TO SUBSTITUTE OR NOT TO SUBSTITUTE? THAT IS THE ANDA QUESTION

Here, Natalie Shortt, Senior Human Factors Specialist; Maija Smith, Human Factors Specialist; and Venetia Dickinson, Human Factors Specialist; all of Emergo by UL, discuss the US FDA's Draft Guidance on how human factors relate to the ANDA process, and how its encouragement to stay close to the reference product may result in some negative consequences.

Regulations within the medical field are continually being refined with an emphasis on improving the protection and wellbeing of all users and patients. The history of medical industry regulation stretches back just over 100 years, thus a multitude of regulations and procedures curtail poor design and ensure device safety and usability. In 2017, the US FDA provided a draft formal guidance document in relation to the human factors (HF) associated with the Abbreviated New Drug Application (ANDA) process: FDA draft guidance UCM536959 – "Comparative analyses and related comparative use human factors studies for a drug device combination product submitted in an ANDA".

The guidance states that when submitting a generic combination product, manufacturers should also consider replicating as closely as possible the user interface (UI) of the reference listed drug (RLD) or "seek to minimise difference from the UI for the RLD".[1] The reasoning is that a patient should be able to switch from the RLD to the new generic without having to undergo additional training or input from a healthcare professional (HCP). This reflects reality as they may be prescribed the generic in place of their usual medication without input from an HCP.

This new guidance explicitly does not replace the usability engineering process outlined in ISO 62366-1:2015,[2] as it states that "FDA does not consider the comparative use human factor studies… to demonstrate the safety or effectiveness".[3] However, it does state that by replicating the UI of the RLD, or by minimising the differences between the UI of the RLD and new generic, applicants may avoid conducting comparative use HF studies.[4]

On the one hand, if manufacturers copy the RLD, they should not need to perform a comparative study. If the RLD itself has HF shortcomings in its design, a usability validation study could lead to a situation whereby the generic device is not determined to be usable by intended users, even if it perfectly mimics the RLD. On the other hand, if a manufacturer changes the design of the generic, for example to address known HF problems with current devices, this may introduce critical design differences which would require a comparative study, which may be costly and time consuming. Therefore, generic manufacturers face a dilemma. Should they copy the RLD design, in which case the generic could be considered by regulators to be "substitutable but not usable"? Or should they innovate, and thus risk the generic being "usable but not substitutable"?

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DECIDING TO REFLECT THE RLD CLOSELY

Avoiding the time and expense of comparative HF studies might not be the only appealing reason for a generics manufacturer to follow the design of the RLD closely. The guidance outlines that an ANDA applicant can rely on the FDA's previous finding that the RLD is safe and effective.[5] UCM536959 intends to apply this thinking to the user interface of the generic combination product.

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Another positive for manufacturers is that if they follow the guidance recommendation that potential applicants should seek to minimise the differences "in the early stages of development",[6] they will have a less complicated design development process overall. In most cases, taking this route will be less time consuming and more cost effective, as the design team has a clear exemplar available to follow, although it should be noted that on some occasions it could be costly to replicate the RLD.

UCM536959 recommends the manufacturer to employ threshold analysis to identify the UI differences of the generic combination product when compared with the RLD.[4] The analysis may identify a number of outcomes:

- **No design differences** that would likely mean that FDA will not request "certain information and/or data, such as data from comparative use human factors studies"
- **Minor design differences** if the identified differences "do not affect an external critical design attribute" and FDA view these minor differences as acceptable
- **Other design differences** if the differences in the UI design "may impact a critical external design attribute that involves administration of the product". In this case FDA "may request that applicants provide additional information and/or data, such as data from a comparative use human factors study".[7]

In cases where the threshold analysis outcome determines there are "no differences" or acceptable "minor differences", there may be no need for a HF comparative study, again potentially saving time and costs. It certainly would appear to be a less risky approach regarding the potential approval from the FDA, as it has approved the RLD already.

