Drug Disease Model Resources

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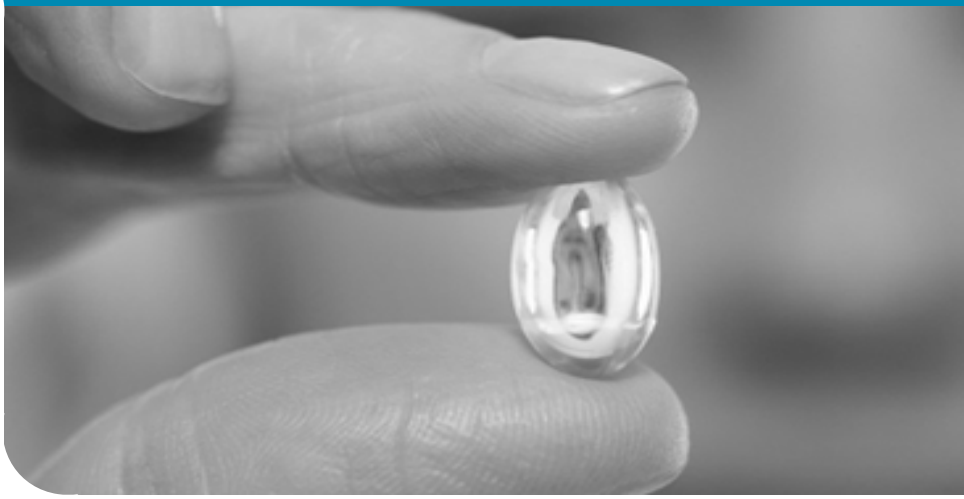

PharmML – Using Data

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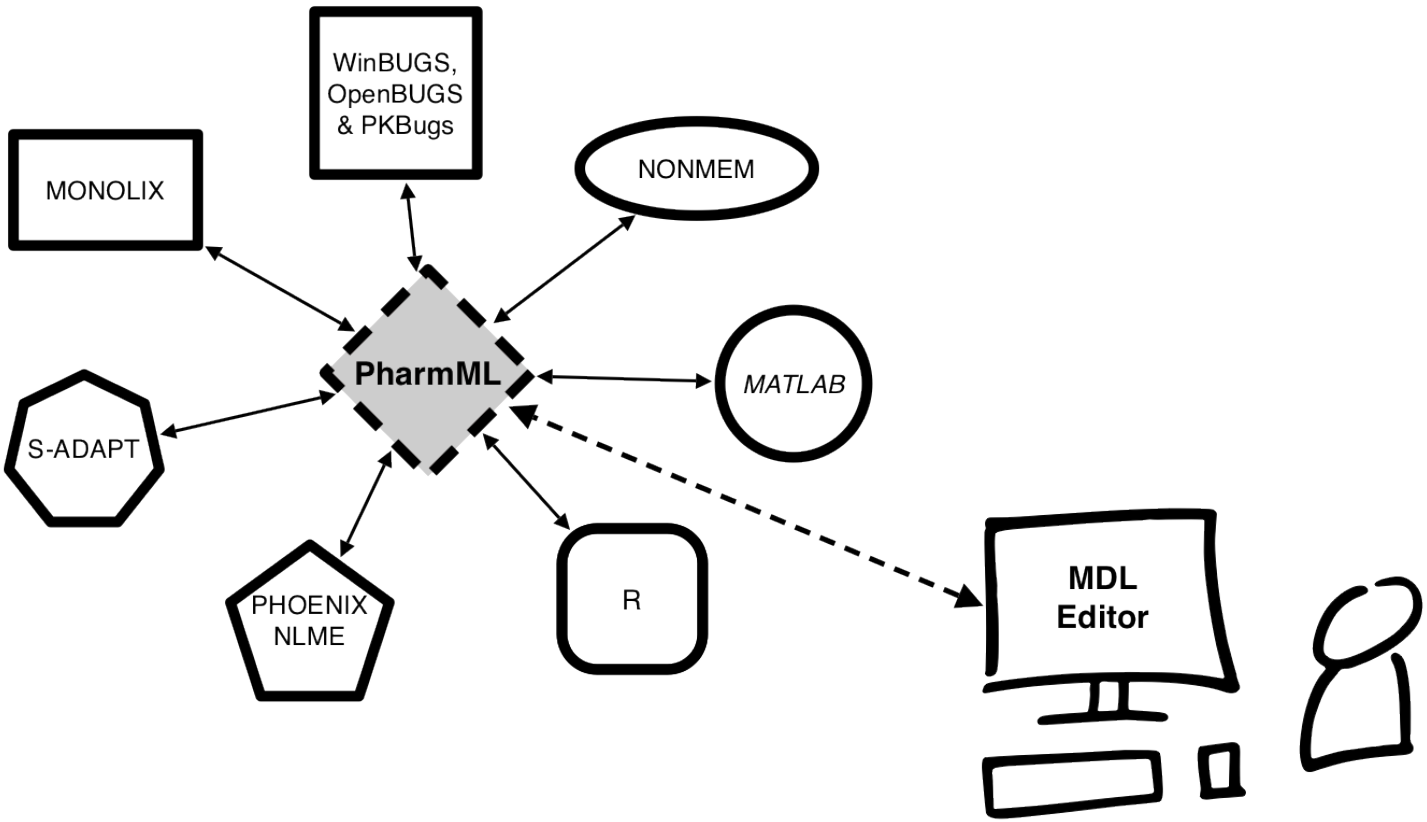
On behalf of the DDMoRe consortium

