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Extended npde diagnostics for the between subject-variability and residual error models

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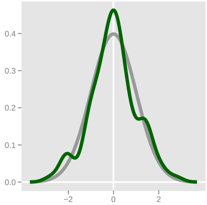
This presentation

- EBE and IWRES diagnostics: limitations
- Improvement of EBE and IWRES diagnostics: **npde's**
  - Recap: What are npdes?
  - What are the *new* npdes?
- Experiences
- Conclusions
  - What do the new npdes offer?
  - How can we use them?

Diagnosis of random effects models

- Between subject variability: **E**mpirical **B**ayes **E**stimates
- Diagnostic plots:



Distribution

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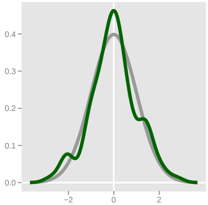

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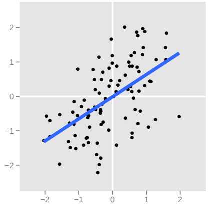

EBE $\sim$ EBE

Diagnosis of random effects models

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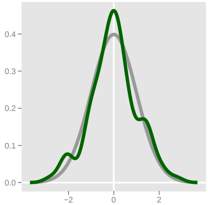

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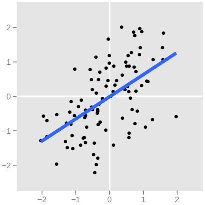
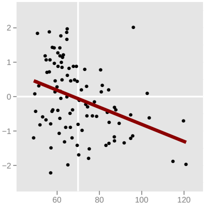


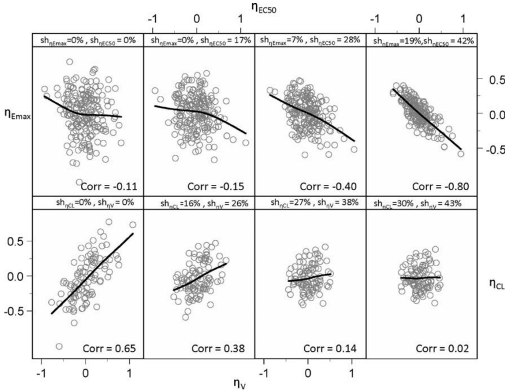
EBE ∼ EBE



EBE ∼ covariates

Diagnosis of random effects models

Limitation: η-shrinkage [1]



η-shrinkage: With decreasing information content, EBE's shrink towards the population estimate

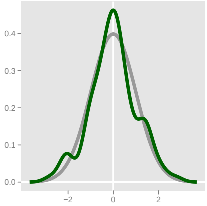
[1] Karlsson & Savic, *Clin Pharmacol Ther* 2007

Diagnosis of random effects models

- Residual error: **I**ndividual **W**eighted **R**esiduals:

  $$\text{IWRES} = \frac{\hat{y}_{ij} - y_{ij}}{\sigma}$$

- Diagnostic plots:



Distribution

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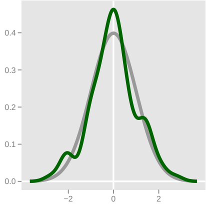

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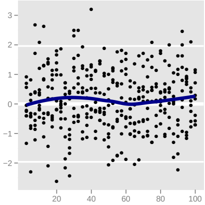

IWRES $\sim x$

Diagnosis of random effects models

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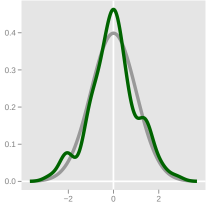

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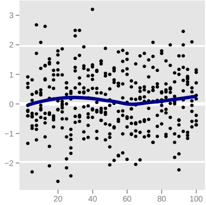

