



# Combination Drug Applications: Nonclinical Reviewer Perspectives

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# Disclaimer

The opinions expressed in this presentation are solely my own and do not reflect those of the FDA, nor Agency policy

# Outline

- Overview of Nonclinical Studies for Combination Drug Applications
- **Case Study #1**: New Molecular Entity (**NME**) + Marketed Drug (**MD**) example
- **Case Study #2**: Antibody (**Ab**) + **Ab** example
- **Case Study #3**: **NME/MD Peptide** + MD (**Insulin**) example
- FDA Biologic Transition plan

# Additional Studies to Support NME + MD Combination

## 1. $\leq 90$ -day Bridging study

- **Single, most appropriate species**
- ***Required to support clinical studies  $\geq 3$  months***

## 2. Embryo-Fetal Development (EFD) study may be required

- Single, most appropriate species

## 3. Efficacy study may be required

- Drug interaction affecting efficacy
  - Applies primarily to life-threatening indications with products approved under the Animal Rule

## 4. Additional studies may be requested

- Synergistic drug interaction with unknown mechanism
  - PK, PD, or overlapping toxicity

# EFD Study?

## FDA Guidance\*

- EFD study **should** be conducted
  - “Embryo-fetal development studies of the combination should be conducted...”
- EFD study is **not** required
  - If **either alone** poses a risk
    - “[If] the marketed products are already **known** to have significant risk for developmental toxicity (e.g., one of the marketed drugs has been assigned a pregnancy category “D” or “X”).”

## ICH M3(R2) guidance

- EFD study **is** required
  - Combination poses a developmental risk
    - “concerns exist, based on the **properties** of individual components, that their **combination** could give rise to a hazard for humans.”
- EFD study is **not** required
  - If **either alone** poses a risk
    - WOCBP population and “**individual agent(s)** have shown findings indicative of embryo-fetal risk, combination studies are not recommended”
  - **Neither alone** poses a risk
    - “If nonclinical embryo-fetal studies have indicated that **neither agent** poses a potential human developmental risk, combination studies are not recommended.”

\* FDA Guidance for Industry Nonclinical Safety Evaluation of Drug or Biologic Combinations

# EFD Study? ICH Supercedes

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**Option: Submit an IND or pre-IND question to the FDA Division covering the pursued indication**

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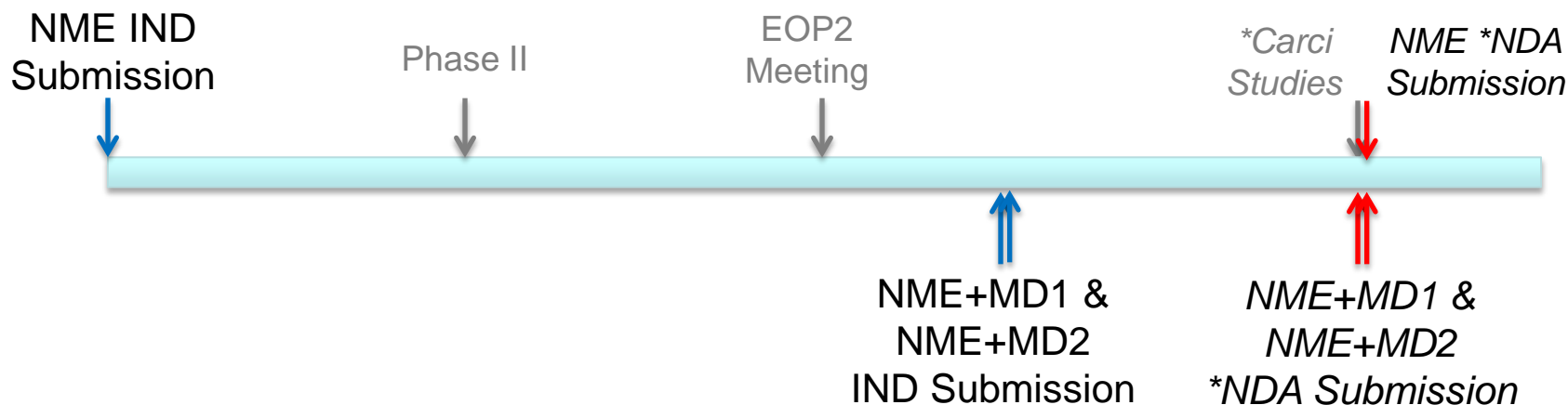
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- Case Study #2: Ab + Ab example
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# Case Study #1

## NME + 2 different MD's

- NME + MD1
  - SGLT2 Inhibitor + Biguanide
- NME + MD2
  - SGLT2 Inhibitor + dipeptidyl peptidase 4 (DPP-4) inhibitor