imi efpia

PharmML

as element of the interoperability platform



Main objectives

- Encoding of
  - Models
  - Trial design
  - Basic tasks
- Annotation

PharmML
data coverage overview

- Input data: ✔
- Output data: –

Structure

- Typical **Pharmacometrics project** is usually described by
  - Experimental Data
  - Trial execution model
  - Structural model
  - Population/Individual parameter model
  - Covariate model
  - Correlation structure of the random effects
  - Inter-subject, inter-occasion and higher orders of variability
  - Residual error model
  - Observation model
  - Task model

- **PharmML** is organised in
  - Model Definition
    - Structural Model
    - Covariate Model
    - Parameter Model
    - Variability Model
    - Observations Model
  - Trial Design
    - Structure
    - Population
    - Individual Dosing
  - Modeling Steps
    - Simulation/Estimation Step
    - Step Dependencies

Basic comparison to SB

- The details are in the parameter model
  - Population/typical value of a parameter
  - Covariates
    - Continuous – Age, Height, Body weight,…
    - Discrete – Gender, Ethnicity, Pharmacogenomics, …
  - Correlations
  - Variability, e.g. inter-individual variability
    - Explained – e.g. by covariates
    - Random

Model Definition – Covariates

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Data source – 1

Covariate model The only covariate is Weight, W, and it is a continuous covariate:

$$W \sim \mathcal{N}(pop_W, \omega_W)$$

The following transformation is applied:

$$\log(W/70)$$

and the initial values are:

$$pop_W = 70.07, \quad \omega_W = 14.09$$

Model Definition – Observations

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Data source – 2

Observation model We apply a residual error model to the output variables Cc and E from the PK and PD models respectively.

Output Variable	***Cc***	***E***
Observation Name	Concentration	PCA
Units	mg/l	$\%$
Type	Continuous	Continuous
Model	Combined	Constant
Parameters	$a = 0.5, \quad b = 0.1$	$a = 4$