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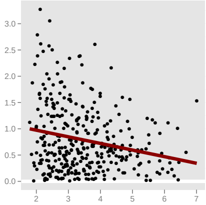
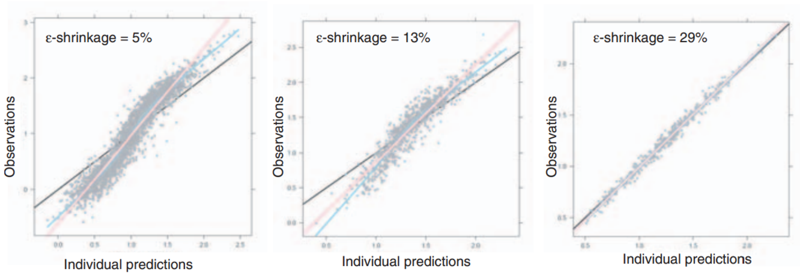


|IWRES| $\sim \hat{y}$

Diagnosis of random effects models

Limitation: ϵ-shrinkage [2]

E_{max} model fitted to data simulated with a sigmoidal E_{max} model



[2] Karlsson & Savic, *Clin Pharmacol Ther* 2007

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Proposed solution

- Calculate npdes of EBE and IWRES:
  - **EBE**$_{npde}$
  - **IWRES**$_{npde}$
- Compares EBE and IWRES to expected distributions
  - Not/less affected by shrinkage?

Recap: What are npdes?

- **N**ormalized **p**redictive **d**istribution **e**rrors [3]
- Location of observations in own expected distribution
  - Expected distribution obtained by simulation
  - npdes are expected to follow $\mathcal{N}(0, 1)$
  - original npdes called $\mathbf{DV}_{npde}$ here

[3] Brendel et al, *Pharm Res* 2006

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npdes, calculation [5]

- Simulate n new datasets from model M
- Substract the expectation[4] from Y_i and Y_i^{sim}:

$$\mathbb{E}(Y_i) = \frac{1}{K}\sum_{k=0}^{K} Y_i^{sim(k)} \tag{1}$$

$$Y_{i,ecorr} = Y_i - \mathbb{E}(Y_i) \tag{2}$$

$$Y_{i,ecorr}^{sim} = Y_i^{sim} - \mathbb{E}(Y_i) \tag{3}$$

[4] obtained through simulation

[5] Comets et al. *Comput Methods Programs Biomed* 2008

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npdes, explanation

- Decorrelation: [6]
  - Observations:
$$Y_i^* = \frac{Y_{i,ecorr}}{var(Y_i)^{1/2}} \tag{4}$$
  - Simulations:
$$Y_i^{sim(k)*} = \frac{Y_{i,ecorr}^{sim}}{var(Y_i)^{1/2}} \tag{5}$$

[6] "square root of matrix" calculated e.g. using Cholesky decomposition

npdes, explanation

- Now, rank decorrelated observations:

$$pde_{ij} = F^*_{ij}(y^*_{ij}) \approx \frac{1}{K}\sum_{k=0}^{K} \delta^*_{ijk} \tag{6}$$

pde_{ij} should follow $\mathcal{U}(0,1)$ if K is large

- Finally:

$$npde_{ij} = \frac{pde_{ij}}{\Phi} \tag{7}$$

$npde_{ij}$ should follow $\mathcal{N}(0,1)$ if K is large

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New npde diagnostics: procedure

Instead of DV_{npde}, calculate EBE_{npde} and IWRES_{npde} [7]

- Simulate n times from model M, unders same design ($n \approx 1000$)
- Re-estimate EBEs in M on generated datasets (MAXEVAL=0)
- Calculate EBE_{npde} and IWRES_{npde} based on estimated (from observed data) and re-estimated (from simulations) values

[7] **Note:** So for EBE, decorrelation occors on EBE-level

Simulation analyses

- Investigate power of new npdes compared to original diagnostics
- ability to diagnose model misspecification?

