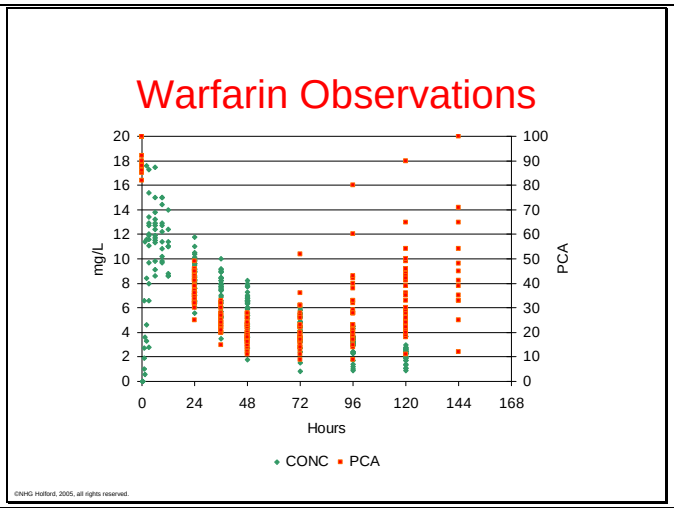
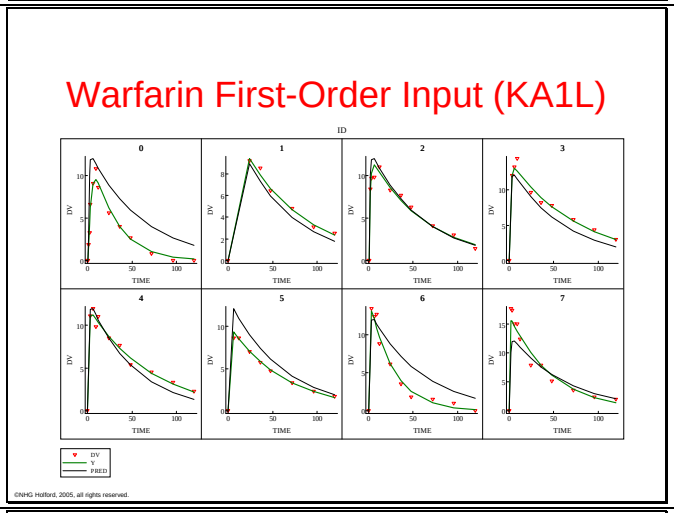
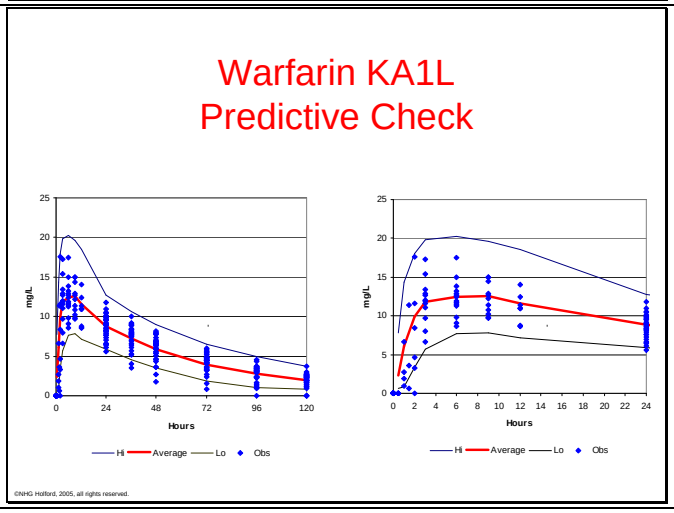
This presentation and associated control stream examples are available from
http://www.page-meeting.org/default.asp?id=26&keuze=abstract-view&goto=abstracts&orderby=author&abstract_id=838

Slide 1	# PKPD ## Workshop Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland, New Zealand 	http://www.page-meeting.org/default.asp?id=26&keuze=abstract-view&goto=abstracts&orderby=author&abstract_id=838
Slide 2	 	PK=Pharmacokinetics PD=Pharmacodynamics Rx=Prescription (Latin *recipe*)

Slide 3	## Warfarin Data
	
	- PKPD Studies in Healthy Subjects
	  – 1.5 mg/kg single oral dose
	  – Total racemic warfarin plasma concentration
	  – Prothrombin complex activity (PCA)
	- 32 subjects, 250 concentrations, 232 PCA
	