\*Submitted Simultaneously

Support NDA for NME Alone



# Case Study #1

## NME Alone

- Characterized NME
  - Primary Pharmacology
  - Pharmacodynamic
  - Secondary Pharmacology
- Full Battery of Nonclinical Safety studies
  - Safety Pharmacology
  - PK/ADME
  - General Toxicology
  - Genetic Toxicology
  - Reproductive & Developmental Toxicology
  - Carcinogenicity

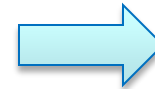
Safety Pharmacology		PK/ADME	
<ul style="list-style-type: none"> <li>✓ Cardiovascular</li> <li>✓ Respiratory</li> <li>✓ CNS Neurological</li> <li>✓ Abuse Liability</li> <li>✓ Pharmacodynamic</li> <li>✓ Immunogenicity</li> </ul>		<ul style="list-style-type: none"> <li>✓ Protein Binding</li> <li>✓ Pharmacokinetics</li> <li><input type="checkbox"/> Absorption</li> <li><input type="checkbox"/> Distribution</li> <li><input type="checkbox"/> Metabolism</li> <li><input type="checkbox"/> Elimination</li> </ul>	
Species	Toxicity		
Mice & Rats	Single-dose (or multiple dose <24 hours) IV & intended route (+14 days observation) → support clinical single-dose Ph I clinical studies. ✓ 2 species - OR - ✓ DRF/escalation MTD study in 1 species		
ND	2-wk repeat-dose study → support clinical studies up to 2 weeks		
Mice: 3-wk, 4-wk, 13-wk Rat: 3-wk Monkey: 5-wk, 15-wk	2-wk to 6-mo repeat-dose study → support clinical studies of ≤ duration of nonclinical study		
	6-mo rodent repeat-dose study → support clinical studies > 6 months* - OR -		
	6-mo non-rodent repeat-dose study → support clinical studies > 6 months*		
Genetic Toxicity		Carcinogenicity	
<ul style="list-style-type: none"> <li><input type="checkbox"/> In Vitro Mutation Assay (Ames)</li> <li><input type="checkbox"/> In Vitro Chromosome Aberration</li> <li><input type="checkbox"/> In Vivo Clastogenicity Assay</li> </ul>		<ul style="list-style-type: none"> <li><input type="checkbox"/> 2-yr Rat                             <ul style="list-style-type: none"> <li><input type="checkbox"/> Protocol submitted</li> </ul> </li> <li><input type="checkbox"/> 18-mo Mouse                             <ul style="list-style-type: none"> <li><input type="checkbox"/> Protocol submitted</li> </ul> </li> </ul>	
Repro Tox			
<ul style="list-style-type: none"> <li><input type="checkbox"/> Segment I: Fertility and Early Embryonic Development</li> <li><input type="checkbox"/> Segment II: Embryonic Fetal Development</li> <li><input type="checkbox"/> Segment III: Prenatal and Postnatal Development</li> </ul>			

# Case Study #1

## Fixed Dose Combination (FDC): NME + MD

### **FDC: NME + MD1**

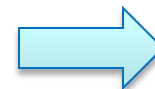
1. 90-day Bridging study



**Support NDA  
for NME+MD1  
FDC**

### **FDC: NME + MD2**

1. 90-day Bridging study



**Support NDA  
for NME+MD2  
FDC**

**EFD Studies have not been required**

# Case Study #1: Bridging Studies

## **NME + MD1**

- Likely synergistic
  - Decreases in body weight and weight gain
  - Increased food consumption
- Likely additive
  - Increased heart organ weight
    - No evidence of damage or dysfunction
- Additive/Synergistic effects 2<sup>nd</sup>-ary to PD
  - Decreased blood Na & creatinine
    - No evidence of kidney dysfunction
- Lower NME exposure

## **NME + MD2**

- Additive/Synergistic
  - Stomach erosion, hemorrhage, glandular mucosa discoloration
    - reversible
  - Increased adrenal gland organ weight & adrenal cortex hypertrophy
  - prostate mixed cell inflammation

**Same NME in FDC with different drug classes**



**Different Additive & Synergistic Tox Profiles of FDC's**

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- Case Study #1: NME + MD example
- **Case Study #2: Ab + Ab** example
- Case Study #3: NME/MD Peptide + MD (Insulin) example
- FDA Biologic Transition plan

# Case Study #2

## Ab + Ab Combination

- Indication for obesity
- 2 separate INDs for each Ab
- PD synergy on body weight and food consumption anticipated
- Range of Fixed Dose Ratios

