently, medical therapies were unable to target the underlying genetic cause of CF and could only address symptoms.

People with CF have inherited two copies of the defective CFTR gene, one copy from each parent. Because the defective CFTR does not function normally, patients experience a buildup of thick mucus in the lungs and other vital organs. Lung disease, the most critical manifestation of CF, is characterized by airway obstruction, infection, and inflammation, such that more than 90% of all patients with CF die of respiratory failure.[3] There is no known cure for CF, and the predicted median age of survival in the US is approximately 39 years.[4]

Patients with CF typically require lifelong treatment, with multiple daily medications, and frequently require hospitalization and potential lung transplantation. Fortunately, throughout the past several years, the advancement of drugs that modulate the defective CFTR protein, or CFTR modulators, has allowed the focus of CF treatment to shift beyond important palliative care measures to disease modification.

With approximately 127 known disease-causing mutations in the CFTR gene – including the most prevalent mutation, F508del, which is found in approximately 86% of all patients with CF – the ability to increase and stabilize mutant protein function, and thus restore fluid and electrolyte balance in the cell, have become the key goals for addressing the underlying cause of the disease.[5,6]

In the F508del mutation, the deletion of an amino acid results in a misfolded CFTR that is targeted for degradation inside the cell. This degradation is facilitated by chaperone proteins, such as the Hsp70/Hsp90 organizing protein, or HOP. As a result, not enough CFTR reaches, or "traffics," to the cell surface, and the F508del mutation is therefore referred to as a trafficking mutation. In addition, any F508del-CFTR that does reach the cell surface is relatively unstable and is rapidly retrieved from the cell membrane, a process that is also facilitated by chaperone proteins. In the US, approximately 47% percent of patients with CF are homozygous and have two copies of this mutation, and approximately 39% of patients with CF are heterozygous and have one copy.[7]

GAME-CHANGING CFTR MODULATORS

The development of two particular classes of CFTR modulators in recent years – potentiators, which help with protein channel opening, or "gating," and correctors, which assist in CFTR protein folding and trafficking, have changed the entire treatment paradigm for the CF community.

In early 2012, ivacaftor (Kalydeco®) became the first CFTR potentiator approved in the US for people with a gating mutation, G551D, in the CFTR gene.[8] In gating mutations, enough CFTR gets to the cell surface, but the channels do not

stay open long enough for adequate chloride transport. By prolonging the opening of the channel, the clinical development program was able to show that treatment with Kalydeco resulted in significant and sustained improvement in lung function for the 4% of CF patients with this mutation.[9]

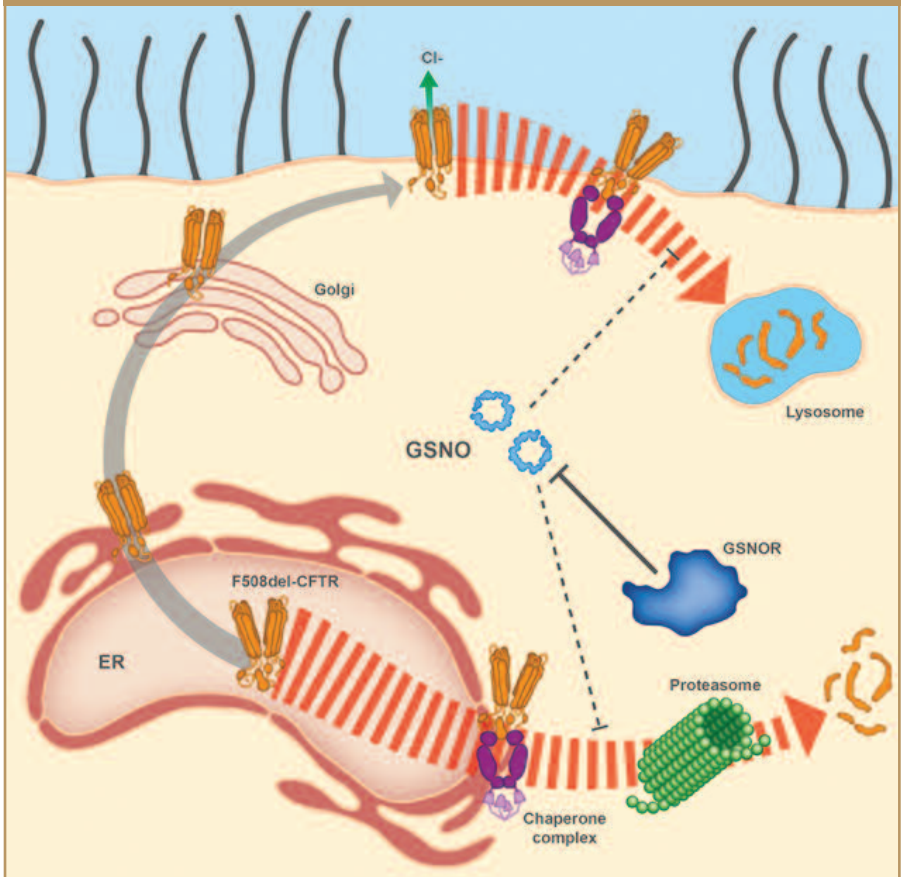
Meanwhile, researchers were also working on how to address the complexity of the defects that plague the F508del mutation. With this mutation, there are defects in trafficking, gating, and membrane stability.