Furthermore, if the design of the generic is close to the RLD, end users might already be familiar with the UI and therefore some may be more accepting of it. This would satisfy the desired recommendation that the switch from the RLD to the generic should not require additional training or intervention from an HCP.[4]

Keeping the design of the generic combination product as close as possible to the RLD design to avoid "other differences" when conducting the threshold analyses might also be seen as a low-risk strategy. However, the assessment of design differences is subjective, and it is possible for manufacturers to underestimate the differences in the UI design and class them as minor when they should, in truth, be classed as "other differences". Another possibility is that they may acknowledge the difference but argue that the difference improves the usability of the product. Although the generic manufacturer could be right, it can be difficult to argue that a specific difference does not affect or improve the usability of the generic combination product if there is no evidence present to demonstrate this. This can result in submitting the ANDA application without conducting a comparative HF study that the FDA recognise as being necessary evidence for the approval of the generic combination product, which may set back timelines. This could be considered too great a risk for some manufacturers.

However, maintaining similarity with the RLD's UI raises a question as to whether this approach to HF in an ANDA submission might negatively affect the potential improvement of the generic product's usability. Technology and manufacturing capabilities tend to progress and can lead to new design opportunities that would not have been possible at the time when the RLD product was developed. It could be that by choosing to minimise design differences, the potential improvement of the product (and possibly improvement to patient safety) is disregarded.

ADDRESSING RECOGNISED CONCERNS OF THE RLD'S UI

In principle, ANDAs allow a manufacturer to launch a generic combination drug product "to provide a safe, effective, lower cost alternative" to the RLD.[8] By using an ANDA, products can, in theory, get to market more quickly, and give HCPs a wider variety of treatment options. However, does the new HF guidance impede innovation in the design and usability of generic combination products?

The rate of technological advancement is important to consider. Technology is constantly in development to improve usability, function and even compliance with respect to device use. Due to the ANDA HF guidance, a company could look to replicate old technology currently on the market, that may have been designed before usability engineering even became accepted as a necessity. Taking these steps would minimise differences and the likeliness of comparison testing, but it would inhibit the adoption of new technology.

In instances where manufacturers follow the design of the RLD, predicate devices on the market are becoming not just the building blocks for new devices, but the entire structure. This could lead to the same post-market adverse events occurring as companies look to reduce the time and testing it takes to get their product launched.

Over the past two decades, the British Standards Institute (BSI) has found that there have been "alarming trends"[7] in post-market events for medical devices that can be attributed to UI design issues. This suggests that usability needs to be continuously advanced – not impeded.

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Combination products, such as autoinjectors and inhalers, have a known history of use errors due to poor use-related design. These use problems cause improper drug delivery, poor symptom control, delays in treatment and overdoses.[9] Figure 1 illustrates just one possible user error and the consequences thereof.

The guidance states that the proposed generic product may develop a user interface that has certain differences, however these differences may only be accepted by the FDA if they are "adequately analysed" and "scientifically justified".[10] A company may choose to improve a design to remove known UI concerns. However, in doing so they are at the risk of altering the design to the point where a negative threshold analysis outcome becomes a distinct possibility. Without appropriate analysis, the guidance states that in this case the generic manufacturer could be required to perform comparative use HF studies, adding to the cost of the project and delaying the time to market.

In this sense the regulation might dissuade companies from making necessary changes to a device. A generic combination product that has had few interface alterations would have a positive threshold analysis, but fail to reduce the known use errors of the reference product. A concern is that companies may find it an easier route to copy a product that users know, rather than looking to innovate safer solutions. The requirement to perform a comparative study gives making changes to the UI a negative connotation that requires time and money to justify, rather than highlighting the improvements or innovation.

CONCLUSION

Medical device regulations are clear in their desire to mitigate risk and improve device safety. However, at what point do known use errors become accepted into a design? This is a question that regulatory agencies, as well as medical device companies, need to think carefully about for not only the future of the industry, but the wellbeing of users.

ABOUT THE COMPANY

EMERGO by UL's human factors research & design (HFR&D) team is a highly-experienced, global team that specialises in early-stage user research, product design, usability testing and user interface design. With a primary focus on medical devices and combination products, the team has extensive experience helping clients bring safe and effective products to market and ensuring best-in-class user experiences. The team includes over 60 specialists and has offices in the US, UK, the Netherlands and Japan.