	- O'Reilly RA, Aggeler PM, Leong LS. Studies of the coumarin anticoagulant drugs: The pharmacodynamics of warfarin in man. Journal of Clinical Investigation 1963;42(10):1542-1551
	- O'Reilly RA, Aggeler PM. Studies on coumarin anticoagulant drugs Initiation of warfarin therapy without a loading dose. Circulation 1968;38:169-177
	
		A classical clinical pharmacology study from 40 years ago.
		Prothrombin complex activity is inversely proportional to the International Normalized Ratio (INR)

Slide 4		Two features to notice about the time course of warfarin concentration and effect on PCA: Peak concentration is about 6 h while greatest effect is at 72 h Most marked between subject variability in PCA occurs when PK variability is least
Slide 5		Individual “post hoc” predictions of concentration fit the time course well and should be adequate for driving the pharmacodynamic model.
Slide 6		The visual predictive check reveals that the model overestimates the early variability in concentration.

Slide 7

Immediate Effect Model

- Two Basic Approaches
  - $PRED
    - Write model for CP
  - PREDPP
    - ADVAN2
    - ADVAN6 Differential Equations

An immediate effect model uses central compartment concentrations to predict the drug effect.
Concentrations can be predicted using $PRED or one of the PREDPP library ADVAN subroutines. Using ADVAN subroutines is usually easier to code but the model is not so clear.

Slide 8

Central Compartment Using ADVAN2

```
$SUB ADVAN2 TRANS2
$PK
; Define LN2
 IF (NEWIND.LE.1) THEN
      LN2=LOG(2)
 ENDIF
```

```
; Define parameters
   KA=LN2/TABS
   ALAG1=TLAG
   S2=V
   V2=V

$ERROR

   CP=A(2)/V ; or CP=F
   IF (DVID.LE.1) THEN
      Y=CP*(1+RUVCV) + RUVSD
   ENDIF

   CE=CP
   PCA=E0 + EMAX*CE/(C50+CE)
   IF (DVID.EQ.2) THEN
      Y=PCA + RUVFX
   ENDIF
```


TABS is the half-life of absorption. The absorption rate is parameterised in terms of TABS but because ADVAN2 requires a value for KA it must be calculated from TABS in the code.
The NEWIND variable is a built in feature of NONMEM. When it is <= 1 it means this is the first record for this individual. The variable LN2 is calculated from LOG(2) just once for efficiency.
Note how the DVID data item is used to distinguish predictions of concentration (DVID=1) from predictions of PCA (DVID=2).

Slide 9

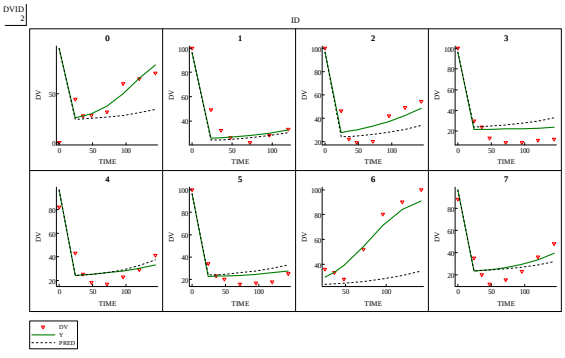
Data for Joint PKPD Model

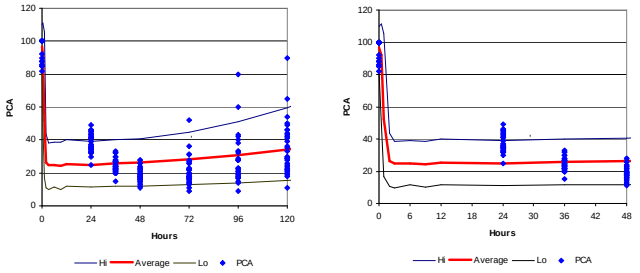
#ID	time	wt	age	sex	amt	dvid	dv	mdv
0	0	66.7	50	1	100	0	.	1
0	0	66.7	50	1	.	2	.	1
0	0.5	66.7	50	1	.	1	0	0
0	1	66.7	50	1	.	1	1.9	0
0	2	66.7	50	1	.	1	3.3	0
0	3	66.7	50	1	.	1	6.6	0
0	6	66.7	50	1	.	1	9.1	0
0	9	66.7	50	1	.	1	10.8	0
0	12	66.7	50	1	.	1	8.6	0
0	24	66.7	50	1	.	1	5.6	0
0	24	66.7	50	1	.	2	44	0
0	36	66.7	50	1	.	1	4	0
0	36	66.7	50	1	.	2	27	0
0	48	66.7	50	1	.	1	2.7	0
0	48	66.7	50	1	.	2	28	0