In 2015, the first pharmacological approach to improve CFTR function in patients who are homozygous for the F508del mutation was approved.[10] Lumacaftor/ivacaftor (Orkambi®) utilizes a combination of a CFTR corrector and a potentiator. The combination affects CFTR protein function through enhanced protein folding and channel opening, but has yielded only modest improvements in lung function, as compared with the more clinically significant improvement observed for potentiator (ivacaftor) monotherapy in subjects with CFTR gating mutations, underscoring again the complexity of the F508del mutation.[11,12] It is believed that because these two classes of modulators do not directly address F508del-CFTR cell degradation and membrane stability, a management strategy that can overcome these shortcomings may in fact complement the current approach of using a combination of two CFTR modulators.[13,14]

A third, new type of CFTR modulator under investigation, known as a CFTR stabilizer, aims to increase CFTR stability by reducing degradation inside the cell and prolonging CFTR membrane residence time. The drug candidate, cavosonstat (N91115), is orally bioavailable and restores levels of S-nitrosoglutathione (GSNO) by inhibiting the catabolic enzyme of GSNO, known as S-nitrosoglutathione reductase (GSNOR). GSNO is the human body's most abundant low-molecular-weight S-nitrosothiol, or SNO, and while SNOs are normally present in the human airway, concentrations tend to be reduced in patients with CF, contributing to the dysfunction of CFTR.[15,16]

Restoring GSNO levels in CF helps by modifying the function of CFTR chaperone proteins that play essential roles in CFTR degradation. This modification of chaperone proteins by GSNO results in their dissociation from CFTR and prevents degradation. For example, preclinical studies have shown that GSNO nitrosates and thus modifies the function of HOP, a key chaperone protein, and that this modification of HOP reduces the degradation of CFTR. Increased stability inside the cell and at the cell surface results in increased and prolonged CFTR activity.[17-19]