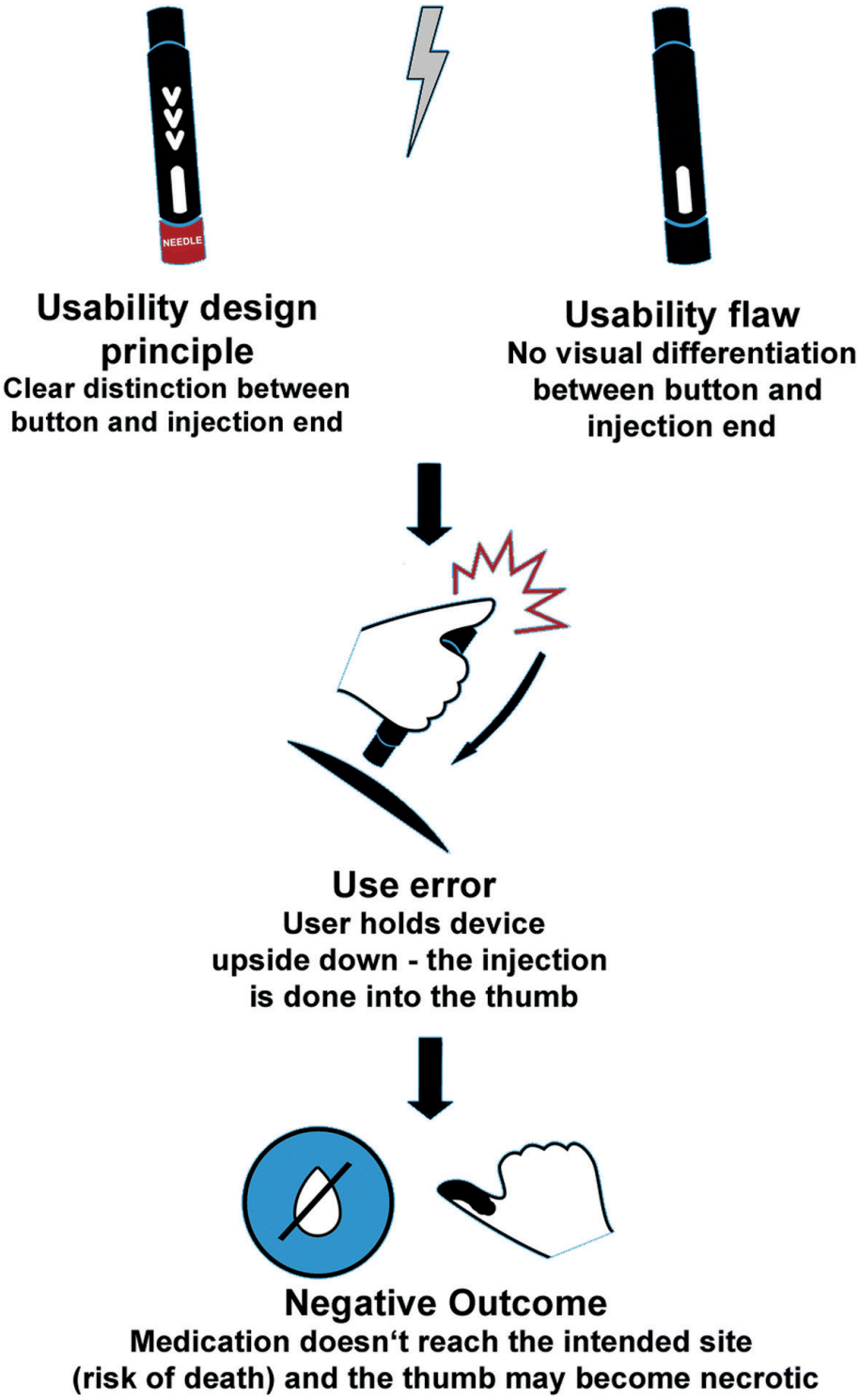

Figure 1: Schematic representation of the cause-and-effect chain between a use error and the negative outcome. Originally from Weinhold T et al, "Improving the safety of disposable auto-injection devices: a systematic review of use errors". AAPS Open, 2018 Vol 4(7). Reprinted under Creative Commons 4.0.