NONMEM requires that all observations are in a single DV column. In order to distinguish concentrations from effects (PCA) the DVID data item is used to identify the kind of DV. A DVID of 0 is used to indicate a dose record, 1 for a concentration record and 2 for a PCA record. Note that MDV is used to indicate if there are missing observations e.g. this subject does not have a PCA observation at TIME=0.

Slide 10	**Central Compartment Using $PRED**
	
	`$PRED`
	`; Get DOSE from AMT`
	`IF (NEWIND.LE.1) THEN`
	`LN2=LOG(2)`
	`DOSE=0`
	`ENDIF`
	`IF (AMT.GT.0) DOSE=AMT`
	
	`; Define parameters`
	`KA=LN2/TABS`
	`KE=CL/V`
	
	`; Adjust time for lagtime`
	`IF (TIME.LE.TLAG) THEN`
	`TNOW=0`
	`ELSE`
	`TNOW=TIME-TLAG`
	`ENDIF`
	
	`; Plasma concentration`
	`EXPKA=EXP(-KA*TNOW)`
	`EXPKE=EXP(-KE*TNOW)`
	`CP=DOSE*KA/(V*(KA-KE))*(EXPKE-EXPKA)`
	
	`IF (DVID.LE.1) THEN`
	`Y=CP*(1+RUVCV) + RUVSD`
	`ENDIF`
	
	`CE=CP`
	`PCA=E0 + EMAX*CE/(C50+CE)`
	`IF (DVID.EQ.2) THEN`
	`Y=PCA + RUVFX`
	`ENDIF`
	
		Note that DOSE must be defined on every record so it is obtained 'on the fly' from the AMT value. The AMT value is only >0 at TIME=0.

Slide 11	**Central Compartment Using ADVAN6**
	
	`$SUBR ADVAN6 TOL=3`
	`$MODEL`
	`COMP (DEPOT)`
	`COMP (CENTRAL)`
	`$PK`
	`; Define LN2`
	`IF (NEWIND.LE.1) THEN`
	`LN2=LOG(2)`
	`ENDIF`
	`; Define parameters`
	`KA=LN2/TABS`
	`ALAG1=TLAG`
	`S2=V`
	
	`$DES`
	`GUT=A(1)`
	`DCP=A(2)/V`
	
	`RATEIN=KA*GUT`
	`DADT(1)= -RATEIN`
	`DADT(2)= RATEIN - DCP*CL`
	
	`$ERROR`
	
	`CP=A(2)/V`
	`IF (DVID.LE.1) THEN`
	`Y=CP*(1+RUVCV) + RUVSD`
	`ENDIF`
	
	`CE=CP`
	`PCA=E0 + EMAX*CE/(C50+CE)`
	`IF (DVID.EQ.2) THEN`
	`Y=PCA + RUVFX`
	`ENDIF`
	
		Note the variables defined in $DES cannot have the same name as variables in other blocks e.g. you cannot define CP=A(2)/V in $DES and also in $ERROR. In this example the variable name DCP is used in $DES and the variable name CP is used in $ERROR.

Slide 12	**Warfarin Immediate**  	Individual 'post hoc' predictions from the immediate effect model describe most of the time course of PCA but in general the time of the predicted greatest effect is earlier than the observed effect.

Slide 13	**Warfarin Immediate Predictive Check**  	The visual predictive check shows clearly the systematic bias with the greatest effect coming too early.
Slide 14	**Delayed Effect Effect Compartment Model** • Two Basic Approaches – $PRED • Write model for CP and CE – PREDPP • ADVAN4 Very small peripheral compartment • ADVAN6 Differential Equations 	The visual predictive check points to using a model with a delayed effect. The simplest form of delayed effect model uses an effect compartment. This is usually considered an empirical model but if the delay in effect is only a few minutes then it might be a reasonable way to described the time course of drug distribution from plasma to the site of action in an organ. $PRED and ADVAN6 can be used to write exact solutions to the effect compartment model. Because ADVAN6 has to solve differential equations it is slower. ADVAN4 can be used by making the peripheral compartment have a negligible volume. This is helpful for complex dosing histories that would be hard to code in $PRED.