FIGURE 1

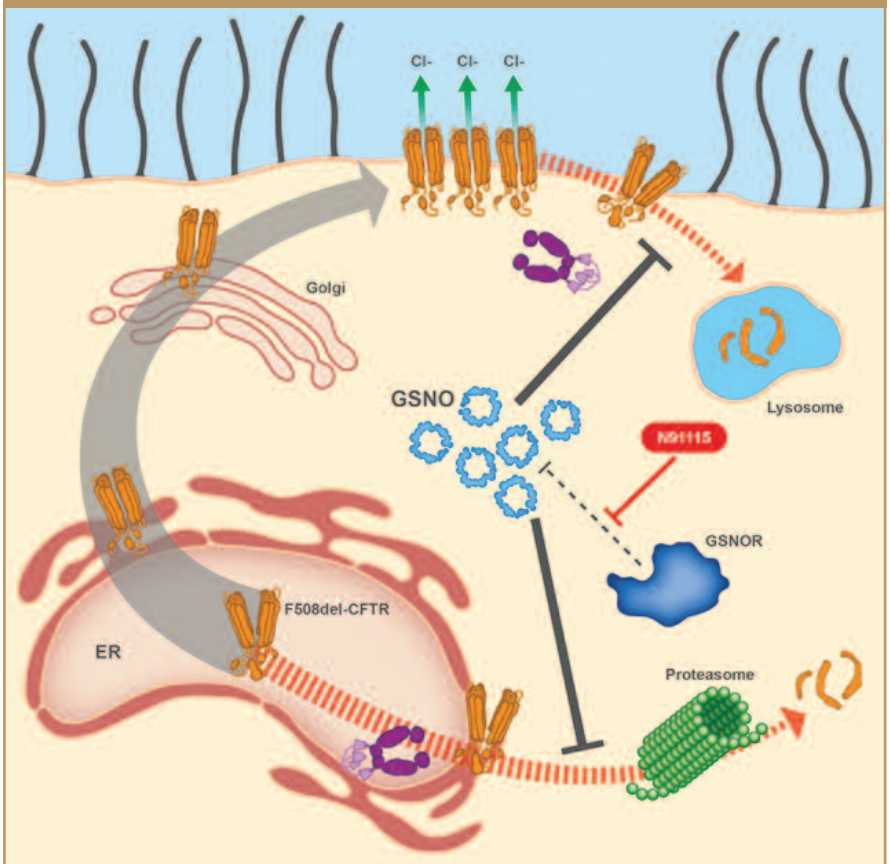


Proposed mechanism of action for cavosonstat. GSNO can modulate protein function via S-nitrosation of cysteine residues on proteins, including on molecular chaperones, such as HOP, which are known to facilitate the degradation of CFTR inside the cell and at the cell surface.20-23

GSNOR INHIBITION AS A COMPLEMENTARY APPROACH

In preclinical studies, cavosonstat was shown to be a potent, selective, and reversible inhibitor of GSNOR and that GSNOR inhibition in fact increases GSNO levels. It increased measures of F508del-CFTR function when used alone, as well as when added to correctors, potentiators, and combinations of

FIGURE 2



Cavosonstat (N91115) inhibits GSNOR, subsequently decreasing catabolism of GSNO.[24] Restoring GSNO levels is thought to increase nitrosation of HOP and other chaperones.[25] This allows more CFTR to traffic to the cell surface and improves stability of the protein at the cell surface.

correctors and potentiators. By increasing GSNO levels, cavosonstat increases CFTR stability through modification of chaperone proteins involved in CFTR degradation, which is independent of, and complementary to, the mechanisms of corrector and potentiator therapies. These data provided the rationale for developing cavosonstat as an add-on therapy to available CFTR modulators.[20-21]

Cavosonstat has progressed through initial Phase I studies and is now being tested in Phase II. In October 2015, Nivalis Therapeutics, a clinical-stage biopharmaceutical company, announced topline results from a Phase Ib clinical study evaluating cavosonstat as the only CFTR modulator in adult CF patients with two copies of the F508del mutation. The randomized, double-blind, placebo-controlled, parallel group study included 51 adult CF patients who were randomly assigned to receive placebo or cavosonstat at doses of 50, 100, or 200 mg administered twice daily for 28 days. The trial demonstrated that cavosonstat was safe and well tolerated over the dose range studied.

The pharmacokinetic profile demonstrated that cavosonstat was absorbed rapidly, as indicated by the 2-hour time to peak concentrations and exhibited linear and predictable exposure levels. While not powered to demonstrate statistically significant clinical efficacy, there was a trend toward a modest reduction in sweat chloride at the highest dose studied that may suggest a threshold effect for CFTR modulation (Day 28 placebo difference -5.2 mmol/L, 95% CI -11.7, 1.4, p = 0.11, within-dose group change -4.1 mmol/L; p = 0.032).[22]

A Phase II program is currently investigating cavosonstat in combination with correctors and/or potentiators, based on the rationale that the distinct mechanism of action of cavosonstat on CFTR processing and cell surface stability may complement the effects of other CFTR modulators in subjects with the F508del mutation and with gating mutations. Based on the results of the Phase Ib study, doses of 200 and 400 mg administered twice daily were chosen for the initial studies. This past July, Nivalis announced that the last patient enrolled in the larger of the two Phase II clinical studies of cavosonstat had received their first dose. In this study, cavosonstat is being evaluated for the treatment of CF patients, who have two copies of the F508del mutation, when added to Orkambi™ (lumacaftor/ivacaftor). The primary clinical efficacy outcome will be the absolute change from baseline in percent predicted FEV1. A total of 138 patients have been enrolled at 46 sites in the US, and topline results are expected by the end of 2016.