Model Definition – Dosing

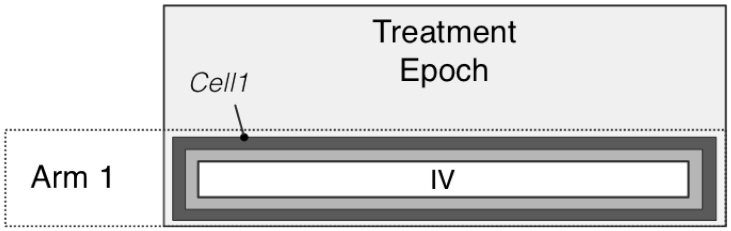
Trial Design

The dosing regimen for the trial

Data source – 3

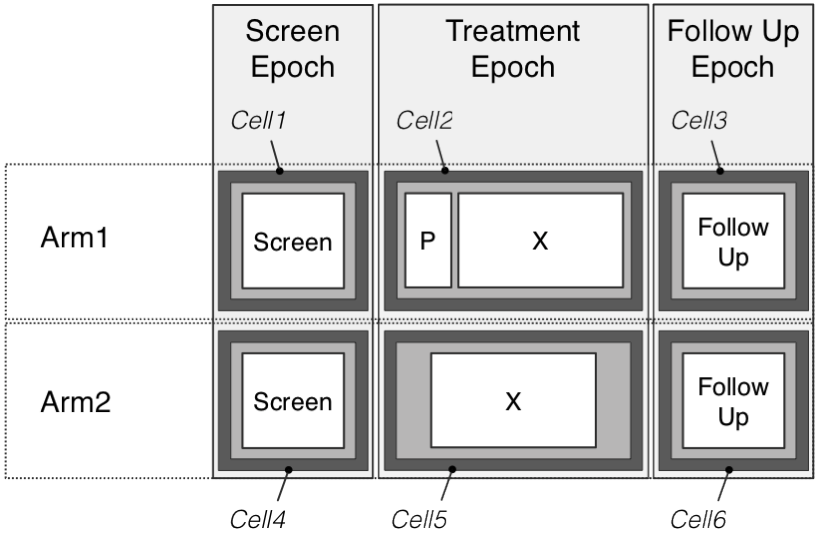
Example 1

Arm	1
Number of subjects	33
Dose variable	D
Dosing Amount	100
Dose Units	mg
Dose per kg	no
Dosing times (h)	0

