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Clinical Significance of Therapeutic Peptide and Protein Drug Interactions: A Call to Action

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Although insulin was discovered more than 100 years ago, the significant shift toward biotherapeutic drug development only began at the start of this century. This issue of *Clinical Pharmacology & Therapeutics* (*CPT*) presents two White Papers on therapeutic peptide and protein drug–drug interactions (DDIs). They make the case that the science and best practices in this area have not been keeping up with the rapid growth in the development of these biological modalities. Säll *et al*. report findings from a cross-industry therapeutic peptide DDI working group consisting of drug metabolism and pharmacokinetics experts from 10 leading pharmaceutical and biotechnology companies, established in 2020 under the sponsorship of the European Federation of Pharmaceutical Industries and Associations (EFPIA; www.efpia.eu). This working group surveyed 10 pharma companies involved in the development of peptide drugs to better understand the type and timing of DDI studies commonly undertaken for such therapeutics, and compiled a database containing *in vitro* and clinical DDI data from submission packages for peptide drugs approved between January 2008 and August 2021.[1] In parallel, Coutant *et al*.[2] compiled a position paper on therapeutic proteins' DDIs on behalf of the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ; www.iqconsortium.org), which originated as a response to the 2020 US Food and Drug Administration (FDA) draft guidance.[3]

At a high level, both White Papers conclude that DDIs for therapeutic peptides and proteins are still very much emerging scientific areas in drug development and regulatory guidance. At present, there is even a lack of clarity on the distinction between a peptide and a protein in the context of therapeutics development[1] (**Figure 1**). As a rule of thumb, the smaller the peptide the more potential DDIs can be expected to mimic conventional small molecules, whereas DDIs for large proteins will typically be determined by different, complex biological mechanisms, such as cytokine modulation and disease state.[1] Coutant and colleagues from the IQ consortium postulate that for therapeutic proteins that modulate cytokine release and action, disease state and severity are the primary determinants DDIs.[2] On the basis of this, they recommend, for example, that clinical DDI studies for therapeutic proteins are not necessary in diseases like psoriasis.[2]

Both White Papers are a call to action to develop a better understanding of the scientific basis and clinical significance of DDIs for therapeutic peptides and proteins. Currently, there is a lack of a consistent approach in drug development, limited understanding of the unique mechanisms underlying therapeutic peptide and protein DDIs, and a one-size-fits-all regulatory framework which does not consider the actual clinical significance of potential DDIs

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Received April 2, 2023; accepted April 3, 2023. doi:10.1002/cpt.2899

Figure 1 *Clinical Pharmacology & Therapeutics* June 2023 cover image: Clinical significance of therapeutic peptide and protein drug interactions: a call to action.

on a case-by-case basis.[1,2] Specific next steps proposed by the authors are:

1. Gather more information about indirect disease—DDIs, including their effects and which disease states are of clinical concern;
2. Consider collecting inflammatory biomarker data in phase II or phase III clinical trials of therapeutic peptides and proteins that treat inflammatory disease;
3. Investigate and develop new physiologically-based pharmacokinetic tools to aid in understanding the time course and mechanisms of certain types of DDIs[3];
4. Publishing positive and negative results from peptide/protein DDI studies;
5. Application of complex *in vitro* organ-on-a-chip systems;
6. Analyzing the physicochemical properties for a large set of diverse compounds in correlation with *in vitro* DDI parameters related to CYPs and transporters to determine the relevance of different *in vitro* DDI studies.

Säll and co-workers from the EFPIA working group should be commended for compiling and making available *in vitro* and clinical DDI data for 31 therapeutic peptide drugs approved between 2008 and 2021,[1] which should be a unique resource for clinical pharmacologists working in this area. The editorial team of *CPT* encourages others to follow this example and share case studies and databases to advance the science and best practices in this critical area of clinical pharmacology and therapeutics.

FUNDING
No funding was received for this work.

CONFLICT OF INTEREST
The author declared no competing interests for this work.

1. Säll, C. *et al*. Industry perspective on therapeutic peptide drug–drug interaction assessments during drug development: a European Federation of Pharmaceutical Industries and Associations White Paper. *Clin. Pharmacol. Ther.* **113**, 1199–1216 (2023).
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3. Bach, T., Wu, N. & An, G. Pharmacometric model of agalsidase-migalastat interaction in human: a novel mechanistic model of drug-drug interaction between a therapeutic protein and a small molecule. *J. Pharmacokinet. Pharmacodyn.* **50**, 63–74 (2023).