A second Phase II proof-of-concept study is evaluating the effect of cavosonstat as add-on therapy to Kalydeco™ (ivacaftor) in adult patients who have one copy of the F508del mutation and a second mutation that results in a gating defect in the CFTR protein. In the US, approximately 4% of patients have gating mutations, such as G551D, which are treated with potentiators to help the channels open, or "gate," properly. The first patient was enrolled in May 2016. Topline results from this study are expected in the first half of 2017.

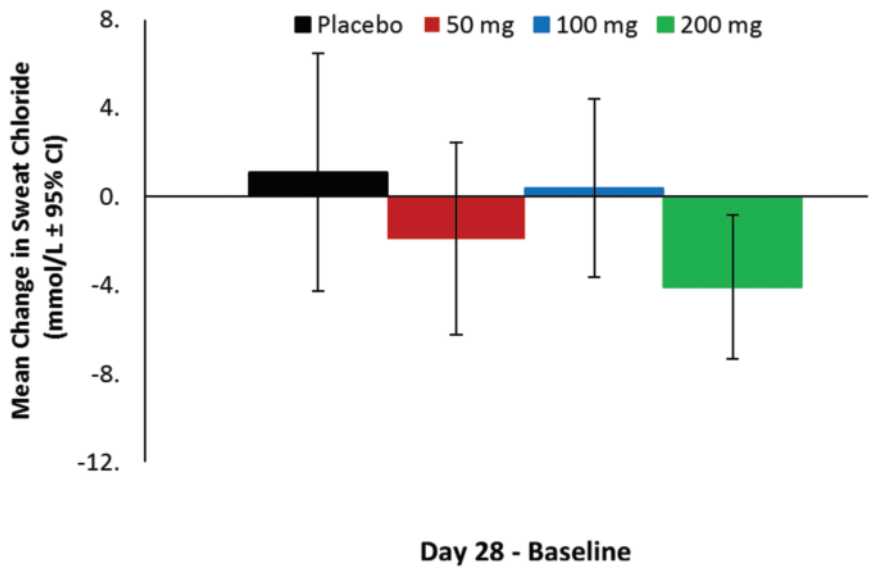
The US FDA has granted cavosonstat Orphan Drug Designation in cystic fibrosis, a program that provides a special status to drugs and biologics intended to treat, diagnose, or prevent diseases and disorders that affect fewer than 200,000 people in the US, as well as Fast Track Designation. Through the Fast Track program, cavosonstat may be eligible for priority review at the time of a new drug application (NDA) filing and may also be eligible to submit completed sections of the NDA on a rolling basis before the complete application is submitted.

RESPIRATORY DISEASE APPLICATIONS

Increases in bio-available nitric oxide (NO) are associated with anti-inflammatory and smooth muscle relaxant effects, especially in organ systems characterized by smooth muscle and endothelial/epithelial layers, such as the lung and cardiovascular system.[23] In CF, ancillary anti-inflammatory effects may provide clinical benefit as the GSNO pathway inhibits inflammatory mediators that are associated with the pathophysiology of the disease. Smooth muscle effects may also improve airway function and be complementary to Orkambi.

Asthma is another inflammatory lung disease where the role of GSNOR has been well studied.[24] GSNOR is endogenously present in the lung, and increased activity of this enzyme leads to less GSNO-mediated smooth muscle relaxation.[25] GSNO levels are lower in the airways of asthmatics than unaffected individuals.[26] In addition, GSNOR knockout mice have exhibited an increase in lung S-nitrosothiols and are protected from allergen-induced airway hyper-responsivity.[27] Restoring levels of GSNO in mice has also been shown to increase beta-adrenergic receptor expression and prevented agonist-stimulated desensitization, effects that were believed to be secondary to nitrosation of G protein-coupled receptor 2 (Grk2).[28] Reversing beta-adrenergic receptor desensitization could play a key role in treating asthma. Nivalis' preclinical GSNOR inhibitor program has previously demonstrated anti-inflammatory effects and the prevention of airway hyperresponsiveness in animal models of asthma and in patients with asthma.[29] All of these findings support the rationale for future clinical studies of GSNOR inhibitors in asthma.