# Case Study #2

## 2 Individual Ab INDs

- Individual IND characterization for a biologic
- Define drug exposure and clearance in toxicology species
- Determine fraction bound and unbound to serum, assuming free fraction is active pool

Safety Pharmacology		PK/ADME	
<ul style="list-style-type: none"> <li>✓ Cardiovascular</li> <li>✓ Respiratory</li> <li>✓ CNS Neurological</li> <li>✓ Abuse Liability</li> <li>✓ Pharmacodynamic</li> <li>✓ Immunogenicity</li> </ul>		<ul style="list-style-type: none"> <li>✓ Protein Binding</li> <li>✓ Pharmacokinetics</li> <li><input type="checkbox"/> Absorption</li> <li><input type="checkbox"/> Distribution</li> <li><input type="checkbox"/> Metabolism</li> <li><input type="checkbox"/> Elimination</li> </ul>	
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\* Both rodent and non-rodent chronic studies required for clinical studies > 6 months.

# Case Study #2: Ab + Ab

- 90-Day Bridging Study
  - Additional studies may be requested, since PD synergism is anticipated
  - Include arms with individual Abs and doses “reasonably similar” to allow evaluation of the degree of synergism
- Feedback on pre-clinical doses given that a range of ratios will be investigated in the clinic
  - *“Specific dosing ratios would most likely not limit clinical dosing and that adequate support would come from the doses and systemic exposure achieved with the individual compounds in preclinical studies.”*
  - *“This presumes that different ratios of the components do not change the toxicity profile to the extent that extrapolating results to an untested ratio becomes untenable. “*
  - *“recommended that the non-clinical and clinical ratios be reasonably similar, because uncertainty will increase if the ratio used clinically substantially differs (e.g., multiple-fold) from the ratios tested non-clinically.”*



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- **Case Study #3: NME/MD Peptide + MD (Insulin) example**
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# Case Study #3

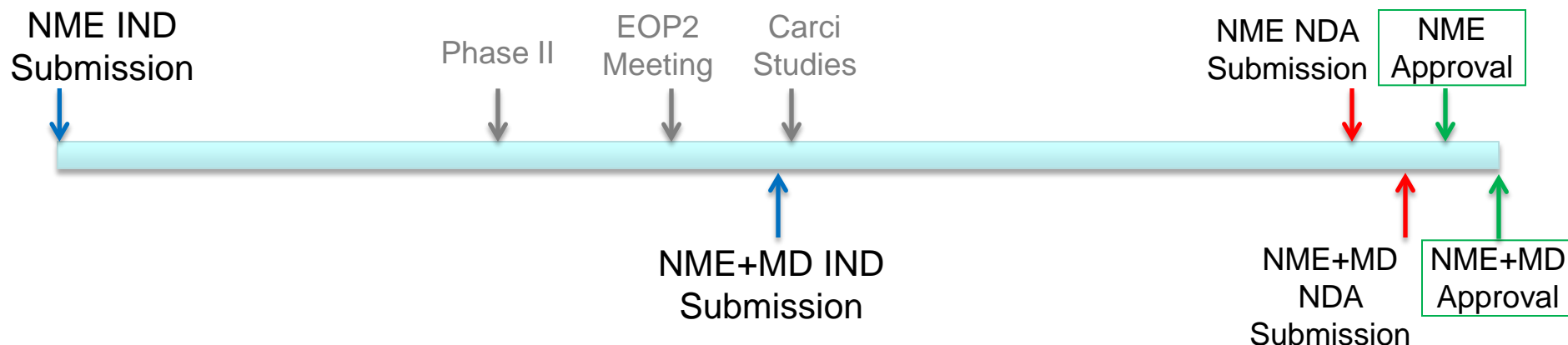
## NME/MD (peptide) + MD (Insulin) FRC

- Glucagon-like peptide-1 (GLP-1) receptor agonist + recombinant human insulin
  - NME: synthetic 44 a.a. peptide
  - MD: Insulin with prolonged absorption properties
- 2 fixed-ratio solutions
  - Maximum NME dose
  - Range of insulin doses
  - Prefilled pen-injector **Device**

# Case Study #3

## NME/MD peptide

- NDA for peptide alone
  - 1 of 6 GLP-1 receptor agonists approved for T2DM
- Phase I, II & III trials with insulin co-administrations and/or FRC
- Timeline:



