## Mechanism of Interaction

**DDI minimum information models definitions**

<https://docs.google.com/spreadsheets/d/1dhUp496riwZ0AHqRP7I85oEvuP2jjEI0rcw1Fcm2zI8/edit#gid=0>

### Edited User-Centered Definition (Qualtrics)

**Mechanism of Interaction:**

An assertion about the process(es) by which a drug-drug interaction clinical consequence occurs.

### Proposed User-Centered Definition (Qualtrics)

**Mechanism of Interaction:**

A description of the molecular process(es) by which a drug-drug interaction clinical consequence is thought to occur.

**For example:**

* An acute hypertensive reaction is likely when epinephrine is given in the presence of timolol eye drops and a CYP2D6 inhibitor (in the presence of a CYP2D6 inhibitor, a normal patient will respond as a CYP2D6 poor metabolizer would): “Timolol is a nonselective beta-blocker, and timolol eye drops have been shown to produce systemic beta-blockade. Timolol is metabolized by CYP2D6, and patients who are deficient in CYP2D6 (PMs) have been shown to develop higher timolol plasma concentrations following timolol ophthalmic aqueous drops.”
  + **Source**: Footnote 24 to [Beta-blocker - Epi Decision Table](https://pitt.co1.qualtrics.com/CP/File.php?F=F_cZykzdoKFxi0b09), NIH Project: R21-HS023826-01; Title: Individualized Drug Interaction Alerts; Authors: Daniel C. Malone, University of Arizona; John Horn, Philip Hansten, University of Washington.
* “Non-steroidal anti-inflammatory drugs (NSAIDs) have antiplatelet effects which increase the bleeding risk when combined with oral anticoagulants such as warfarin. The antiplatelet effect of NSAIDs lasts only as long as the NSAID is present in the circulation, unlike aspirin’s antiplatelet effect, which lasts for up to 2 weeks after aspirin is discontinued.“
  + **Source**: Description of the interaction, [Warfarin-NSAID Decision Table](https://pitt.co1.qualtrics.com/CP/File.php?F=F_29xiLSLtHky74vX), NIH Project: R21-HS023826-01; Title: Individualized Drug Interaction Alerts; Authors: Daniel C. Malone, University of Arizona; John Horn, Philip Hansten, University of Washington.

*Note: The goal of these examples is to describe the mechanism of interaction in such a way that someone with clinical knowledge will be able to comprehend the mechanism.*

**Feedback Themes**

* “Molecular” - some interactions do not occur at the molecular level; alternatively, a specific process may not be known
  + Examples: Neither features a molecular process
* Describing the mechanism of a drug-drug interaction vs. the mechanism of the clinical consequence that results from the interaction
* Would we want to include types of interactions in future definitions?

**Content and Standard Qualtrics Comments**

* **3 Strongly agree** 
  + **Appropriate** 
    - Should "drug-drug interaction clinical consequence" be changed to "drug-drug interaction's clinical consequence"? The consequence seems to be possessive.
    - no comment (2)
* **2 Agree** 
  + **More General**
    - Consider removing the word "molecular. Some interactions may take place at a cellular level, or even at a protein level. Molecular infers that all interactions can be dissected to a molecule - which may not be the case**.**
      * neither example explains the interaction at the molecular level, which emphasizes the point to remove that word from the definition.
  + **Appropriate**
    - no comment (1)
* **5 Somewhat agree**
  + **More General**
    - I am not sure about two things in this definition: / 1) "molecular process" is definitely important, however only few of such processes are clear so far...In the second example, there is no molecular process mentioned at all. However the second example is still about mechanism of interaction....I guess mechanism of interaction has different levels, molecular processes are ideal, however there are still other levels, such as cellular, organic levels... / 2) "is thought to occur" sounds like less scientific....
      * 1) I may not emphasize the interaction processes are at the molecular level only... / 2) I may change "is thought to occur" to "is shown to occur" or "is proved to occur" or something similar...
  + **Appropriate**
    - Are the processes always molecular?
      * Would it be useful to give justification for the definition? (e.g. Mechanistic info makes better decisions possible, so that e.g. time periods or underlying genotypes can be taken into account).
    - I would say it's a heuristic to allow us to figure out if other drugs that share the same mechanisms could be affected by this.
  + **Less General**
    - It seems that this is an information content entity by saying "description of biological processes". It's better to make it clear in the definition that "description" is actually refer to the "information content entity."
    - Examples don't give a clear description of a biological process. As for my ontological mind, I would like to see it corresponding to a GO term, or any sort. The first example's key word is "Timolol is metabolized by CYP2D6", and the second one is "NSAIDs have antiplatelet effects which increase the bleeding risk when combined with oral anticoagulants". Is it possible to find a corresponding biological process for these?
    - This definition focuses only on molecular processes. However, sometimes the description of a DDI is more general, for example, as the additive effect of two central nervous system depressant drugs. / Indeed, the second example reflects this. The example describes that the DDI is due to the antiplatelet and anticoagulant effects of two drugs, but we don't know anything about the molecular processes underlying them.
    - I think that the inclusion of different types of mechanisms (e.g., as subclasses of "Mechanism of Interaction") is relevant (if not now, in further developments).
* **1 Neither agree nor disagree**
  + **More general**
    - Something we have struggled with at PHS for a while is that we cannot agree on the term "drug-drug interaction". Several purists in our group (myself included), argue that this term can be misleading in the sense that many of our "interactions" are actually physiological potentiations. For example, your example 1 (CYP2D6), there is no actual "interaction" happening between any two drugs (i.e., drug molecule A is not binding to drug molecule B). Rather, there is a physiological effect caused by drug A, this effect in turn alters the metabolism of drug B and thus leads to increased effect of drug B. Arguably, some other non-drug process could lead to the same physiological effect of drug A and thus the same effect of drug B, but this would not be called a drug-drug interaction. / / Some place we see a lot of this is when we talk about QTc "interactions". Drug A increases QTc, drug B increases QTc, thus drug A + B yield big increase QTc. But, there is no actual "interaction" between drug molecules taking place. / / Perhaps a better term for this would be "Mechanism of clinical consequence"? / / Also, the examples are not great. The first does not even mention 2 drugs, but rather mentions patients that are deficient.
* **1 Somewhat disagree**
  + **Appropriate**
    - Suggestion: A description of the molecular process(es) that result in a drug-drug interaction.