  (better than EBE / IWRES)

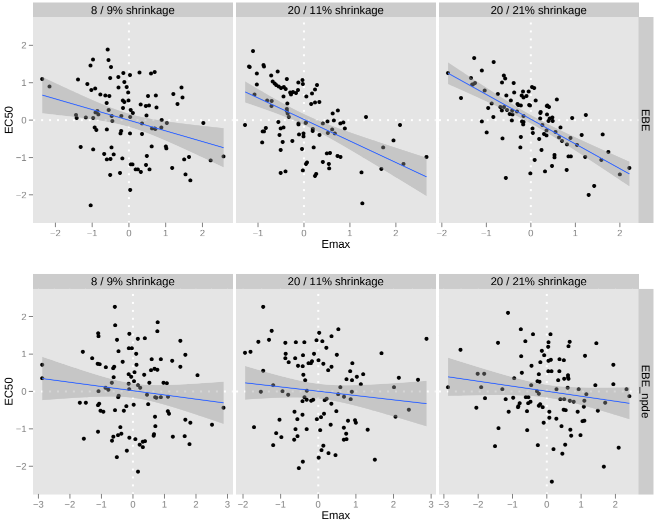
  - in cases of increasing η- and ϵ-shrinkage
  - not inducing false correlations?

EBE_{npde}: correlation between η (1)

- $Emax$ / EC_{50} problem
- No correlation $Emax_i \sim EC_{50,i}$ in M_{sim}
- η-shrinkage induced by removing datapoints

EBE_{npde}: correlation between η (1)

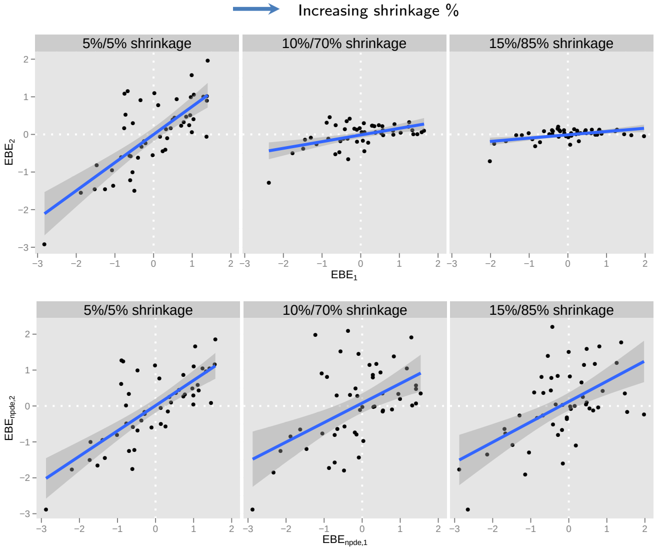
Increasing shrinkage %



EBE_{npde}: correlation between η (2)

- 1 cmt - IV problem
- Correlation $CL_i \sim V_{d,i}$ in M_{sim}: 50%
- η-shrinkage induced by removing datapoints

EBE_{npde}: correlation between η (2)



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EBE_{npde}: correlation with covariates

- 1 cmt - IV problem
- Correlation $CL_i \sim Weight_i$ in M_{sim}
- η-shrinkage induced by removing datapoints

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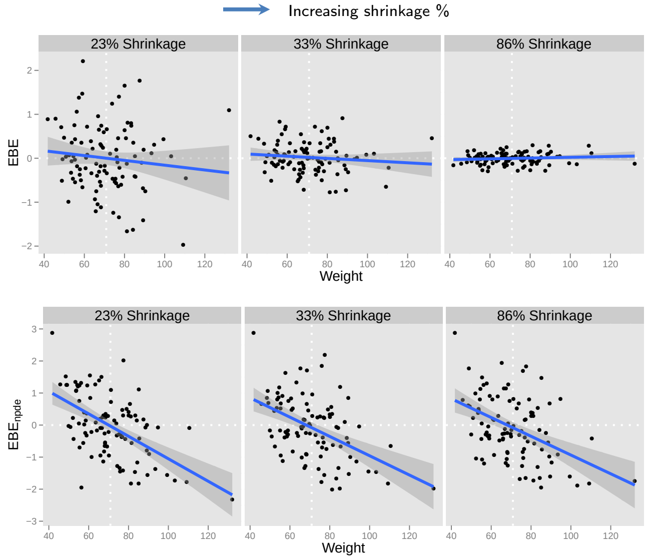
EBE_{npde}: correlation with covariates