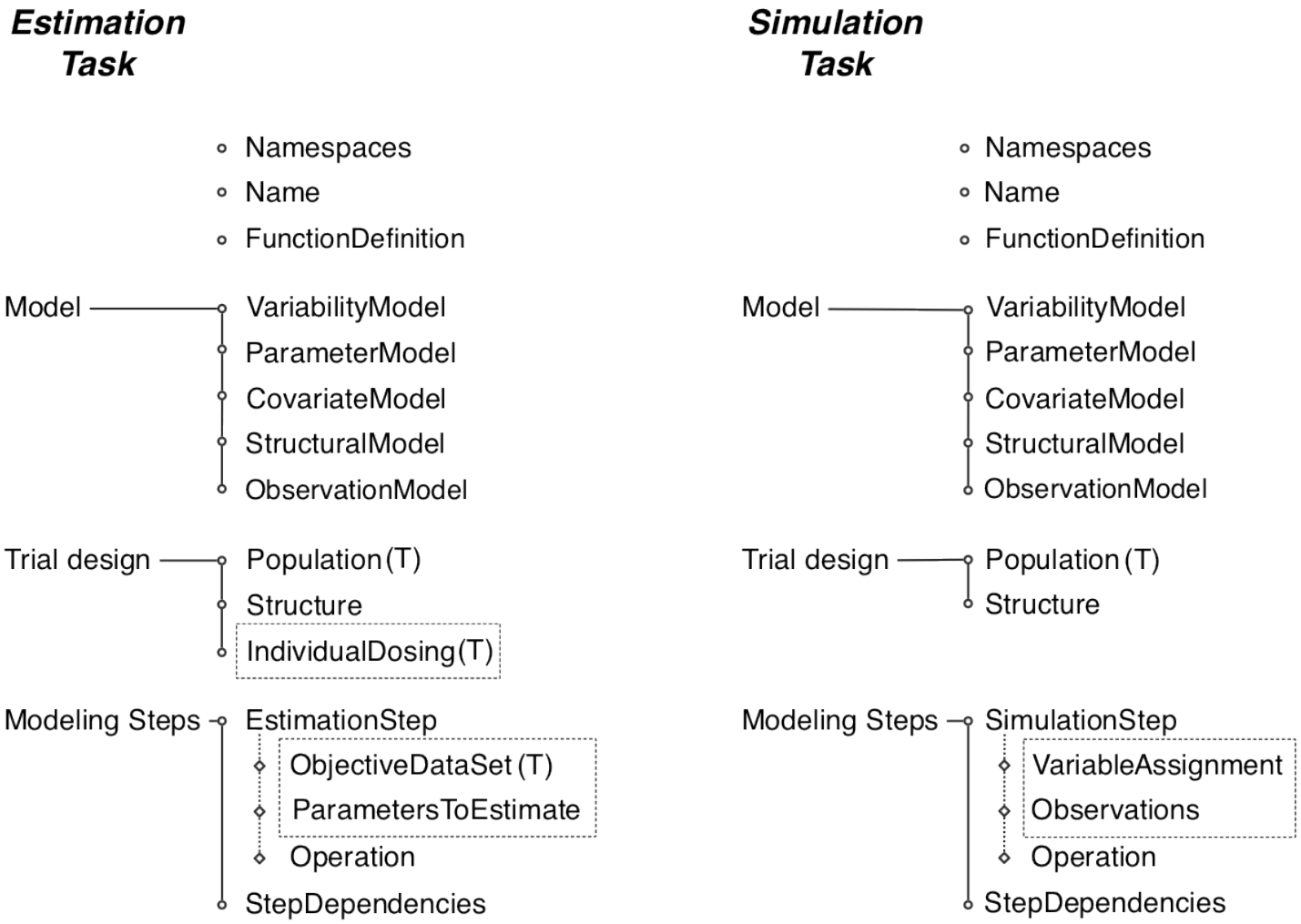


Example 2

Segment	Activity	Treatment	DoseTime	DoseSize	Target Variable
TA	OR1	OR bolus	0 : 12 : 72	150	Ac
TA	OR2	OR bolus	0 : 24 : 72	100	Ac



