COMBINATION PRODUCT DATA BRIDGING

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AGENDA

- Published Guidance from FDA on Clinical Bridging
- Examples of When Data Bridging May Be Necessary
- Potential Data Package to Support Device Bridging
- Clinical Home Use Study Design
- FDA Feedback on Need for Clinical Home Use
- Leveraging Pre-existing Data
- Conclusions

FDA HAS PUBLISHED GUIDANCE ON BRIDGING… LIMITED BUT HIGHLIGHTS 3 AREAS

Guidance for Industry Rheumatoid Arthritis: Developing Drug Products for Treatment DRAFT GUIDANCE (May 2013):

We acknowledge that changes to the drug product delivery system may occur. Changes in the formulation, excipients, or device components may affect the drug product delivery characteristics and clinical performance of the drug-device combination product. The extent of clinical data needed to support such changes depends on the nature of the change and the development stage. For example, **a transition from a prefilled syringe to an autoinjector delivery system involved the following, at minimum:**

- **Human factors studies to evaluate potential use-related risks of the modified combination product**
- **A pharmacokinetic bridging study that demonstrates similar delivery of the drug product to the same biospace across a range of body weights**
- **Real-life patient handling experience to assess device performance as discussed above.**

Depending on the extent of the proposed changes, additional clinical data may be needed to support efficacy and safety, including immunogenicity.

WHEN DO WE NEED TO BRIDGE DATA FOR A COMBINATION PRODUCT?

- **There are many situations where data bridging might be necessary.**

SITUATION	EXAMPLE
Delivery system not used in pivotal trials for a new drug program	A new product intended for both prefilled syringe (PFS) and autoinjector (AI) presentations, but only the PFS was used in pivotal trials because the AI was not available
Development of a novel delivery system for an approved drug	Development of an on-body injector for a drug that is only available in PFS and AI.
Design change to the drug delivery system for an approved drug	Addition of a manual needle guard to a marketed product with classic PFS
New intended user	An HCP-use only product filing for self-administration claim
Other special situation	A biosimilar product filing for interchangeability claim

POTENTIAL DATA PACKAGE TO SUPPORT DEVICE BRIDGING

1	Drug Product Compatibility (DP) + Design Verification (DV)
2	DP + DV + PK
3	DP + DV + PK + Human Factors (HF)
4	DP + DV + PK + HF + Clinical Home Use (CHU)
5	Phase 3 Pivotal Trial

CLINICAL HOME USE STUDY

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‘REAL-LIFE PATIENT HANDLING EXPERIENCE’ ACHIEVED THROUGH CHU STUDY DESIGNS

Clinical investigation to assess the ability of the device to deliver a full dose of Investigational Drug (ID) when used by the intended user as a home use device.

Not intended to evaluate device HFE/UE

[20] The term “HF Actual-Use Validation study” has a different meaning than similar terms such as “user study” or “actual use study”. The term “HF Actual-Use Validation study” applies to only the evaluation of the user interface and associated critical tasks. In contrast, the terms “actual use” or “user study” (without the “HF” qualifier) often refer to clinical studies such as a major clinical study to evaluate safety and effectiveness of prolonged home use or to an open label safety study. Those studies have different purposes or mixed purposes and are outside the scope of this document. FDA recommends against referring to these different or mixed purpose studies as HF studies.

Human Factors Studies and Related Clinical Considerations in Combination Product Design and Development – DRAFT Guidance from CDER/CBER/CDRH/OCP (Feb 2016)

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CHU STUDY DESIGNS INCLUDE BOTH DISCRETE AND OLE EXAMPLES

	Day 1 (Baseline)	Week X	Week X	Week X	Week X	Week X	Week X	Week X	Week X
Self-injection	X	X	X	X	X	X	X	X	X
Subject Self-injection Questionnaire		X	X	X	X	X	X	X	X