**Background Information:**

* **DIDEO**:
  + **Drug Interaction Mechanism**: An information content entity that represents a drug interaction as a directional series of molecular processes.
    - Comment: An instance of this entity would represent the biochemical process by which pharmacokinetic or pharmacodynamic DDI is thought to occur.
* **DINTO:**
  + **DDI Mechanism**: The process or processes by which one drug B alters the disposition and/or effect of another drug A.
    - **Pharmacodynamic DDI mechanism**: A pharmacodynamic mechanism is a DDI mechanism by which a drug B produces an alteration, which can be an increase or decrease, of the effects of another drug A, without leading to an alteration in the disposition of drug A.
    - **Pharmacokinetic DDI mechanism**: A pharmacokinetic mechanism is a DDI mechanism by which one drug B alters the pharmacokinetic process of another drug A, leading to an alteration, which can be an increase or decrease, in the disposition of this drug.

**Themes**: in their comments, task force members appear to be concerned about:

* Covering unknown mechanisms
* Pharmacokinetic vs. pharmacodynamic mechanisms
* Representing the pathway vs. a description
* Order of events

**Suggested User-Centered Definition (Google Sheets)**

* **Mechanism of the Interaction:**
  + **A description of molecular pathway(s) involved in the elicitation of the clinical adverse event(s).**
* Comments
  + We need to be clear here what we intend to represent: the actual pathways or the description. The description is only an information entity. It cannot bear any properties that are biological, e.g. "is involved in clinical adverse event", since what is involved is not the description, but the pathways.
    - if a representation of a pathway is not a description, then use representation.
    - representation- description, that is all fine. I just wanted to make sure we are all in agreement that what we intend to represent here is the description as opposed to the actual pathway. Some of the examples seem to point to the fact that there is a disconnect.
  + My concern is how to cover those unknown mechanisms. Since the pathway is a chain reaction, so as biological processes, to which point is the starting and ending of the mechanism? Is the mechanism a serial pathways, or biological processes? We know that GO biological processes and pathways are different.
    - I agree. We ran into exactly this issue when developing DIDEO. I don't have strong feelings of how we model this, as a description or as actual processes. I just wanted to point out that if we go with a description this creates certain constraints. For example, looking at Maria's comment: mechanism precedes DDI would be impossible (at least using the RO definition of precedes), since mechanism wouldn't be a process-like entity.
  + All abnormal phenotypes have (one or more) mechanisms by which they are manifested. The idea here is to describe how this occurs, in the cases where it has been studied. I would say that mechanisms of actions are often descriptive, although pathway diagrams indicate key entities and their interactions, and more sophisticated kinetic models can generate the outcomes of interest
    - Many thanks. That clarifies things a lot.
* **Other Comments** 
  + Specific pathway involved (to help identify therapeutic alternatives)
  + Pharmacokinetic vs pharmacodynamic
  + molecular targets, biological processes affected
  + A DDI can occur by the conjunction of several PK or PK and PD mechanisms (although most of times one of them has more relevance than others).
* In DINTO a DDI mechanism "precedes" always the occurrence of a DDI. Therefore, if the mechanism occurs (e.g., Drug A inhibits the activity of enzyme E which metabolizes Drug B) the DDI occurs (and it would lead in this example to a PK consequence (such as decrease of clearance (or CL) of Drug B or increase of its serum levels) independently of if the clinical consequence occurs or not.
* "We did an extensive work in DDI mechanism in DINTO, and hope that you agree with our definitions. DDI mechanism is defined in DINTO as “The process or processes by which one drug B alters the disposition and/or effect of another drug A.” I include here only the hierarchy, and definition can be found in the ontology:
  + DDI mechanism
    - pharmacodynamic DDI mechanism
      * physiological effect alteration
      * physiological effect antagonism
      * physiological effect potentiation
    - target activity alteration
      * agonistic DDI mechanism
      * antagonistic DDI mechanism
    - pharmacokinetic DDI mechanism
      * carrier activity alteration
        + carrier activity induction
        + carrier activity inhibition
        + carrier activity saturation
    - enzyme activity alteration
      * enzyme activity induction
      * enzyme activity inhibition
      * enzyme activity saturation
    - transporter activity alteration
      * transporter activity induction
      * transporter activity inhibition
      * transporter activity saturation
    - non-absorbable complex formation