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THE EVOLVING & CHALLENGING REGULATORY LANDSCAPE FOR COMBINATION PRODUCTS

In this piece, Alice Maden, PharmD, Global and Regional Regulatory Affairs Manager, and Kathleen O'Sullivan, MS, RAC, Worldwide Director, Regulatory Affairs, both of BD Medical, take the practical example of a drug product filled in a BD Hypak™ glass prefillable syringe to describe how the worldwide regulatory environment of combination products has rapidly evolved. BD's Regulatory Affairs team has adapted their support offerings and customised solutions to assist customers from the pharmaceutical and biotechnology industry to sustain this major change.

During the past two years, the pharmaceutical industry has received clear signals from regulatory authorities indicating that worldwide regulatory expectations on container closure systems and delivery systems for parenteral medical products are rapidly evolving. Global examples are seen in the US, EU and Japan regulations.

United States

In the US, the Final Rule for Current Good Manufacturing Practices (cGMPs) for Combination Products was published by the FDA on January 22, 2013 and issued under 21 CFR Part 4. Industry had been waiting for several years since the initial publication of the proposed rule by the Agency in 2009, which had first been drafted in 2004. In 2013 with the issuance of the final rule, FDA expected the industry to have completed implementation by July 22, 2013. The FDA's goal in issuing the rule was to enhance consistency of regulatory requirements for these types of products, as well as to encourage innovation.

Within the new guidance was the concept of a 'streamlined approach' to the application of the good manufacturing practices or quality system regulation (QSR). Under the rule, the requirements in sections 210 and 211 of 21 CFR were applicable to combination products containing a drug, while in part 820 the quality system regulations were applicable to combination products containing a device. Streamlining meant it was unnecessary to include all provisions of both systems, but enabled the leveraging of the necessary elements required from each system of cGMPs and QSR. One system of cGMP /QSR requirements would apply for a single entity or co-packaged combination product using elements from both 21 CFR parts 210 and 211, and part 820 for drug/device combination products. An example of a combination product that would leverage both drug and device GMPs/QSR would be a drug contained in a prefilled syringe.

At the time of the publication of the final rule, FDA recognised that industry would have some unanswered questions related to the rule and had plans to issue several other guidance documents to meet these needs and address any gaps. These additional guidances would include clarification on topics, such as human factors studies, post market changes, stability, retention samples, and information required for prefilled syringes, in addition to the applicable standards, and others specifically related to combination products. Subsequently several guidance documents or draft guidance documents were issued including the following:

- 01/2015 Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products, Draft Guidance
- 06/2013 Technical Considerations for Pen, Jet, & Related Injectors Intended for Use with Drugs & Biological Products
- 04/2013 Glass Syringes for Delivering Drug and Biological Products: Technical

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Information to Supplement International Organization for Standardization (ISO) Standard 11040-4

- 01/2013 Submissions for Post-approval Modifications to a Combination Product Approved Under a BLA, NDA, or PMA

The industry is facing several complexities today, such as how to manage products that have been in the market place for many years prior to combination product regulations and prior to the device amendments of 1976. Products in some cases have existed on the market for up to fifty years, were designed according to the practices of their time and have been proven to be safe and effective products. A troubling question facing some manufacturers is whether or not these products can be manufactured according to today's newer standards, and successfully pass the required tests using current technologies.

Another area requiring clarification is the issue of change control of "legacy" products on the market for many years. Changes would naturally be expected to conform to today's standards. However, manufacturers' ability to do this again comes into question as do the implications of not changing anything because of the knowledge that such products may not meet newer requirements, i.e. requirements that were not around at the time the product was designed initially. This avoidance of change may impede the desire to enhance the product.

Additionally, there is the question of how inspections would occur on older marketed products and the expectations of the regulators during such inspections. As the combination product regulations and additional guidance evolves in the US, manufacturers of combination products are now facing these conundrums along with a need for clarification on matters related to reserve samples, calculation of yield, human factors, stability testing and design controls for combination products.

Europe

In Europe, further to the PIP breast implant debacle, new proposals [1] for the regulation of medical devices were published by the European Commission (EC) in September 2012. These two draft regulations are currently under discussion at the EC and the European Parliament and are expected to replace the existing three medical device directives in the future. The main purpose of these new regulations is to ensure safer medical devices and to provide more transparency in order to regain users' and patients' trust.

