Human Factors Studies in Biologic License Applications for injectable Device-Biologic Combination Products

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Introduction

The use of biologic drugs continues to grow in the United States and worldwide, with biologic products accounting for approximately 20% of global spending on pharmaceuticals.\textsuperscript{1, 2} Globally, six of the top ten selling drugs in 2015 were biologic products, compared to three of the top ten in 2011.\textsuperscript{3, 4} This increase in market share reflects the health demand for targeted therapies with lower side effects and improved patient outcomes for a variety of conditions, including those which were historically treated by daily administration of small molecule drugs.\textsuperscript{5} Additionally, the delivery of these biologic products is becoming more sophisticated, as current pharmaceutical development focuses not only on the properties of the drug or biologic product, but also on how to best deliver the product to the patient and overall lifecycle management.\textsuperscript{6} The increased emphasis on the use of Quality by Design (QbD) tools, such as the Target Product Profile reinforces this expectation of deliberately planned products and helps sponsors to realize these benefits during development and review cycles.\textsuperscript{7}

While biologics historically have been delivered intravenously in a healthcare setting, there is a recent increase of self-administered subcutaneous dosage forms as long-term therapies for chronic diseases such as diabetes.\textsuperscript{8} These are classified as biologic-device combination products; delivery systems include pre-filled syringes, pens and auto-injectors.\textsuperscript{9} The number of first time approvals for combination products continues to increase year over year (Fig. 1). In 2015, 33% of the Biologics License Applications (BLA) approved by the US Food and Drug Administration’s (FDA) Center for Drug Evaluation and Research (CDER) included at least one combination product offering (Fig. 1).\textsuperscript{10, 11} Of the biologics combination product formats approved from 2006-2015, 60% were approved in 2014 and 2015; a total of 20% of the approvals were market extensions.

\textbf{Figure 1. CDER Biologics License Approvals by Year Including Supplements for Combination Presentations}
Changing to a self-administered biologic-device combination product decreases hands-on time in a physician’s office, improves patient adherence, improves therapeutic effect and reduces cost. However, these products must be used appropriately to yield therapeutic benefit and ensure patient safety. Therefore, human factors studies are critical to assessing whether the device design of the biologic delivery system and instructions for use are adequate to ensure that the benefits of self-administration are fully realized. With this trend towards combination products, many BLA sponsors are challenged to meet the regulations associated with devices. Specifically, they must conduct and submit human factors validation studies to ensure their injectable biologic-device product is suitable for the intended use. Recently, the FDA has published cGMP regulations for combination products as well as a draft guidance outlining the expectations for the combination products human factors studies in these applications. This paper reviews injectable device-biologic combination products approved by CDER from 2006-2015, including the product demographics, results and regulatory challenges associated with the human factors studies.

**Background and regulations for human factors studies**

Therapeutic biologic products regulated by CDER include monoclonal antibodies, peptides, protein therapies and recombinant DNA and RNA technologies. The pipeline for biologic drugs continues to grow in relation to small molecules; FDA Director of the Office of Biotechnology Products Steven Kozlowski recently estimated there are 1300 active biologics Investigational New Drug Applications (IND) at FDA. Historically, most biologics were designed to be administered by a trained healthcare provider via injection or infusion, including products which are lyophilized and require reconstitution or intravenous products. Increasingly, drug and device combination products are being introduced, either during initial approval or as part of life cycle management. For example, Benlysta, used the treatment of Lupus, is currently supplied as a lyophilized powder which is reconstituted for intravenous use and is infused over an hour in a physician’s office or outpatient center. The treatment regimen is bi-weekly infusions for the first three treatments, followed by infusions every four weeks. A new BLA was filed in September 2016 which will allow for once weekly subcutaneous injections, self-administered in a homecare setting using a pre-filled syringe or auto-injector.

Human factors studies have long been a requirement for medical device development and validation to establish that the human and device interface is safe and effective for the intended use by the end user. The recent introduction of combination product cGMP regulations, 21 CFR § 4, emphasize that combination products do not lose their individual regulatory identities when they are combined. Therefore, a biologic-device combination product must meet the requirements for both the biologic and device components. The design controls and validation which are inherent to devices, including human factors studies, are a regulatory requirement for biologic device combination products.

A human factors study examines how the user interacts with the device or combination and ensures that the design of the product and the instructions for use sufficiently mitigate the risk of misuse, ensuring safety and efficacy of the product and minimizing medication errors. A typical human factors study includes a risk analysis, a formative human factors study and a human factors validation study.

