Simplifying OINDP regulations

Addressing the complex international regulatory environment governing Chemistry, Manufacturing, and Controls (CMC) for Orally Inhaled and Nasal Drug Products (OINDPs)

Risk Management Working Group of the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS)

A recent survey by IPAC-RS identified over 100 international Chemistry, Manufacturing, and Controls (CMC) regulations and guidelines currently applicable to Orally Inhaled Nasal and Drug Products (OINDPs) and revealed, surprisingly, that no common definition now exists for this group of products. Such a large body of regulations seems disproportionate to the number of products manufactured and sold in this specialized segment of the pharmaceutical industry, even considering the fact that OINDPs contain elements of both pharmaceutical products and medical devices, which makes it reasonable to expect that the regulatory burden should be somewhat higher than for separate drug and device products.

New product developers and those seeking entry as generic producers, component suppliers, or contract test laboratories must follow a complex and fragmented set of international requirements and review processes in order to achieve marketing approvals globally, and the inherent inefficiencies contained within this system add significant cost. In addition to the sheer number of regulations, regional views on management and administration of those regulations, especially the integration of drug product and device requirements, often diverge.

A continued need for regulatory simplification

In the late 1980s, the formation of the International Conference on Harmonization (ICH) addressed an analogous situation that existed for typical dosage forms like oral tablets and capsules: a convoluted regulatory framework with non-uniform approaches to the assessment of approval applications and differing views on the type and amount of data needed to insure conformity with regulations. Since 1989, the ICH's efforts have led to the removal of many of those barriers to development for manufacturers and to more effective use of regulatory reviewers' time as the need for multiple question/answer cycles was reduced. Additionally, consumers have gained better access to high quality products. The Global Harmonization Task Force (GHTF) has undertaken similar activities in the medical device arena since 1992.

Despite progress made in each of these areas independently, the situation with OINDPs remains unresolved. For one thing, the volume and revenue flow from OINDPs, while growing, remains small in comparison to other pharmaceutical dosage forms, and only a handful of manufacturers are affected, which may be one of the reasons that ICH and GHTF have not become involved thus far. Also, as hybrid products, OINDPs rely on two separate regulatory systems that are not integrated on a national level let alone an international one. Finally, no commonly accepted definition of what constitutes an OINDP exists, leaving nothing upon which to construct a regulatory framework for harmonization or to use as a basis for judging which subset of existing pharmaceutical or device requirements must be considered.

A practical definition and a companion set of decision rules for determining if a product should be classified as an OINDP would simplify these efforts, and a risk-based approach offers the opportunity to create a simpler scheme that can form the foundation of an internationally harmonized regulatory framework.

The consistent identification and the application of safety and performance principles as part of the risk management process offers significant benefits to patients, manufacturers, and regulatory authorities.

A quality risk management strategy will allow developers to design, manufacture, and demonstrate the suitability of particular OINDP drug products for their intended uses and allow patients earlier access to new technologies and treatments. Following these principles will help to ensure that products have predictable registration, sustainability in the market place, and compatibility with Quality by Design (QbD) principles. Moreover, this approach offers the potential to eliminate differences between jurisdictions, thereby decreasing the redundancy of regulatory requirements.

Historic factors and the current state of CMC regulation

From the first appearance of pMDIs in the 1950s, regulators almost universally classified them as pharmaceutical products despite the complexity of device technology embedded in their function. The contemporary judgment, still somewhat applicable today, deemed that the drug represented the principle element, and the device merely enabled delivery of the drug. The immaturity of medical device regulation in the late 1950s and early 1960s made fitting pMDIs into already existing regulatory schemes for approval and marketing authorizations of pharmaceutical items the most logical strategy.

Defining pMDIs as pharmaceutical items also proved convenient in allowing regulators to address product quality through the mechanism of pharmacopoeial standards, which historically had proven themselves as adequate CMC controls for a wide variety of pharmaceutical products. General product requirements at the time were relatively homogeneous throughout the world, although some differences in the technical details of testing standards existed, particularly between the US and European pharmacopoeias.