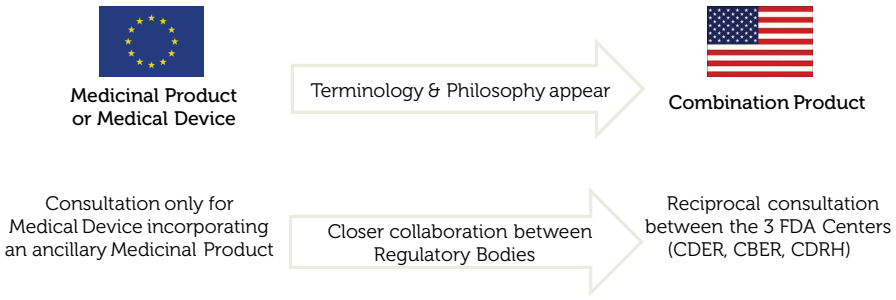

Figure 1: The philosophy of combination products, which has been established in the US for several years, is gaining acceptance in Europe.

Among the numerous pillars of this updated regulatory framework, most of them are specific to the medical device industry, such as better qualification of Notified Bodies, unannounced audits by Notified Bodies for manufacturers of CE-marked medical devices, or unique device identification (UDI) systems for an enhanced traceability. **More specifically, in the draft regulation on medical devices, some parts are more focused on combination products with the following changes: The term "combination product" which has been used for a long time in the US appears for the first time in Europe.**

Using an example of a drug product filled into a BD Hypak™ glass prefillable syringe, it is clear in the language of "*sections 3.9. Final provisions (Chapter X)*", "*Whereas (9)*" and "*Legislative Financial Statement section 1.5.4. Coherence and possible synergy with other relevant instruments of the draft regulations*" that this constitutes a combination product.

Also, in the framework of improved synergies with other legislations including medicinal products, the draft regulation focuses on compliance of drug/device combination products with the list of essential requirements governing medical devices in Europe, as clearly indicated in "Section 3.9 Final provisions (chapter X)". This requirement is already applicable today but every European institution agrees that "compliance with this requirement is not currently verified as part of the authorisation process for the medicinal product".

The practical consequence for manufacturers of drugs in prefilled syringes is that they will have to provide clear demonstration of the compliance of the syringe part of their combination product with the applicable sections of this list of essential requirements.

This represents an important step forward in the growing philosophy of combination products in Europe (Figure 1).

Japan

In the third geography of the ICH Organisation, the Japanese Pharmaceutical Affairs Law (PAL) was updated in November 2014 to include a new, adapted regulatory strategy option for combination products.

In the past, pharmaceutical companies planning a submission for the Japanese market consisting of a drug product filled in a BD Hypak™ glass prefillable syringe had to file two separate submissions. A medical device application including the syringe information had to be submitted to the Pharmaceuticals & Medical Devices Agency (PMDA) for review. In addition, a second file focused on the drug product and referencing the medical device approval, once available, had to be submitted separately to the Ministry of Health Labour and Welfare (MHLW) for review.

As of November 2014, a new option became possible allowing a combined approach whereby pharmaceutical companies submit to the MHLW one combination product application including both the drug product and medical device information together. This is yet another sign that the combination product trend is strengthening.

REGULATORY AFFAIRS AT BD

BD's Regulatory Affairs Team, which has a breadth of experience in providing comprehensive, informed regulatory support and consultation, aligns its regulatory offering while meeting the evolving expectations of its customers.

This support is based on two central deliverables:

- The letter of authorisation (LOA), which we deliver to customers for the registration of our BD Hypak™ glass prefillable syringe and other container closure systems in the US, Canada and Australia.
- The Technical Dossier, which we deliver to our customers for registration in other territories.

Other Geographies

Due to the recent changes and evolving requirements from health authorities regarding container closure and delivery

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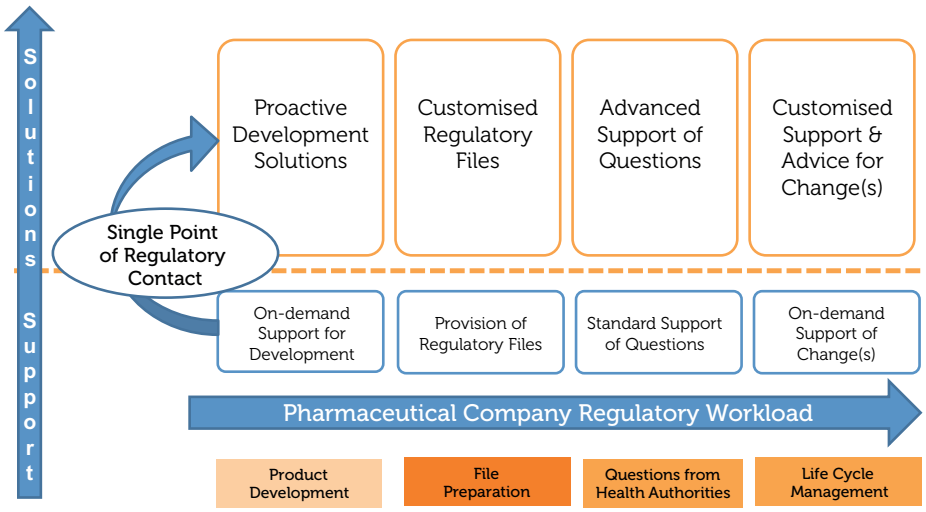