Conclusions EBE_{npde}

- EBE_{npde} more powerful than EBE in cases of η-shrinkage:
  - Able to find correlations in Ω (when truly present)
  - Does not falsely induce correlation in Ω

  - Identify covariates
  - Does not falsely induce covariate relationships

$IWRES_{npde}$: residual error diagnosis(1)

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- *Emax* / EC_{50} model
- **Prop + Add** error model in M_{sim}
- Only **Add** component in M_{est}

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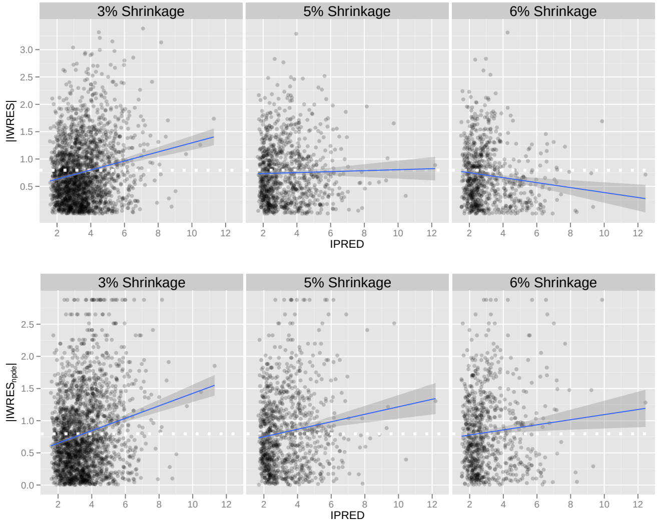
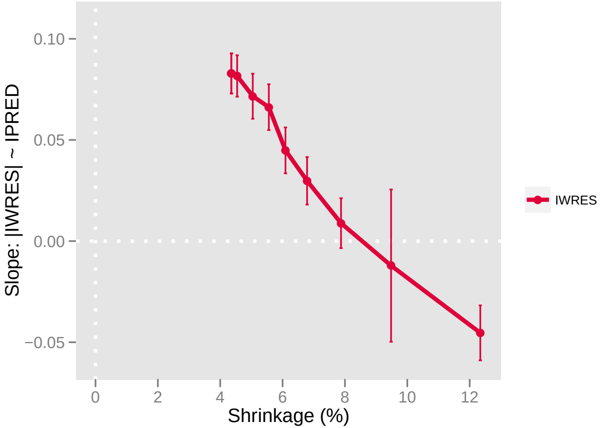
IWRES$_{npde}$: residual error diagnosis(1)

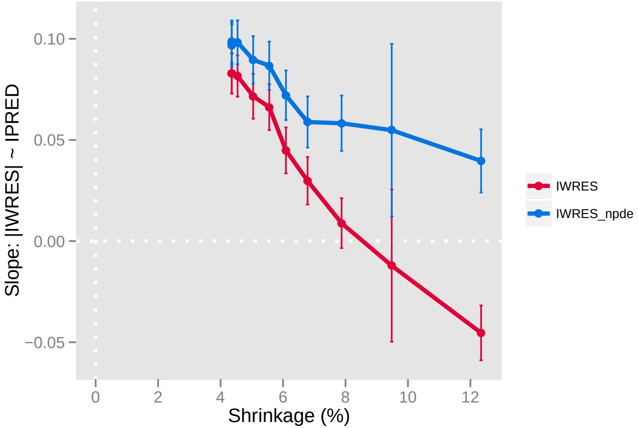
Increasing shrinkage %



IWRES$_{npde}$: residual error diagnosis(1)



IWRES$_{npde}$: residual error diagnosis(1)