Organizations and agencies affecting OINDP regulation:

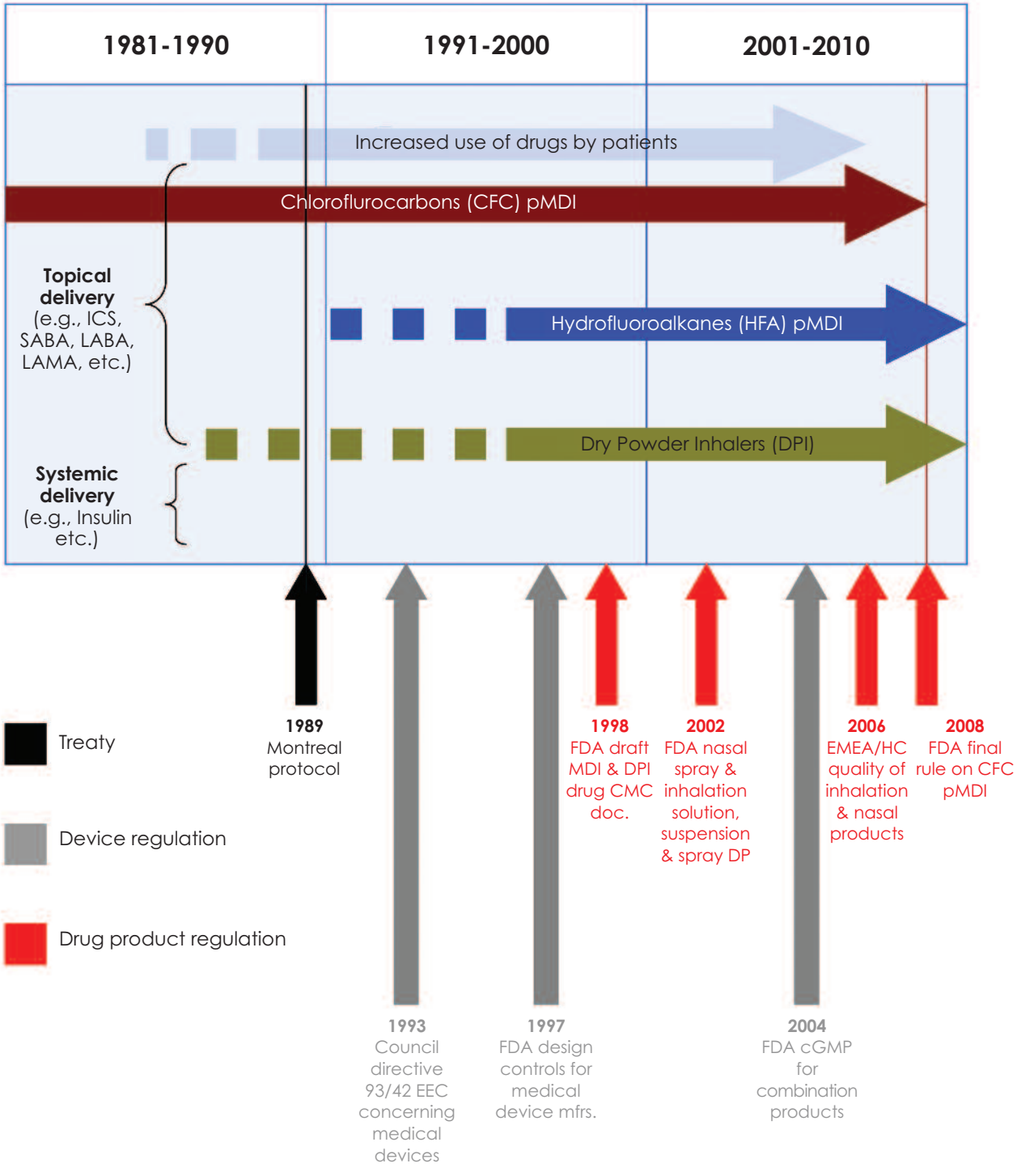
- European Union
  - EMEA (European Medicines Agency)
  - European Commission: Medical Device Directives
- US FDA
  - CBER (Center for Biologics Evaluation and Research)
  - CDER (Center for Drug Evaluation and Research)
  - CDRH (Center for Devices and Radiological Health)
- Health Canada
- Japan MHWL (Ministry of Health, Labor and Welfare)
- Pharmacopoeias (US, European, Japanese)
- International Organization for Standardization (ISO)
- Regulatory/Industry Harmonization Initiatives
  - GHTF (Global Harmonization Task Force)
  - ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use)
- Trade associations such as:
  - IPAC-RS (International Pharmaceutical Aerosol Consortium on Regulation and Science)
  - ASTM (American Society for Testing and Materials)
  - PQRI (Product Quality Research Institute)

Beginning in the 1980s, this regulatory model for OINDP faced a series of challenges that led to the current complex array of international directives (Fig. 1). Among the most important factors were an increase in the size of the OINDP patient population, the impact of the Montreal Protocol, and the use of orally inhaled and nasal drug products for systemic drug delivery.