Figure 2: BD's comprehensive set of agile, customised regulatory affairs solutions, encompassing early development through life cycle management.

systems, BD's Regulatory Affairs Team has more recently launched several initiatives in alignment with this evolving environment.

Based on a case-by-case discussion between our customers and a single point of regulatory contact from our team, we are in a position to leverage global regulatory expertise to support and collaborate with our customers, and help them not only attain their registration goals, but provide ongoing consultation and services throughout the product lifecycle.

A COMPREHENSIVE & GRADUAL OFFER

BD's offering is comprehensive and gradual, from *ad hoc* requests to proactive case-by-case collaboration and partnership. To support our customers in their product development and filing phases, we have developed a regulatory dossier, a Customised Common Technical Dossier (CTD) for Customers designed to fit into the format and content of regulatory submissions, offering the convenience of integrating our "ready-to-use" document into their submission, saving time and effort and potentially shortening approval timeline.

This solution, when provided to our customers, has proven to be invaluable, resulting in fewer questions from the health authority and no blocking point related to the BD Products embedded. This success is further evidenced by increasing requests for this offer from our customers. Additionally, BD – recognising customers' challenges when purchasing components for their combination products – proactively sought out advice on its Customised CTD by going beyond the usual barriers of a supplier of components. We presented the Customised CTD principle to the UK MHRA during a Scientific Advice meeting in November 2013. According to the MHRA: "The scope of data presented has been considered as a good supportive data package."

Related to this customised CTD is the customised follow-up consultation provided in the event of questions from European health authorities. A single point of regulatory contact supports the pharma customer in case of any questions from the health authority with respect to BD products, in a timely, responsive manner. Further, this customised solution will be useful to customers who wish to launch or modify an existing product on the European market. It is particularly valuable for the entry of biosimilars to the European market as this is an area where it is critical to be expeditious and "right the first time". In this area of biosimilars, customised filing support using the skills of an experienced regulatory group can make a valuable difference in navigating the complex regulatory environment.

In Japan, we are in a position to provide our worldwide customers entering this market with regulatory dossiers for the BD components they use. Our offer has been evolving in alignment with the new law issued in November 2014 and we now provide customers with device sections of combination product regulatory files, among other available services. This device section is included in the customer's combination product application and the complete dossier is then submitted to the MHLW for review and approval.

For a mature product, pharmaceutical companies may want to switch to a more advanced container closure system or to an additional presentation, such as the addition of an auto injector to an existing marketed prefilled syringe. Whether this lifecycle management activity is intended to maintain or gain share of sales, to improve product technology, or to increase patient compliance, our Regulatory Affairs team has developed lifecycle management tools to simplify such a switch by clarifying the expected regulatory impact and by providing the expertise to aid a smooth transition.

Container closure and delivery systems are becoming a pillar of combination product development. In the past, Pharmaceutical Companies typically did not consider available container closure and delivery system options before Phase III clinical studies, evolving health authority expectations are now pushing for an integrated approach starting at a very early stage. As highlighted, BD Regulatory Affairs has developed a comprehensive set of agile, customised solutions, encompassing early development through life cycle management (Figure 2), to streamline and facilitate timely approvals or product maintenance for our customers, thereby supporting their marketing and launch strategies.

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Innovation Across the Patient Care Continuum

You and your company are focused on creating new, innovative medicines. And despite ever-increasing complexity, heightened regulatory scrutiny and other marketplace challenges, you're developing new ideas for a bright healthcare future.

At **BD Medical – Pharmaceutical Systems**, we know that innovative drugs need innovative delivery systems. This means we must continuously deliver advanced solutions and exciting new choices to help make your products great. What does innovation mean at BD?

- **A broad portfolio** of drug delivery systems, including glass and plastic prefillable syringes, self-injection systems, safety and shielding systems and needle technologies
- **Sophisticated consultative and analytical services** to help ensure drug compatibility and seamless systems integration while accelerating time-to-market and reducing risk
- **An unbending emphasis on innovation**, paired with the highest level of technical expertise

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