During risk analysis, critical tasks performed by the end user are established and analyzed. These tasks, if performed incorrectly or not at all, could result in misuse. For example, improper
use of an auto-injector may result in a wrong dose or missed dose of the biologic product. It also may cause user harm through an unintentional needle stick from improper storage or handling. The risk analysis may utilize a failure modes and effects analysis (FMEA) which considers the failure mode, severity of risk, probability of occurrence and ability to detect the failure. Based on the results, risk mitigations are identified along with residual risks. This analysis is used as a tool throughout the design phase and influences the final product design.25

Next, there are formative human factors studies which are iterative and occur during the product design phase. These studies assess usability risks in real time development and change the product as necessary to address these risks. These may include modifications to the device design or the patient labeling. These formative studies are also used to establish the human factors validation protocol.26

The human factors validation study establishes that the combination product can be used with the risks of serious misuse appropriately mitigated. This study includes pre-defined criteria and assesses a representative population under typical conditions of use. The representative study may include patients, providers and caregivers. Patient demographics and special populations (e.g. visually impaired or arthritic) are considered and final device design and labeling is used. Training and patient and experience levels are additional variables which may be considered in the validation study.27

**Experimental**

For this original research paper, FDA approved Biologics License Applications listed in CDER’s drug approvals by year from 2006-2015 were tabulated and the labeling studied to determine how many of these products were available in injectable combination product formats.28 The publicly available summary basis of approval (SBOA) packages for each biologic-device combination product were then downloaded from the FDA website and reviewed.29 Demographics such as combination product device type, indication and labeling were tabulated. Human factors study data and agency feedback were tabulated and trends noted. Figure creation and statistical analysis was performed using JMP software. The data is presented per approved combination product; if a BLA has multiple combination product presentations (e.g., pen and pre-filled syringe), both are included in the data set as discrete entries.

**Demographics for injectable device-biologic combination products**

Demographics of the combination products were evaluated to understand the patient population and product mix. The indications for these self-injectable products are typically chronic disease states, the most common are hypercholesterolemia, diabetes and rheumatoid arthritis (Fig. 2).

The most common injection frequency for the self-administered biologic products is every 7 to 14 days (Fig. 3), aligning with a need for convenient home use. The majority of recent biologic applications have multiple combination product formats; 71% of the new BLAs approved in 2014 and 2015 have both a prefilled syringe and pen, while only one application prior to 2014 had multiple formats. The most common device is a pre-filled syringe although the use of auto-injectors and pens are increasing; prior to 2013, all but one approval was for a prefilled syringe. In 2014 and 2015, there has been an equal mix among prefilled syringes, auto-injectors and pens (Fig. 4).
Figure 2. CDER Approved Biologic Combination Products by Primary Indication, 2006-2015
Figure 3. Frequency of Administration in Days of Biologic Combination Products, 2006-2015

Figure 4. Biologic Combination Approved Device Types, 2006-2015
Human Factors Studies Survey
A total of 20 injectable biologic combination products were approved by CDER from 2006-2015. Little data were available in the SBOAs regarding initial product design risk assessments and formative human factors studies; these studies are mentioned in passing. Anecdotally, the sponsors who utilized these formative studies and risk assessments in their design and pre-review of protocols by FDA fared better in the formal validation studies.

Of the approved products, 30% of the reviews had no documentation of completed human factors or usability validation studies; all applications without documented human factors studies were for pre-filled syringes in applications approved in 2012 or earlier. More recent pre-filled syringe applications as well as all pen and auto-injector formats included human factor validation studies in the SBOA (Fig. 5). This coincides with establishment of the combination product cGMP regulations and FDA presentations emphasizing the need for human factors validation.30, 31

![Figure 5. Human Factors Studies Validation in Application by Product Type](image)

Human factors validation studies for fourteen (14) products were analyzed in detail for this review. All human factors studies were conducted under an IND and submitted at the time of the Biologics License Application. Generally, the validation studies were designed to evaluate the user group’s ability to safely and effectively use the product as intended in the given environment. Studies included different user types, and varied in age, experience with self-injection, and in some cases, visual or physical impairments. Several validation studies also challenged impact of training on the ability to successfully administer the medication. All studies appeared adequate in the estimation of the FDA for this aspect, as no comments or information requests were noted related to the selection of the population used in the human factors studies. All human factors studies included patients, some included caregivers and healthcare
providers and most studies included these groups in lower numbers (Fig. 6). On average, the largest number of subjects in a study were patients. If a secondary validation was required, the number of subjects was fewer than the original study.

![Figure 6. Boxplot of Number of Subjects Participating in Primary Human Factors Validation](image)

The recent applications consistently include consults from the Center for Devices and Radiologic Health (CDRH) and the Division of Medication Error Prevention and Analysis (DMEPA) for review of the human factors validation studies and more recently are standardized in format. There is consistency in the FDA personnel who are consulted to review these human factors studies.

During human factors studies validation, it is expected that the sponsors define a set of user requirements or tasks that must be met to satisfy the validation criteria. Sponsor packages varied in the number of tasks which were validated (range n=5 to n=22); they also varied in the criticality (range n=0 to n=16) and description of the tasks depending on the device. The variability in both number of tasks and criticality is subjective based on sponsor assessment.