As the incidence of respiratory diseases worldwide has risen, [1] and greater access to therapies has increased the number of patients using OINDPs, the number of regulations has risen concurrently. Concerns expressed by regulators in talks at conferences along with anecdotal evidence from industry experts seem to suggest that regulators believe that the existing standards afford insufficient protection.

Figure 1

Evolution of the current OINDP CMC regulatory landscape



The reason for these concerns is unknown, but it is conceivable that regulators are responding to an increase in complaints and/or adverse event reports as the worldwide use of OINDPs has risen, even if the percentage of patients experiencing product quality problems has not.

In the late 1980s, the Montreal Protocol initiated the phaseout of chlorofluorocarbons (CFCs), which at the time were commonly used as propellants in pMDIs. As a result, many pharmaceutical development programs turned into unexpectedly costly and lengthy efforts to reformulate existing products with the preferred replacement, hydrofluoroalkanes (HFA). New information gathered as companies conducted extensive basic and applied research to understand how to reformulate with HFA challenged long held assumptions about performance and relevance of in vitro test criteria.

The Montreal Protocol also accelerated innovation and renewed interest in alternative and novel inhalation delivery systems such as dry powder inhalers (DPIs) and soft mist inhalers (SMIs) that avoid the use of propellants altogether. These systems, some of which incorporate digital technologies, active power supplies, or dynamic feedback loops also challenged many of the traditional ideas about product quality controls.

Interest in the pulmonary portal for systemic delivery as a way to circumvent first pass metabolism or to obtain intravenous-like pharmacokinetics without pain during administration increased during the 1990s. The large molecule chemical entities or biologics contained in some of these types OINDP may require a different set of controls to ensure quality than those typically applied to more common small molecule drugs intended to produce only a local therapeutic effect in patients with existing airway disease. For example, the new systemic agents, unlike the majority of current OINDP, are used primarily by patients with healthy airways, making changes in lung function arising from the acute or chronic use of such products especially undesirable.

Regulatory approaches by region

At the same time, more subtle changes occurred in the ways that different regions elected to regulate the drug product and device elements of OINDPs. In particular, major differences emerged between European and US regulatory agencies. In the European Union, when drug and device elements are separable, the Medical Device Directives apply for assessing conformity of the delivery mechanism, while the relevant pharmacopoeial and/or medicines standards apply to the drug portion. Where the drug and device are inseparable, only pharmacopoeial and/or medicines standards [2] apply, with no consideration whatsoever given to device regulations.

Taking the opposite approach, the FDA continues to classify products based on a determination of which element, the drug or the device, contributes more to the treatment effect. The agency considers inhalation products containing any pharmaceutical agent as drug products subject to review and approval primarily by the Center for Drug Evaluation and Research (CDER), yet mechanical components of inhalation systems as devices, such as nebulization devices sold separately from the drug containing element, fall under the responsibility of the Center for Devices and Radiological Health (CDRH). More recently, innovations in combination products that further blur the distinctions between the drug and device elements have added another dimension to OINDP approval in the US.

Other standards bodies such as the major pharmacopoeias, the International Conference on Harmonization (ICH), and the International Organization for Standardization (ISO) have also contributed to the drug or device regulatory landscape (see sidebar on p. 15). The more than 100 separate international standards, guidelines, and guidances applicable to inhalation delivery each contain at least one requirement that companies must meet to realize a global submission for marketing approval.

Updating regulatory structures with quality risk management

Advances in medical device technology and the growth of the medical device industry precipitated changes in the regulatory structure for managing risk and product quality. In contrast to the pharmacopoeial based structure, which relied heavily on sampling and end product testing, medical device regulation emphasized a systematic process utilizing risk analysis, design control, and supply chain integrity.

Although the currently established conglomeration of regulations will persist for some time into the future, standards committees are now applying risk management principles to the production of pharmaceuticals, as exemplified by the (ICH) Guideline on Quality Risk Management (Q9). Similarly, in 2002, the FDA recognized the inefficiency of the current paradigm and introduced an initiative on pharmaceutical quality for the 21st century to modernize the agency's regulation of drugs and biological products.