Slide 15	**Effect Compartment Using $PRED**
	`$PRED`
	`; Get DOSE from AMT`
	`IF (NEWIND.LE.1) THEN`
	`LN2=LOG(2)`
	`DOSE=0`
	`ENDIF`
	`IF (AMT.GT.0) DOSE=AMT`
	`; Define parameters`
	`KA=LN2/TABS`
	`KE=CL/V`
	`KEQ=LN2/TEQ`
	`; Adjust time for lagtime`
	`IF (TIME.LE.TLAG) THEN`
	`TNOW=0`
	`ELSE`
	`TNOW=TIME-TLAG`
	`ENDIF`
	`; Plasma concentration`
	`EXPKA=EXP(-KA*TNOW)`
	`EXPKE=EXP(-KE*TNOW)`
	`CP=DOSE*KA/(V*(KA-KE))*(EXPKE-EXPKA)`
	`IF (DVID.LE.1) THEN`
	`Y=CP*(1+RUVCV) + RUVSD`
	`ENDIF`
	`; Effect compartment model concentration`
	`EXPKQ=EXP(-KEQ*TNOW)`
	`CEEXKE=EXPKE/(KA-KE)/(KEQ-KE)`
	`CEEXKA=EXPKA/(KE-KA)/(KEQ-KA)`
	`CEEXKQ=EXPKQ/(KA-KEQ)/(KE-KEQ)`
	`CE=DOSE*KA*KEQ/V*(CEEXKE+CEEXKA+CEEXKQ)`
	`PCA=E0 + EMAX*CE/(C50+CE)`
	`IF (DVID.EQ.2) THEN`
	`Y=PCA + RUVFX`
	`ENDIF`
	
		The effect compartment model for a first-order input one compartment model requires an additional exponential term.

Slide 16	**Effect Compartment Using ADVAN4**
	
	`$SUB ADVAN4 TRANS4`
	`$PK`
	`; Define LN2`
	`IF (NEWIND.LE.1) THEN`
	`LN2=LOG(2)`
	`ENDIF`
	
	`; Define parameters`
	`KA=LN2/TABS`
	`ALAG1=TLAG`
	`S2=V`
	`V2=V`
	
	`KEQ=LN2/TEQ`
	`V3=V2*0.0001 ; negligible volume`
	`Q=V3*KEQ`
	
	`$ERROR`
	`CP=F`
	`IF (DVID.LE.1) THEN`
	`Y=CP*(1+RUVCV) + RUVSD`
	`ENDIF`
	
	`CE=A(3)/V3`
	`PCA=E0 + EMAX*CE/(C50+CE)`
	`IF (DVID.EQ.2) THEN`
	`Y=PCA + RUVFX`
	`ENDIF`
	
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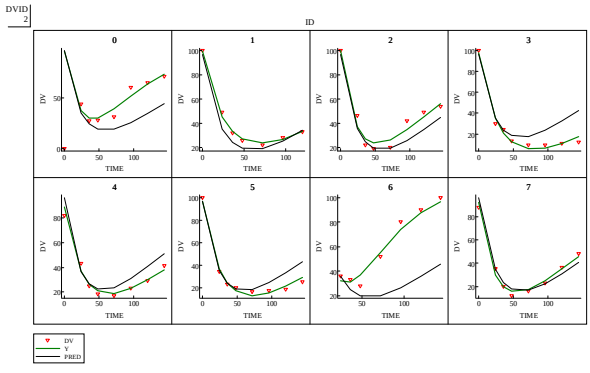
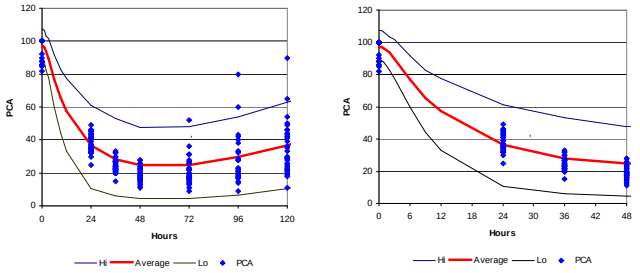
		Note how the peripheral compartment volume is scaled to be a very small fraction (0.0001) of the central compartment volume. This ensures it will have a negligible influence on the model predictions for the central compartment concentrations.