CHU STUDIES ARE SMALL WITH THE PRIMARY ENDPOINT AS SELF-REPORTED SELF-INJECTION

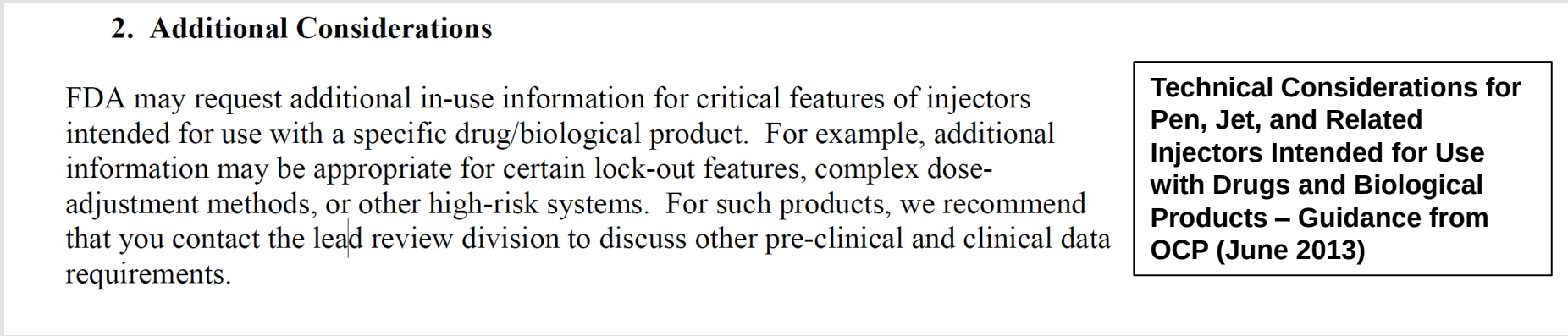
- **Sample Size:** 50 - 100
- **Primary Endpoint:** Successful self-injection as evaluated by the proportion of successful injections of the total attempted doses self-administered by subjects in the home-use setting from week 1 through end of study. Tool: Subject Self-injection Questionnaire**.**
- **Secondary Endpoint(s):** 'Efficacy' at week X

  AI system failure (post study analysis) defined as the failure of the device to perform according to device design requirements (yes/no) from week 1 through end of study
- **Safety Endpoints:** Adverse events, serious adverse events, adverse device effects, anti-drug antibodies
- **Statistical Considerations:** Estimation study with no formal statistical hypothesis tested. Primary endpoint is the successful self-injection as evaluated by the proportion of successful injections of the total attempted doses self-administered by subjects in the home-use setting from week 1 through end of study.

CHU QUESTIONNAIRE ZEROS IN ON INFORMATION FOR COMPLETE INJECTION

Questions address the users perspective on whether an injection was completed and may also include queries for:

- Rating for ease of use
- Evaluation of cues used to determine that a complete dose was delivered
- How the instructions were used



2. Additional Considerations

FDA may request additional in-use information for critical features of injectors intended for use with a specific drug/biological product. For example, additional information may be appropriate for certain lock-out features, complex dose-adjustment methods, or other high-risk systems. For such products, we recommend that you contact the lead review division to discuss other pre-clinical and clinical data requirements.

Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products – Guidance from OCP (June 2013)

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CHU STUDIES PROVIDE INFORMATION BEING REQUESTED BY CDER AND OCP

POSITIVE ASPECTS	NEGATIVE ASPECTS
• Limited study artifacts from simulated environment and simulated use due to actual injections • May be able to collect clinical measures (PK, PD) as an objective measure of ability to self-inject *(not usually the intended direction of study design – questionnaire is preferred)*	• Inadequate to test design and use limits • Doesn't approximate the worst case scenario, such as users receiving minimal or even no training • Limited ability to catch "close calls" or patterns of misuse • Limited ability to observe and query users on use errors

FDA FEEDBACK ON PFS, AUTOINJECTORS AND ON-BODY DEVICES

- **Division of Oncology Products (DOP)**
- **Division of Bone, Reproductive and Urologic Products (DBRUP)**
- **Division of Metabolism and Endocrinology Products (DMEP)**
- **Division of Pulmonary, Allergy and Rheumatology Products (DPARP)**
- **Division of Neurology Products (DNP)**

FDA REQUIREMENT FOR CLINICAL ACTUAL USE STUDY (2011-2016)

FDA Division	Prefilled Syringe (PFS)	Autoinjector (AI)	On-body Injector
A	--	--	*YES*
B	*NO* (x2)	*NO* *NO* (x2) *YES*	--
C	*YES*	*YES*	--
D	*YES*	*YES*	--
E	*YES*	*YES* NO (x2)	*YES*

VARIABILITY IN FDA DIVISION REQUIREMENTS, EVEN BETWEEN THE SAME AUTOINJECTOR

1) **None** needed:
   - Can leverage another product or no requirement for CHU

2) CHU study required but design **Inline** with published guidance:
   - Primary endpoint of successful self-injection as evaluated by the proportion of successful injections of the total attempted doses self-administered by subjects in the home-use setting. Limited secondary endpoints (eg, device failure analysis) and safety endpoints included (AEs, ADEs, ADAs).

And....