Defining OINDP

The lack of an accepted definition for OINDPs causes some the problems underlying the confusing regula-

tory environment. The differences within this class of products, as varied as pMDIs, DPIs, nebulizers, soft-mist inhalers, and nasal sprays, make defining the category difficult, but the products display enough commonality in some critical features to allow the establishment of a clear and practical definition.

The IPAC-RS Risk Management Working Group suggests defining an OINDP as:

1) A delivery system containing a substance, or mixture of substances intended to furnish a pharmacological action or other direct physiological effect in humans;

2) A defined amount of the substance(s) is (are) dispersed into an aerosol form by the system;

3) The aerosolized form is available for transport to the lower respiratory tract, nasal cavity, or nasal sinuses, where "aerosol" refers to a gas-borne suspension of solid or liquid particles, and "lower respiratory tract" refers to the trachea, bronchi, bronchioles, alveolar ducts, and alveoli.

A decision tree constructed using this definition provides a tool for determining whether a system constitutes an OINDP or not (Fig. 2).

Identifying performance targets

Using the new definition, the working group has identified four major performance targets:

1. Achieving reliable and consistent aerosolization, delivery, and deposition of the intended agent

Figure 2

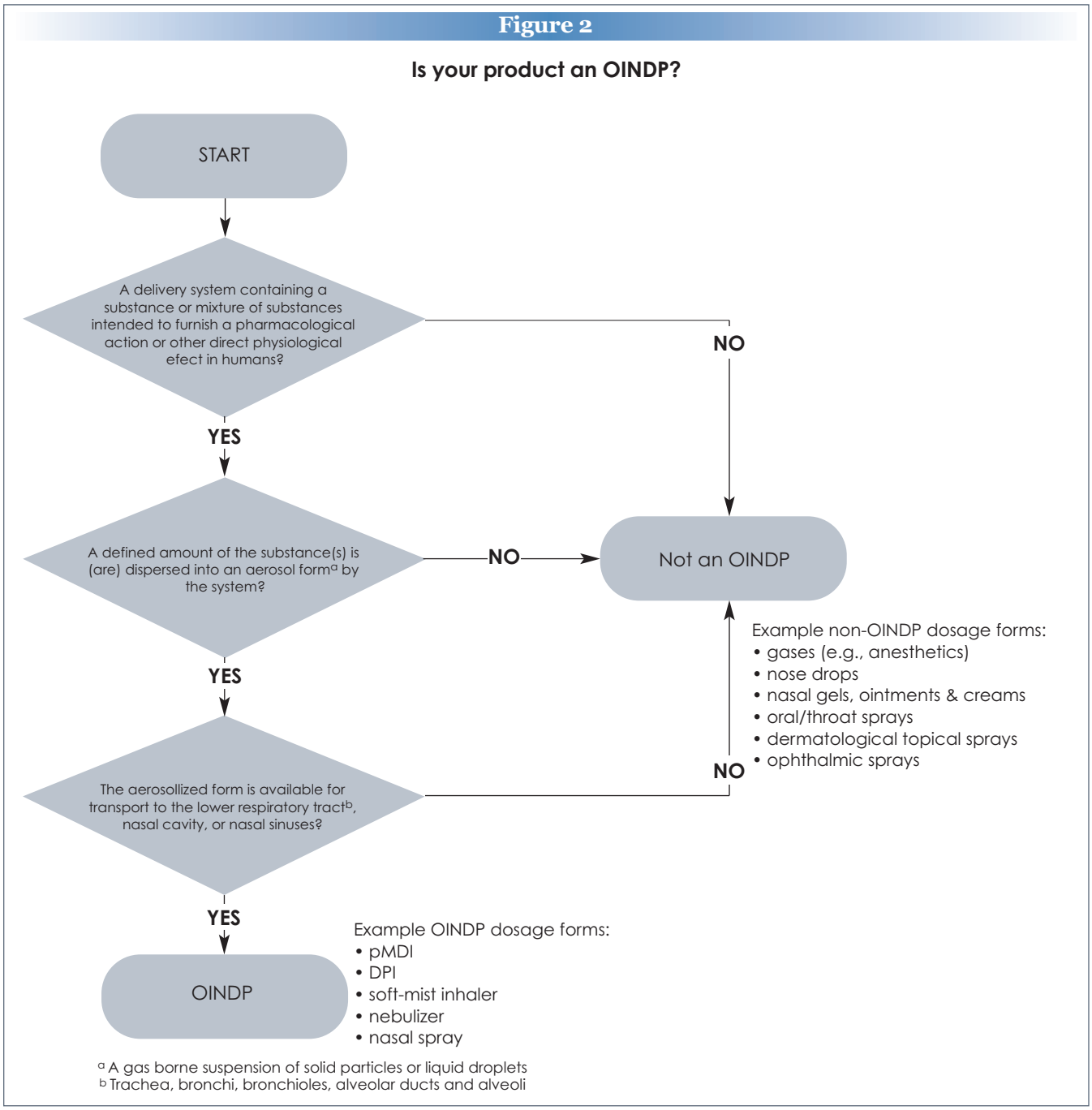


Table 1

Overview of OINDP performance targets and risk categories

	Four major performance targets			
Four major risk categories	Reliable & consistent aerosolization	Excluding unintended materials	Encouraging proper use	Minimizing the likelihood of unintended effects
Device				
Formulation				
Device/formulation interaction(s)				
Patient factors				

Each OINDP may have unique risks to be systematically identified, assessed, and mitigated during development or by quality control schemes

2. Excluding unintended materials such as foreign particulates, leachables, microbiological material, infectious and/or sensitizing agents, or impurities from an OINDP

3. Encouraging proper use and minimizing chances of misuse of an OINDP

4. Reducing the likelihood of unintended effects.

The working group has also categorized four risk sources that contribute to success or failure in achieving performance targets:

1. Device elements, including primary and secondary packaging, or integrated dose counting mechanism

2. Formulation elements

3. Interaction of device and formulation

4. Patient factors.