# Case Study #3: Nonclinical Studies

## NME/MD peptide + Insulin

- Pharmacology Studies
  - **Potential PD interaction**
    - Mechanistic in vitro studies
    - *Acute glycemic effects in db/db mice and dogs*
  - **Potential PK interaction**
    - Acute plasma exposure PK studies in dogs
- Toxicology
  - **Potential toxicologic interaction?**
    - Apoptosis in rat thyroid carcinoma cells
    - Proliferation in human pancreatic beta cells
    - CV function with single dose in dogs
  - *Local tolerance studies in rabbits*

Required by the Guidance  
Submitted with Ph I protocol

# Case Study #3: Pharm, PD & PK

- **Potential PD interaction**

Required by the Guidance  
Submitted with Ph I protocol

- Mechanistic in vitro studies

- Insulin does not inhibit ligand binding to GLP-1 receptor
- NME does not bind insulin receptor
- No cross-receptor activation or inhibition

- **Acute glycemic effects**

- Significant increase in glucose lowering
  - Additive in db/db mice
  - Less than additive in dogs
- Improved glucose tolerance in dogs
  - Additive suppression of glucose surge

- **Potential PK interaction**

- Acute plasma exposure PK studies in dogs
  - Slightly lower NME  $T_{1/2}$

# Case Study #3: Toxicology

- **Potential toxicologic interaction?**

Required by the Guidance  
Submitted with Ph I protocol

- Apoptosis in rat thyroid carcinoma cells

- To address GLP-1R agonist class warnings for C-cell hyperplasia & neoplasia, as well as C-cell adenoma & carcinoma at high doses of the NME/MD peptide
- Reduction in apoptosis at very high doses of combination, but far above clinical exposures

- Proliferation in human pancreatic beta cells

- To address GLP-1R agonist class-related pancreatic hypertrophy in animals and pancreatitis in post-marketing reports
- No interaction with combination

- CV function with single dose in dogs (6-2011)

- To address small risk with each component
- No combination-related changes

- ***Local tolerance studies in rabbits***

- No significant combination-related findings

# Case Study #3: Conclusions

## NME/MD peptide + Insulin

- Anticipated PD-related glycemic interaction
  - Additional risk of hypoglycemia
- • No pharmacological interaction
  - No cross-receptor activation
- • No significant PK interactions
- No combinatorial toxicologic Interactions
  - safety profile of the fixed dose combination was comparable with that of the individual components

→ Extensive experience with Insulin

3-month bridging study was **not** required, even prior to NME market approval

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- **FDA Biologic Transition**



# Biologic Transition: Concerns

## Insulin Makers To FDA: Clarify 'Transition' Impact On Drug/Biologic Combos

23 May 2016 | NEWS



by Sue Sutter

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## US FDA Biologic Transition Plan Creates 'Dead Zone' For Applications, Sponsors Fear

*This article was originally published in SRA*

23 May 2016



by Sue Sutter

@PinkSheetSutter

sue.sutter@informa.com

- Concern for loss of Hatch-Waxman protections and exclusivity when products are removed from the Orange book.
- Which pathway(s) should **combination products** be submitted?
- Concern about a “Dead Zone” or “Blackout Period”
  - could last for years because sponsor’s would feel the need to wait to submit their drug application until after the transition date.
  - **Disruption of ongoing reviews** of applications submitted after March 2019

# FDA Biologic Transition\*

## **Biologics Price Competition and Innovation Act (BPCI Act)**

- abbreviated licensure pathway in section 351(k) of the Public Health Service (PHS) Act for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed biological reference product
- **Transition Provision:** Insulin, human growth hormone and protein products [traditionally approved as drugs under the Food, Drug and Cosmetic (FD&C) Act] will be licensed as biological products
  - Includes **all proteins**
    - **Protein:** alpha amino acid polymer with a specific defined sequence >40 amino acids
  - Does **NOT** include **peptides** (≤40 amino acids) or **chemically synthesized polypeptides**
    - **Chemically synthesized polypeptide:** “...alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in size.”
  - Affected products will be **considered biologics, not drugs**
    - Previously approved products will no longer be “listed drugs” and will be removed from the “Orange Book”

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    - **Protein:** alpha amino acid polymer with a specific defined sequence >40 amino acids
  - Does **NOT** include **peptides** (≤40 amino acids) or **chemically synthesized polypeptides**
  - *Ch* is made
  - er
- Affe
- Pr
- fr

Transition Date = **March 23, 2020**

- 10-year transition period began in 2010

# Biologic Transition: Impact on New Product Applications

- Affected NDA [505(b)(1) & 505(b)(2)] or ANDA [505(j)] applications (submitted after March 2019) will need to be **resubmitted as BLA, 351(a)** or **351(k)** applications prior to approval (after March 23, 2020)
  - No approvals under Sec. 505 for a biological product subject to the transition provisions that is pending or tentatively approved on March 23, 2020. Such applications may be withdrawn and resubmitted under 351(a), the traditional BLA pathway, or as a biosimilar under 351(k).
  - Nevertheless, the **review process** of study data will have begun during the **interim**

No Significant Disruption of Ongoing Reviews Anticipated

# Biologic Transition: Impact on Nonclinical

- How does the Biologic Transition Plan affect nonclinical development programs?
  - How are nonclinical requirements going to be different?
- How does the Transition affect Combination product applications with qualifying components?