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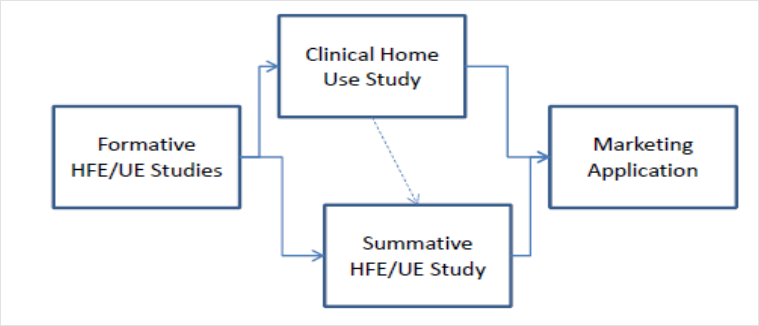
VARIABILITY IN FDA DIVISION REQUIREMENTS, EVEN BETWEEN THE SAME AUTOINJECTOR

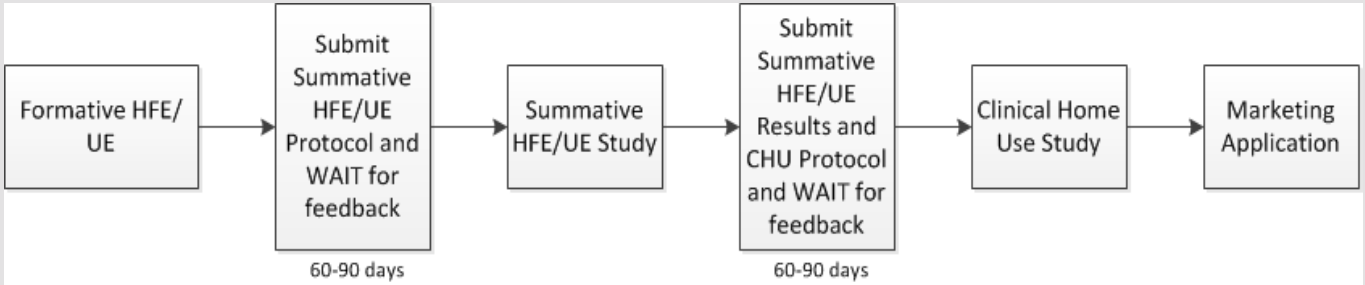
3) CHU study required but design **More extensive** than published guidance:
   - Agency recommendations:
     - Completion of all HF testing prior to introduction of the device into the clinic
     - Sponsor await feedback on both HF and CHU study protocols prior to initiation
     - FDA review HF data prior to starting the clinical study (60-90 days and usually no commitment to a specific timeline for review)
   - Requirement that the CHU study provide objective data of successful injection (possibly bridging back to efficacy data). This includes clinical measures to adequately assess the impact of patient self-administration.
   - Requirement that the tools used in the CHU study for self-report be robust and validated

CONSECUTIVE SEQUENCING OF HFE/UE AND CHU ADDS TIME BUT REDUCES REGULATORY RISK

~ 10 months



~ 18 months



Significant issue: No timeline for review

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DATA LEVERAGING STRATEGY

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IS IT POSSIBLE TO LEVERAGE EXISTING DEVICE DATA?

Yes, it's possible to leverage data from both approved products and development programs, but leveraging existing data may not be as simple as it seems.

Some reasons to NOT leverage existing data:

- Need to provide strong justification of leveraging strategy in Design History File (DHF) and submission
- Potential impact on other documents in the DHF
- Potential implication across programs from which data are leveraged
- Might not produce time-savings
- Additional chance of an information request during filing review and risk of delaying approval

BEFORE MAKING THE DECISION TO LEVERAGE DATA…

- **Existing data and impacted documents should be reviewed by SME's and gap analyses should be generated**
  - Decisions should not be made without reviewing in detail if the data fully satisfies the requirements.
  - Example of challenge: Programs conduct new risk assessment differently from previous programs, resulting in inconsistency of risk mitigations to be evaluated in HF Study.
- **Global requirements should be considered**
  - While there is more scrutiny on combination product requirements in the US, a data leveraging strategy accepted by FDA might not be acceptable in other regions.
  - Product ownership in different countries should be considered.
  - Example of challenge: Limited regional experience to understand clinical data requirement for combination product.

KEYS TO SUCCESS WHEN LEVERAGING DATA

- **Data leveraging strategy should be confirmed early**
  - Design control is a step process, so a change in strategy late could affect upstream work completed, resulting in potential deviations.
  - Example of challenge: A formative HF study was completed before the team decided to leverage summative HF data from another program. The team then has to justify why the use errors observed in the more recent formative study have no impact on design.
- **Design review for the verification and validation phase should be completed prior to submission of IND/BLA**
  - To ensure alignment between submission information and internal documentation.
  - Example of challenge: A program submitted the BLA without closing V&V because the outstanding data was not necessary for submission, but during the design review new issue was identified.

CONCLUSIONS

- **Simulated HFE/UE data plus pharmacokinetic data is sufficient to ensure safety and efficacy of the drug delivery device**
  - **Simulated HFE/UE adequately identifies possible usability issues with the product**
  - **Pharmacokinetic data demonstrates similar delivery of the drug product**
- **There's a need for FDA to set transparent policy, to include a standardization of requirements across programs/companies/devices for actual use data requirements for self-administration and home use.**
- **It's possible to leverage data from both approved products and development programs but impact and global requirements should be considered.**

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QUESTIONS?