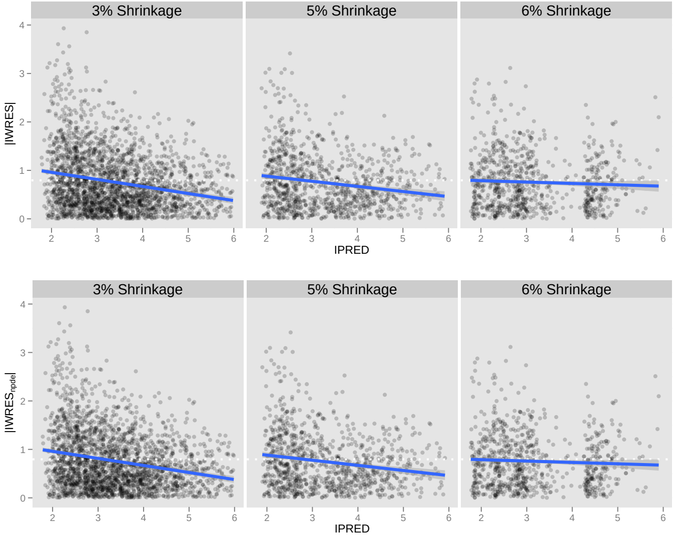


IWRES_{npde}: residual error diagnosis(2)

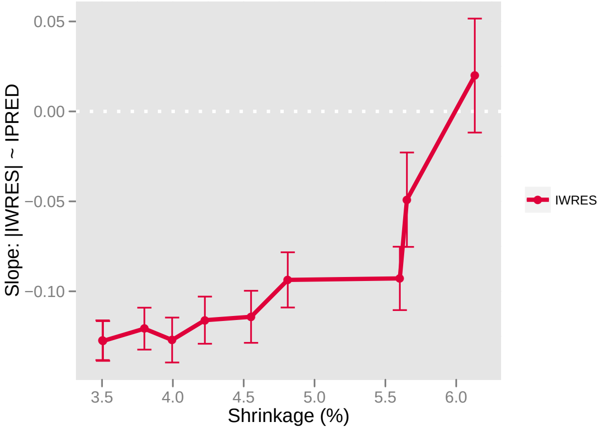
- *Emax* / EC_{50} model
- **Prop + Add** error model in M_{sim}
- Only **Prop** component in M_{est}

IWRES$_{npde}$: residual error diagnosis(2)

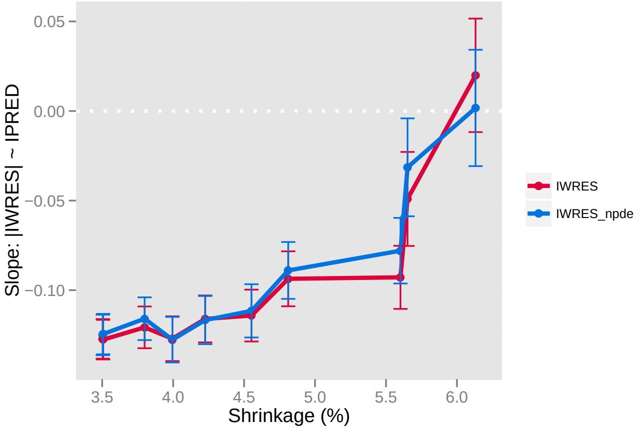
Increasing shrinkage %



IWRES$_{npde}$:


0.05
0.00
−0.05
−0.10
Slope: |IWRES| ~ IPRED
3.5
4.0
4.5
5.0
5.5
6.0
Shrinkage (%)
IWRES

IWRES_{npde}:



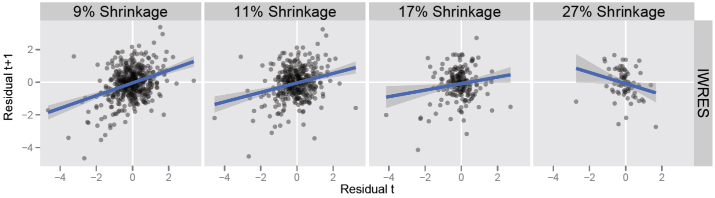
IWRES$_{npde}$: residual error diagnosis(3)