Structure for Estimation/Simulation



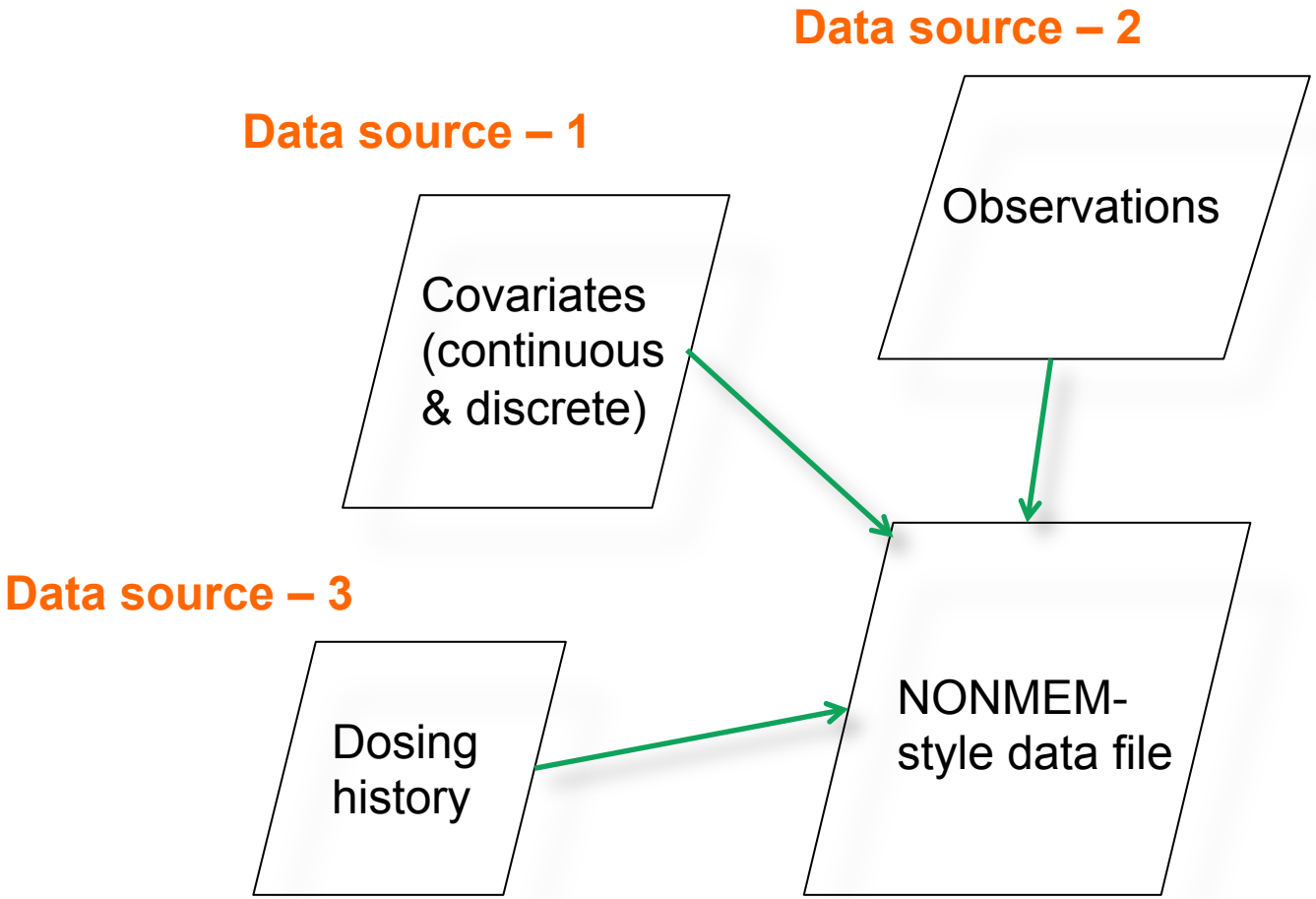
Data – *NONMEM* style

RIBBA2012_PCV.txt

ID	TIME	DV	MDV	DOSE	EVID
1	0	.	1	.	0
1	3.43	45.7	0	.	0
1	5.3	48.03	0	.	0
1	42.13	71.34	0	.	0
1	52.63	79.3	0	.	0
1	54.57	.	1	1	1
1	57.53	72.3	0	.	0
1	59.77	.	1	1	1
1	63.3	72.07	0	.	0
1	68.97	70.24	0	.	0
1	76.53	66.81	0	.	0
1	94.53	60.48	0	.	0
1	106.1	62	0	.	0
1	116.23	72.04	0	.	0
1	121.87	90.16	0	.	0
2	0	50.17	0	.	0
2	11.07	61.68	0	.	0
2	12	.	1	1	1
2	14.09	.	1	1	1
2	14.17	52.82	0	.	0
2	16.17	.	1	1	1
2	16.6	53.36	0	.	0
2	18.26	.	1	1	1
2	19.33	53.28	0	.	0
2	20.35	.	1	1	1
2	22.1	.	1	.	0
2	22.43	.	1	1	1
2	25.13	48.3	0	.	0
2	29.27	40.66	0	.	0
2	33.4	42.4	0	.	0
2	37.43	38.2	0	.	0
2	42.67	42.99	0	.	0
2	48.83	42.76	0	.	0
2	56.4	48.6	0	.	0
2	62.23	55.85	0	.	0
2	65.9	54.71	0	.	0
2	71.37	60.77	0	.	0
3	0	42.71	0	.	0
3	5	50.57	0	.	0