Organizing each of these performance targets and risk categories into a matrix with 16 cells allows developers to identify possible threats to achieving performance targets and their associations with specific OINDP risk sources (Table 1). This approach organizes the complex and fragmented regulatory environment into a logical framework at a conceptual level and provides opportunities to apply risk management and to integrate formal design and planning tools into a development program. A systematic examination of each cell in the matrix and assessment of hazard likelihood, severity, and reliability against failure will highlight areas that require risk mitigation through design, formulation selection, manufacturing processes, or the institution of specific quality control measures.

One of the goals of the working group is to suggest alternatives for overcoming the lack of flexibility to accommodate innovation and novel technology applications that exist in the current regulatory environment. Some of today's OINDP regulations, derived from 1950s pMDI technology, prescribe requirements ill-suited to contemporary OINDPs, and manufacturers must find some way to comply, no matter what contortions are necessary. The matrix framework coupled with well-established risk management tools, offers the necessary flexibility for a wide range of present and future inhaled and nasal drug products, allowing each developer to identify which risks apply to a particular product or technology and to demonstrate a plan for mitigation.

This risk based approach offers the opportunity to organize and consolidate the diffuse set of OINDP requirements into a logical scheme. Most of the existing regulations have the same underlying intent, encouraging the hope that an internationally harmonized regulatory framework for OINDPs will emerge to benefit patients, developers, and regulators. Such simplification will promote further innovation in the area of pulmonary delivery and streamline the pathway to market approval.

References

1. WHO Statistical Information System.

2. EMEA Guideline on the Pharmaceutical Quality of Inhalation and Nasal Dosage Forms.

The authors would like to acknowledge the contributions of Thomas Lindblad, Eric Johansson, and Jim Cameron.

The Risk Management Working Group of IPAC-RS includes Steve Horhota, Boehringer Ingelheim, Highly Distinguished Scientist, CMC Development, Research & Development, Mail Zone 2B, 900 Ridgebury Road, Ridgefield, CT 06877-0368, Tel. +1 203 798-5258, email: steve.horhota@boehringer-ingelheim.com; Svetlana Lyapustina, DBR; Stefan Leiner, Boehringer Ingelheim; Robert Berger, Schering-Plough; Ann Purrington, 3M; Sebastian Kaerger, Novartis; Noel Butterworth, Novartis; Rajni Patel, Boehringer Ingelheim; Barbara Davidson, 3M; Andrew Grant, GSK; and Mary Ann Smith, Nektar.