- Correlated residuals in M_{sim} (**AR**-**1** error model[8])
- Estimate without **AR**-**1** model

[8] Karlsson et al. *JPB 1995*

IWRES$_{npde}$: Serial correlation

Increasing shrinkage %



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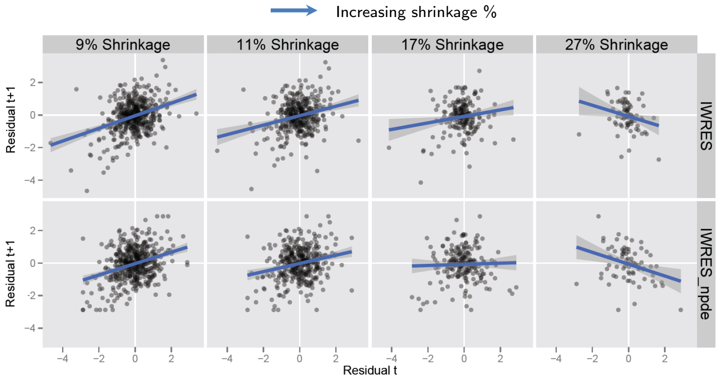
IWRES$_{npde}$: Serial correlation



IWRES$_{npde}$: Serial correlation

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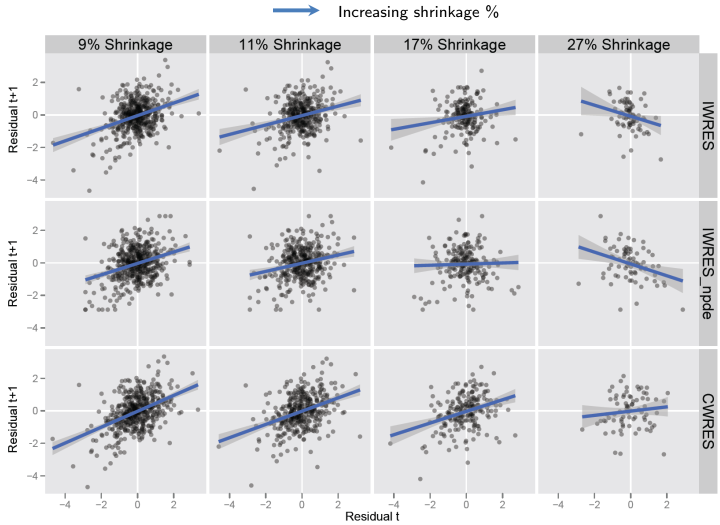

Conclusions IWRES$_{npde}$

- IWRES$_{npde}$ more powerful diagnostic than IWRES?
  - In selected cases of ϵ-shrinkage
  - In some cases, did not improve diagnostic power
  - Other diagnostics could be better in case of ϵ-shrinkage
    - e.g. CWRES[9] for identification of AR-1 correlation

[9] Hooker et al. Pharm Res 2007

Implemented in PsN

Example:

```
ebe_npde run1.mod -dir=npde1 -samples=1000
```

- This will calculate both EBE_{npde} and IWRES_{npde}.
- Diagnosic plots in Xpose will be implemented soon.

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Conclusions

- Diagnostic power $\text{EBE}_{npde} > \text{EBE}$ in cases of η-shrinkage
- Diagnostic power $\text{IWRES}_{npde} \geq \text{IWRES}$ in cases of ϵ-shrinkage
- Applications in model diagnosis:
  - Especially distributions and correlations
  - Covariate analyses
  - Decompose DV_{npde} into EBE_{npde} & IWRES_{npde}: identify level of misspecification

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- Uppsala colleagues

Drug Disease Model Resources

ddmore

imi

efpia

European Federation of Pharmaceutical Industries and Associations

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