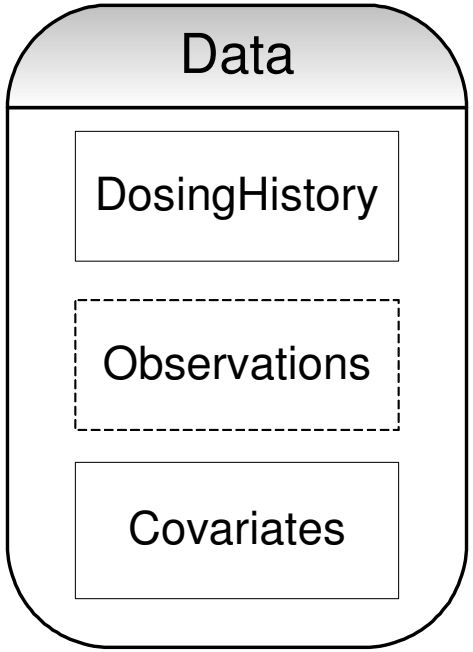
Data – *NONMEM* style

production of data files



Data – *PharmML* style

New format suggestion:
include data in model file



PharmML

– Covariates

```
<IndividualTemplate>
    <IndividualMapping>
        <ds:ColumnRef columnIdRef="id"/>
    </IndividualMapping>
    <ArmMapping>
        <ds:ColumnRef columnIdRef="arm"/>
    </ArmMapping>
    <CovariateMapping>
        <ds:ColumnRef columnIdRef="sex"></ds:ColumnRef>
        <ct:SymbRef blkIdRef="c1" symbIdRef="Sex"/>
    </CovariateMapping>
    <IVDependentMapping>
        <ds:ColumnRef columnIdRef="treat-tab"/>
        <EpochMapping>
            <ds:ColumnRef columnIdRef="epoch"/>
        </EpochMapping>
        <CovariateMapping>
            <ds:ColumnRef columnIdRef="treat"></ds:ColumnRef>
            <ct:SymbRef blkIdRef="c1" symbIdRef="Treat"/>
        </CovariateMapping>
    </IVDependentMapping>
</IndividualTemplate>
```

```
<ds:DataSet>
    <ds:Definition>
        <ds:Column columnId="id" valueType="id" columnNum="1"/>
        <ds:Column columnId="arm" valueType="id" columnNum="2"/>
        <ds:Column columnId="sex" valueType="id" columnNum="3"/>
        <ds:Table tableId="treat-tab" columnNum="4">
            <ds:Definition>
                <ds:Column columnId="epoch" valueType="id" columnNum="1"/>
                <ds:Column columnId="treat" valueType="id" columnNum="2"/>
            </ds:Definition>
        </ds:Table>
    </ds:Definition>
    <ds:Table>
        <ds:Row>
            <ct:Id>i1</ct:Id>
            <ct:Id>a1</ct:Id>
            <ct:Id>M</ct:Id>
            <ds:Table>
                <ds:Row><ct:Id>ep1</ct:Id><ct:Id>A</ct:Id></ds:Row>
                <ds:Row><ct:Id>ep3</ct:Id><ct:Id>B</ct:Id></ds:Row>
            </ds:Table>
        </ds:Row>
        <ds:Row>
            <ct:Id>i2</ct:Id>
            <ct:Id>a1</ct:Id>
            <ct:Id>M</ct:Id>
            <ds:Table>
                <ds:Row><ct:Id>ep1</ct:Id><ct:Id>A</ct:Id></ds:Row>
                <ds:Row><ct:Id>ep3</ct:Id><ct:Id>B</ct:Id></ds:Row>
            </ds:Table>
        </ds:Row>
```

PharmML

– Observations

```
<DataSet xmlns="http://www.pharmml.org/2013/08/Dataset">
    <Definition>
        <Column columnId="ID" valueType="string" columnNum="1"/>
        <Column columnId="TIME" valueType="real" columnNum="2"/>
        <Column columnId="DV" valueType="real" columnNum="3"/>
    </Definition>
    <Table>
        <!-- SUBJECT 1 -->
        <Row><ct:String>i1</ct:String><ct:Real>3.43</ct:Real><ct:Real>45.7</ct:Real></Row>
        <Row><ct:String>i1</ct:String><ct:Real>5.3</ct:Real><ct:Real>48.03</ct:Real></Row>
        <Row><ct:String>i1</ct:String><ct:Real>42.13</ct:Real><ct:Real>71.34</ct:Real></Row>
        <Row><ct:String>i1</ct:String><ct:Real>52.63</ct:Real><ct:Real>79.3</ct:Real></Row>
        <Row><ct:String>i1</ct:String><ct:Real>57.53</ct:Real><ct:Real>72.3</ct:Real></Row>
        <Row><ct:String>i1</ct:String><ct:Real>63.3</ct:Real><ct:Real>72.07</ct:Real></Row>
        <Row><ct:String>i1</ct:String><ct:Real>68.97</ct:Real><ct:Real>70.24</ct:Real></Row>
        <Row><ct:String>i1</ct:String><ct:Real>76.53</ct:Real><ct:Real>66.81</ct:Real></Row>
        <Row><ct:String>i1</ct:String><ct:Real>94.53</ct:Real><ct:Real>60.48</ct:Real></Row>
        <Row><ct:String>i1</ct:String><ct:Real>106.1</ct:Real><ct:Real>62</ct:Real></Row>
        <Row><ct:String>i1</ct:String><ct:Real>116.23</ct:Real><ct:Real>72.04</ct:Real></Row>
        <Row><ct:String>i1</ct:String><ct:Real>121.87</ct:Real><ct:Real>90.16</ct:Real></Row>
        <!-- SNIP -->
        <!-- SUBJECT 21 -->
        <Row><ct:String>i21</ct:String><ct:Real>9.77</ct:Real><ct:Real>72.35</ct:Real></Row>
        <Row><ct:String>i21</ct:String><ct:Real>14.23</ct:Real><ct:Real>66.96</ct:Real></Row>
        <Row><ct:String>i21</ct:String><ct:Real>18.13</ct:Real><ct:Real>56.79</ct:Real></Row>
        <Row><ct:String>i21</ct:String><ct:Real>23.9</ct:Real><ct:Real>60.06</ct:Real></Row>
    </Table>
```