# Nonclinical Studies: Drug vs Biologic

## New Chemical Entity (NCE)\*

- Safety Pharmacology
- PK & Protein Binding
- ADME
- General Toxicology
  - 6 month rodent - **AND** -
  - 9 month non-rodent
- Genetic Toxicity
- Carcinogenicity
- Reproductive & Developmental Tox

## New Biologic Entity (NBE)\*\*

- Safety Pharmacology
- PK & Protein Binding
- General Toxicology
  - 6 month rodent - **OR** –
  - 6 month non-rodent
  - Immunogenicity
  - Local tolerance
- Carcinogenicity
- Reproductive & Developmental Tox

\* ICH-M3

\*\* ICH-S6

# Biologic Transition: Combination Products

- Applications

- Type of application will likely depend on the presence of a biologic

- **BLA:** NBE or MB in the combination

- NBE + NBE, or NBE + MB

- NBE + MD

- NCE + NBE, or NCE + MB

- **NDA:** NCE in the combination

- NCE + NCE, or NCE + MD

- Nonclinical Development

- Combination Studies\*

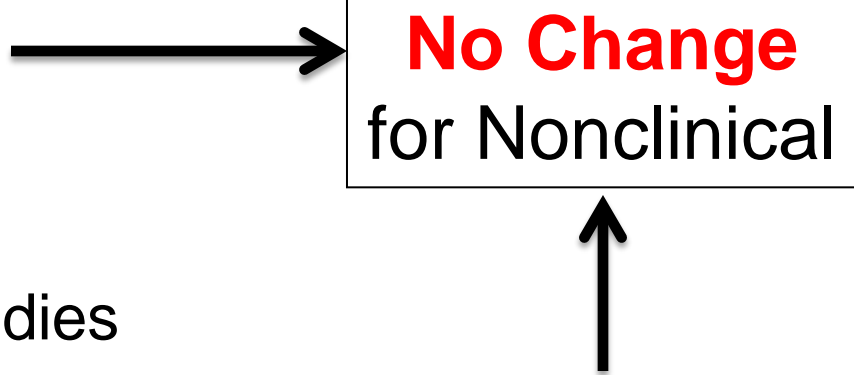
- NDA and/or BLA

- ≤90-day bridging study, PD & PK studies and possible EFD study

**No Change**  
Anticipated for Nonclinical

\* FDA Guidance for Industry: Nonclinical Safety Evaluation of Drug or Biologic Combinations

# Biologic Transition: Impact on Combination Examples

- Ab + Ab combination
    - Submit BLA application
      - NBE + NBE
    - No additional nonclinical studies
  - NME (syn. peptide) + **MB** (Insulin) combination
    - Submit **BLA** application
    - No additional nonclinical studies
- 



# Contacts for FDA Biologic Transition Questions

- For general questions related to FDA's implementation of the BPCI Act
  - Contact Sandra Benton in CDER's Office of Medical Policy at 301-796-2500.
- Products regulated by CDER
  - Biosimilars Program Staff in CDER's Office of New Drugs at 301-796-0700.
  - Reviewing Division
    - Submit Pre-IND or IND questions
- Products regulated by CBER
  - Office of Communication, Outreach and Development (OCOD) at 800-835-4709 or 301-827-1800 or by email to [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov)

# Take Home Messages

- The same NME can have different additive and/or synergistic effects with different MD components
- Nonclinical study requirements for combination products
  - If in doubt or if you think a study isn't needed, submit a question to the FDA division reviewing the product
    - Submit rationale
- Nonclinical doses for FRC or FDC products
  - Include treatment arms of highest dose of each product alone
  - Include treatment arms with FDC or FRC reasonably similar to anticipated clinical doses/exposures
  - Submit dosing questions to the FDA division for concurrence
- Combination applications can be submitted prior to approval, or concurrently with, the application for the NME component.
- In 2019, do not wait until after March 2020 to submit an NDA or ANDA application
  - Review process will have begun
  - No significant changes in nonclinical requirements are anticipated



# Thank You!

## Questions?