FIGURE 3



Change from baseline in sweat chloride at Day 28 by dose group.

SUMMARY

Cavosonstat is a CFTR modulator with a novel mechanism of action that stabilizes and improves mutant CFTR processing. The initial goal of Nivalis' clinical development program is to show that cavosonstat represents a safe and effective option for patients with CF with at least one copy of the F508del-CFTR mutation; and that when used with correctors and potentiators, improves patient outcomes, including lung function.◆

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BIOGRAPHY

Dr. Steven Shoemaker is Vice President, Clinical Research and Development and Medical Director of Nivalis Therapeutics. Dr. Shoemaker earned his BS in Chemistry from Stanford University and his MD from the UCLA School of Medicine. His subspecialty clinical training was in Pulmonary and Critical Care Medicine at the University of Colorado Health Sciences Center.

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External Delivery

The Rodney Dangerfield Effect

By: John A. Bermingham

John A. Bermingham is former Executive Vice President & COO of 1st Light Energy & Conservation Lighting, Inc. and former Co-President and COO of AgraTech, a biotech enterprise. He was also President & CEO of Cord Crafts, LLC; President & CEO of Alco Consumer Products, Inc., Lang Holdings, Inc., and President, Chairman, and CEO of Ampad, all of which he turned around and successfully sold. With more than 20 years of turnaround experience, he also held the positions of Chairman, President, and CEO of Centis, Inc., Smith Corona, Corporation, and Rolodex Corporation as well as turning around several business units of AT&T Consumer Products Group and served as the EVP of the Electronics Group, and President of the Magnetic Products Group, Sony Corporation of America.

You all know Rodney Dangerfield, the man who coined the phrase, "I don't get no respect!" I believe Rodney had some of the best one-liners in show business. Some were a little crude, but most were hysterical.

I learned a long time ago that respect has to be earned, it is never given freely. While everyone wants to be respected, the odds are that you will eventually run into someone who is in a management position that "gets no respect." What do you do if you end up reporting to someone who you do not respect?

Well, let's first look at what it takes to gain the respect of others. This is my opinion, which you may not agree with. But here it goes. I believe it takes two primary traits to earn the respect of others: character and reputation. There are a lot of subheadings that go with these two primary traits, but these are the two biggies.

So, what do you do if you end up reporting to someone who you have no respect for? This is a really tough situation, possibly one of the top three toughest situations. The following is what I would do:

1. Do the best job you are capable of and don't let your lack of respect for your boss affect your performance. I would view it as a training session by your boss on what not to do when you become a manager.

2. Keep a detailed file on problems and concerns your boss is responsible for. Show no emotion in your writing as it won't fly well in a mediation or arbitration hearing. And keep the file at home, not in the office.

3. Do not, under any circumstance, talk negatively about your boss to others. One of them may be a back stabber and go to your boss and tell him/her what you said. A lot of people in companies who have poor skill sets get ahead by relaying to your boss what you have said in a closed-door meeting.

4. You should try to determine why you do not respect your boss. Is it his/her language, poor people skills, incompetence, work ethic, blaming others for their own failures, etc. Once you settle on a reason(s), you should try to determine ways you can work with him/her. Remember, you can only change yourself but not your boss.

5. If nothing works, then I would tune up the resume or wait your boss out. People change responsibilities constantly in companies, so your boss may be somewhere else in a few weeks or months.

Keep in mind that the problem could also be you. It could be a personality conflict or maybe your boss just has some benign bad habits you and others find uncomfortable. Sometimes, with great dignity and respect toward your boss, you might want to ask your boss out to lunch or dinner and put the problem on the table and work it out.

I had a conflict with the President of one of the large corporations I worked for and lost all respect for him. As things were coming to a head, I chose to take him out to dinner and to talk it over. We settled our differences, shook hands, and instead of getting fired, he became a mentor to me. ◆

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