Slide 17	**Effect Compartment Using ADVAN6**
	
	`$SUBR ADVAN6 TOL=3`
	`$MODEL`
	`COMP (DEPOT)`
	`COMP (CENTRAL)`
	`COMP (EFFECT)`
	
	`$PK`
	`; Define LN2`
	`IF (NEWIND.LE.1) THEN`
	`LN2=LOG(2)`
	`ENDIF`
	`; Define parameters`
	`KA=LN2/TABS`
	`ALAG1=TLAG`
	`S2=V`
	`KEQ=LN2/TEQ`
	
	`$DES`
	`GUT=A(1)`
	`DCP=A(2)/V`
	`DCE=A(3)`
	
	`RATEIN=KA*GUT`
	`DADT(1)= -RATEIN`
	`DADT(2)= RATEIN - DCP*CL`
	`DADT(3)= KEQ*(DCP - DCE)`
	
	`$ERROR`
	`CP=A(2)/V`
	`IF (DVID.LE.1) THEN`
	`Y=CP*(1+RUVCV) + RUVSD`
	`ENDIF`
	
	`CE=A(3)`
	`PCA=E0 + EMAX*CE/(C50+CE)`
	`IF (DVID.EQ.2) THEN`
	`Y=PCA + RUVFX`
	`ENDIF`
	
	©NHG Holford, 2005, all rights reserved.
		The solution to differential equation 3 is scaled in terms of concentration. There is no need to define a volume of this compartment. It has no meaning for this model.

Slide 18	**Warfarin CE ADVAN4**  ©NHG Holford, 2005, all rights reserved.	The individual 'post hoc' predictions are much better than using the immediate model. This model looks fine. But are we missing something?

Slide 19

Warfarin Ce ADVAN4 Predictive Check



The visual predictive check confirms that the average prediction matches the observed effect time course but the variability is clearly overestimated.

Slide 20

Turnover Using ADVAN6

```
$SUBR ADVAN6 TOL=3
$MODEL
   COMP (DEPOT)
   COMP (CENTRAL)
   COMP (TRNOVR)

$PK
  F3=E0
  KPCA=LN2/TEQ
  RPCA=E0*KPCA
```

```
$DES
   RATEIN=KA*A(1)
   DCP=A(2)/V
   DPCA=A(3)
   PD=1+EMAX*DCP/(C50+DCP)

   DADT(1)=-RATEIN
   DADT(2)=RATEIN - CL*DCP
   DADT(3)=RPCA*PD - KPCA*DPCA

$ERROR
   CP=A(2)/V
   IF (DVID.LE.1) THEN
      Y=CP*(1+RUVCV) + RUVSD
   ENDIF

   PCA=A(3)
   IF (DVID.EQ.2) THEN
      Y=PCA + RUVFX
   ENDIF
```


The turnover family of models describe delayed drug effects where the delay is due to the turnover of a physiological mediator. This is well understood as the mechanism of the delay for warfarin.
The tricky part of this model is the need to modify the data set in order to initialize the PCA mediator compartment. This is done by using the F3 bioavailability fraction for the effect compartment.