PharmML

– Individual Dosing

```
<!-- INDIVUIDUAL DOSING -->
<IndividualDosing>
    <ActivityRef oidRef="activity1"/>
    <IndividualRef columnIdRef="ID"/>
    <DataSet xmlns="http://www.pharmml.org/2013/08/Dataset">
        <Definition>
            <Column columnId="ID" valueType="id" columnNum="1"/>
            <Column columnId="TIME" valueType="real" columnNum="2"/>
            <Column columnId="DOSE" valueType="real" columnNum="5"/>
        </Definition>
        <Table>
            <!-- subject 1 -->
            <Row><ct:String>i1</ct:String><ct:Real>54.57</ct:Real><ct:Real>1</ct:Real></Row>
            <Row><ct:String>i1</ct:String><ct:Real>59.77</ct:Real><ct:Real>1</ct:Real></Row>
            <!-- subject 2 -->
            <Row><ct:String>i2</ct:String><ct:Real>12</ct:Real><ct:Real>1</ct:Real></Row>
            <Row><ct:String>i2</ct:String><ct:Real>14.09</ct:Real><ct:Real>1</ct:Real></Row>
            <Row><ct:String>i2</ct:String><ct:Real>16.17</ct:Real><ct:Real>1</ct:Real></Row>
            <Row><ct:String>i2</ct:String><ct:Real>18.26</ct:Real><ct:Real>1</ct:Real></Row>
            <Row><ct:String>i2</ct:String><ct:Real>20.35</ct:Real><ct:Real>1</ct:Real></Row>
            <Row><ct:String>i2</ct:String><ct:Real>22.43</ct:Real><ct:Real>1</ct:Real></Row>
            <!-- SNIP -->
            <!-- subject 21 -->
            <Row><ct:String>i21</ct:String><ct:Real>1.5</ct:Real><ct:Real>1</ct:Real></Row>
            <Row><ct:String>i21</ct:String><ct:Real>3.17</ct:Real><ct:Real>1</ct:Real></Row>
            <Row><ct:String>i21</ct:String><ct:Real>4.85</ct:Real><ct:Real>1</ct:Real></Row>
            <Row><ct:String>i21</ct:String><ct:Real>6.52</ct:Real><ct:Real>1</ct:Real></Row>
            <Row><ct:String>i21</ct:String><ct:Real>8.19</ct:Real><ct:Real>1</ct:Real></Row>
            <Row><ct:String>i21</ct:String><ct:Real>9.87</ct:Real><ct:Real>1</ct:Real></Row>
        </Table>
    </DataSet>
</IndividualDosing>
</TrialDesign>
```

PharmML
data coverage overview

- Input data: ✔
- Output data
  - Simulated data
  - Estimated parameters
  - Correlation matrices
  - Scalar, Vector, Matrices

Partners

Drug Disease Model Resources

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EFPIA

Academia


SMEs