Some review packages were unclear or redacted to which tasks were considered critical or not. In general, tasks were termed as critical (to the safety and efficacy), essential (to the function of the device) or desirable. A critical failure would result in a missed dose, overdose or underdose or the failure of a patient to correctly select a dose. Essential tasks were related to the ability of the patient to safely handle and store the medication. In one case, it was noted that the FDA disagreed with a sponsor’s assessment of the criticality of a task due to that task impacting dose delivered. This resulted in the sponsor performing a secondary validation study to address the critical task. The failures noted in the primary human factors validation studies were wide ranging. While each application did note some failures, these were not all critical and did not all
require revalidation. The number of acceptable failures also varied. Among the applications, the validation failures by type are summarized in Table 1.

<table>
<thead>
<tr>
<th>Device Assembly and Set-Up</th>
<th>Administration Issues</th>
<th>Product Management Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Assembly errors</td>
<td>• Not waiting for time or device click to indicate full dose administered</td>
<td>• Not allowing medication to warm to room temperature for prescribed amount of time</td>
</tr>
<tr>
<td>• Cap removal issue</td>
<td>• Missed doses and underdosing</td>
<td>• Not selecting proper dose/product</td>
</tr>
<tr>
<td>• Needle assembly issues</td>
<td>• Injection difficulties</td>
<td>• Neglecting to check for expiry or product quality</td>
</tr>
<tr>
<td>• Improper reconstitution</td>
<td>• Wrong angle of insertion for injection</td>
<td>• Not recording injection</td>
</tr>
<tr>
<td>• Opening incorrectly</td>
<td>• Wrong grip on injection site</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Incorrect plunger speed</td>
<td></td>
</tr>
</tbody>
</table>

*Table 1. Human Factors Studies Error Types*

Secondary validation studies were required for 36% of the products to re-evaluate critical errors. In these secondary studies, devices were not modified nor redesigned. These studies focused on modified instructions for use, labeling or packaging in a such a way that it clarified directions for patients. Generally, these secondary studies were recognized as being necessary by the sponsor and completed at the time of submission, but in one case, the secondary validation was requested by the FDA.

Of these applications, none of the human factors validation studies were directly correlated to a complete response action by FDA. However, 86% of the applications had information requests related to the human factors validation study and 21% of the applications had clock extensions due to submission of significant new information related to human factors studies. This is a significant regulatory filing in that impacts timelines for approval and market entry. In 100% of the applications reviewed, FDA requested modification to the instructions for use for the combination product because of the human factors studies. In 21% of the applications reviewed, re-validation was required because of the human factors and a single application required that the Risk Evaluation and Mitigation Strategy (REMS) was modified based on human factor results. In many cases, the FDA also recommended additional training to safely and effectively use the combination product. Also notable was that in the event of failures, FDA considered the failure mode against other commercially marketed combination products to determine if the failure or risk was atypical.

**Best practices in human factors studies**

It is critical for BLA sponsors who of these combination products to fully understand the regulatory requirements around human factors studies. Ideally, human factors validation design is discussed with FDA early and often in the drug development process. In this data set of approved applications, the first mention of human factors occurred in End of Phase 2 (EOP2) meetings for half of the applications; the remainder were mentioned at the point of the pre-BLA
meeting or later. While the average approval time in days didn’t vary between applications in which the human factors studies were mentioned at EOP2 versus pre-BLA, cases of earlier approval times were noted when human factors studies were mentioned at EOP2. (Fig. 7).

Figure 7. A Comparison of Time from Filing to Approval (Days) Based on First Mention of Human Factors Studies

In over half of the applications, the FDA gave instructions to the sponsor that the human factors validation studies would be a requirement of the BLA submission, suggesting that there was not likely specific questions or information from the sponsor on the human factors studies prior to the FDA suggestion. Based on the criticality of human device interface and the new FDA guidance, the best practice is to develop risk assessments and formative human factors data early in the process to develop labeling and handling practices which will best suit the patient population. The applications which were the most successful effectively justified critical steps, established risks and demonstrated a robust design which yielded a low potential of critical failures. The expectation of the FDA based on the data reviewed is not that there are zero failures, but that failure modes are well understood and appropriate controls are put in place. Ultimately, the newer applications are consistent with respect to the reviewer identity and feedback and sponsors could certainly benefit from reviewing these studies prior to design of a combination product study intended for FDA review.

Conclusion

This comprehensive study reviewed CDER approved self-injectable biologic-device combination products from 2006-2015. As the availability of self-injected biologics in innovative devices continues to rise, human factors validation studies will be included in a higher percentage of BLAs. As 86% of these applications received information requests and 100% of these applications were required to revise instructions for use due to the human factors validation
results, it is crucial that sponsors integrate the plan for these validation studies into early design programs and discussions with FDA. The review of prior applications with similar device functionality yields useful information on potential failure modes, and may help a sponsor to facilitate successful development and validation of a safe and effective device interface for the patient.

Acknowledgements

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Endnotes


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