Slide 21

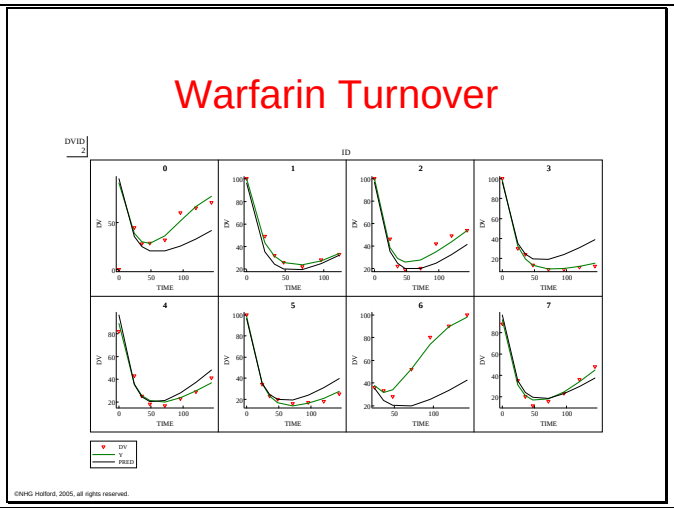
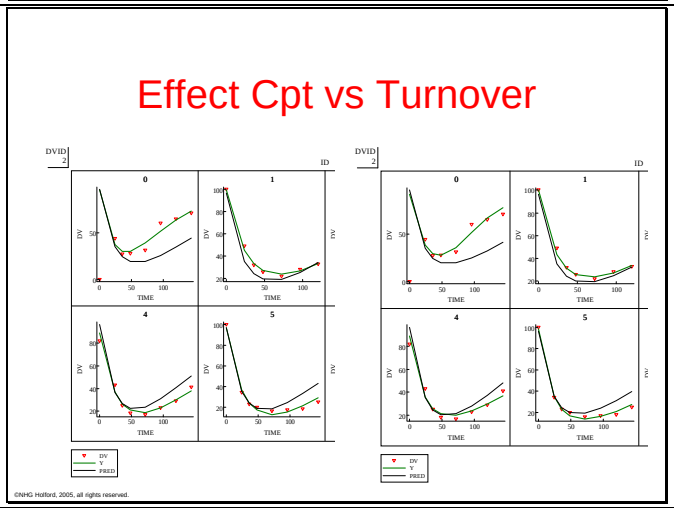
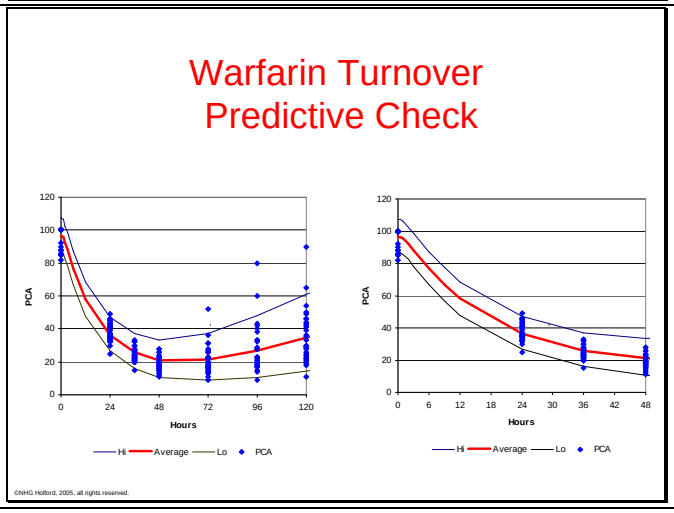
Using Bioavailability Fraction to Initialize A Compartment

#ID	TIME	AMT	CMT
1	0	1	3
1	0	100	1

```
$MODEL
   COMP (DEPOT)
   COMP (CENTRAL)
   COMP (TRNOVR)

$PK
   F3=E0
```


Initial conditions can be defined by a combination of adding a special record to the data set and using the NM-TRAN bioavailability fraction.
The special record is a dose record indicating a nominal AMT of 1 in the desired compartment. This record appears once for every individual at TIME=0.
The bioavailability fraction for AMT values is specified using the Fn variable in $PK (n is the number of the compartment e.g. F1 is the bioavailability for CMT=1). By setting the bioavailability fraction for the compartment, the amount in that compartment at time zero will be equal to AMT=1 multiplied by F and thus the desired initial condition at TIME=0 will be obtained.
The example shows a turnover model with a physiological mediator being defined in compartment 3. At steady state (the initial condition), the concentration of mediator at TIME=0 is E0.
A single record defining the AMT in the mediator compartment must be placed at the start of every individual record.

Slide 22		Turnover model individual “post hoc” predictions
Slide 23		The individual “post hoc” predictions from the turnover model do not look any better than the predictions from the effect compartment model.
Slide 24		The visual predictive check shows that the turnover model describes the variability of the observations much better than the effect compartment model but still does not properly capture the terminal recovery phase in two subjects.