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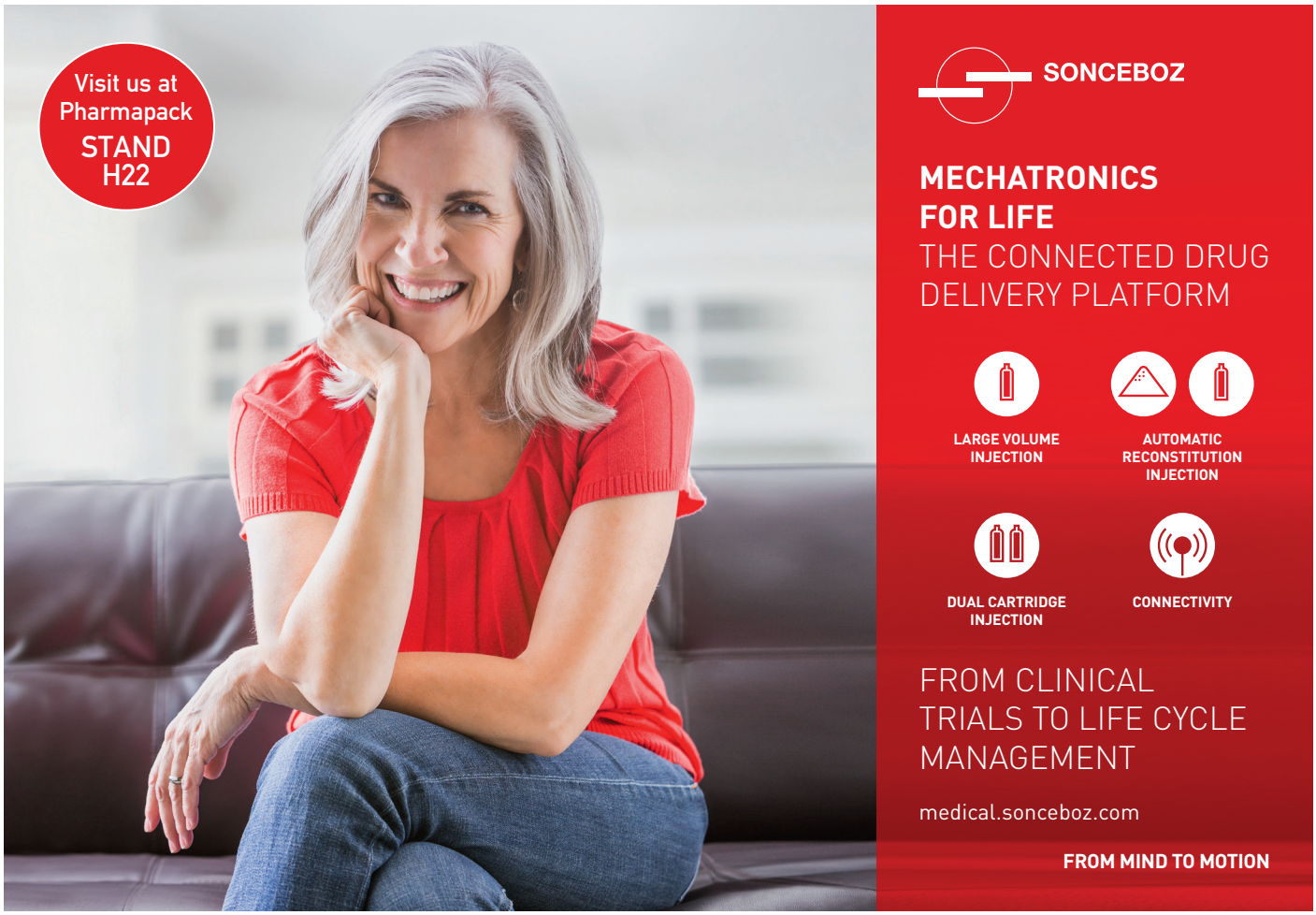

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