Slide 25

Comparison of Models

Run	Obj	Min	Covariance	Eval	Sig
ka1_to_emax_ADVAN6	1202.815	Terminated Inf Obj Func	NONE	657	.
ka1_to_emax1_ADVAN6	1202.816	Successful	OK	367	3.1
ka1_ce_emax_ADVAN4	1271.931	Successful	ABORTED	597	3.3
ka1_ce_emax_ADVAN6	1271.936	Successful	ABORTED	539	3.2
ka1_ce_emax_PRED	1271.939	Successful	OK	608	3.2
ka1_im_emax_ADVAN2	1442.809	Successful	ABORTED	1225	3.0
ka1_im_emax_ADVAN6	1442.809	Successful	OK	929	3.0
ka1_im_emax_PRED	1442.809	Successful	ABORTED	1384	3.5

Fixing Emax to 1 allowed the turnover model to finish successfully.
Whether the covariance step runs is not a helpful criterion of model suitability.

Slide 26

Comparison of Parameters

Run	POP E0	POP EMAX	POP C50	POP TEQ
ka1_to_emax_ADVAN6	96.6	-1	1.18	13
ka1_to_emax1_ADVAN6	96.6	-1	1.18	13
ka1_ce_emax_ADVAN4	96.7	-256	11.1	39.5
ka1_ce_emax_ADVAN6	96.7	-256	11.1	39.5
ka1_ce_emax_PRED	96.7	-257	11.1	39.5
ka1_im_emax_ADVAN2	96.5	-74.3	0.22	.
ka1_im_emax_ADVAN6	96.5	-74.3	0.22	.
ka1_im_emax_PRED	96.5	-74.3	0.22	.

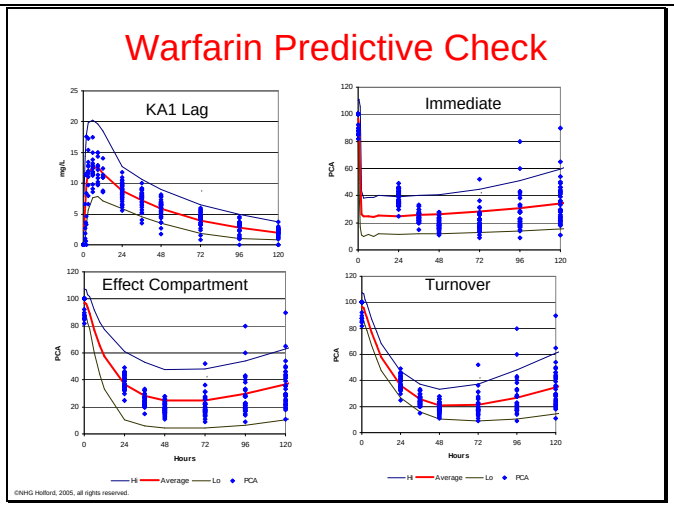
The half-life of PCA is reported in the literature to be about 14 hours. This is very close to the TEQ estimate of 13 hours from this data set. Notice also the more physiological meaning of an Emax of -1 i.e. 100% inhibition of PCA formation.

Slide 27

Comparison of Random Effects

Run	PPV E0	PPV EMAX	PPV C50	PPV TEQ	RUV FX
ka1_to_emax_ADVAN6	0.0533	6.54E-07	0.445	0.104	3.82
ka1_to_emax1_ADVAN6	0.0533	0.00E+00	0.445	0.104	3.82
ka1_ce_emax_ADVAN4	0.0510	1.77E-05	0.224	0.269	3.81
ka1_ce_emax_ADVAN6	0.0510	2.93E-06	0.224	0.269	3.81
ka1_ce_emax_PRED	0.0510	1.78E-04	0.224	0.269	3.81
ka1_im_emax_ADVAN2	0.0000	1.73E-02	0.879	.	8.37
ka1_im_emax_ADVAN6	0.0000	1.72E-02	0.878	.	8.37
ka1_im_emax_PRED	0.0000	1.72E-02	0.878	.	8.37

The residual error is very similar for the effect compartment and turnover models. The turnover model suggests that between subject differences in EC50 are more important than the value predicted using the effect compartment model.

Slide 28		The diagnostic benefits of the visual predictive check are seen clearly for the 3 PKPD models.
Slide 29