General questions

When we download the new version of Monolix/ Simulx every year, how can we delete the old version so it doesn't slow down the computer?	Go to the installation folder: C:\ProgramData\Lixoft (on windows) and delete the folder corresponding to the version you want to delete.
How popular in the industry is your software compared to WinNonlin?	PKanalix is still less common than WinNonLin but the number of companies using PKanalix is growing rapidly.
Is it designed more to support clinical studies or are your customers using it also for nonclinical/animal data?	PKanalix is used for both.
Do you consider developing the MonolixSuite further, e.g., by inclusion of some IVIVE methods and PBPK?	PBPK can be done with other applications of Simulations Plus, such as GastroPlus. IVIVE is not on our short term road map but is under consideration for the long term.
Is it possible to obtain a network license or is it only dedicated to one specific user?	For industry, floating licenses are also possible.
How can we decide and choose between compartmental and noncompartmental analysis?	You can do both, you don't have to choose!

Can I find the software for win32?	MonolixSuite (including PKanalix) is not available for win32 platforms.
Is assessment of dose proportionality possible using this software? E.g., by power model?	No, this is currently not possible.
Is it possible to do compartmental and non compartmental analysis in PKanalix for data with one sampling time point (without repeated measurements)?	You will need to average your data by nominal time point first, before you load it into PKanalix.
What does Q1 and Q3 mean?	Q1 is the first quartile (median of the lower half of the data) and Q3 is the third quartile (median of the upper half of the data).
Is it possible to change the format and resolution of the plots to export them?	The resolution is fixed but the format can be changed by changing the aspect ratio of the PKanalix window before exporting. If the resolution of the png is not enough for you, you can use the svg format, which is vectorial (so infinitely good resolution).
Can Monolix provide guidance to assess the schedule of PK sampling in the protocol based on the predicted PK properties?	This would rather be a simulation task with Simulx. This is out of scope of the current Spring School.
Monika mentioned R codes. Is there a library in the suite or are they available somewhere?	The R API to PKanalix is documented here: https://pkanalix.lixoft.com/pkanalix-api/
Do the lixoftconnectors work with the free R software?	The lixoftConnectors are used in R, yes. They are an R-interface to the C++ calculation engine of the MonolixSuite. The calculations are done with the same C++ code whether you use the GUI or the lixoftConnectors. You need a license to use it.
In the observed data plot, if mean is set to geometric mean, are standard deviations also geometric sd ?	Yes.

Is it possible to perform part of the preprocessing process in PKanalix, like data manipulation-transformation, or append external datasets?	It is not possible yet.
I saw a lot of R scripts in your different tutorials (spring school / FoW / Webinars). Some of them are clearly very useful. Do we have a chance you shared them on your website ? Same for Shiny App generation.	We have shared some pieces of code for using Monolix in R here: https://monolix.lixoft.com/monolix-api/examples/ and for Simulx here: https://simulx.lixoft.com/simulx-api/examples/ We will try to share more examples in the future. We do not share shiny apps for now.
Where can I know which package is necessary to have in R before the installation of lixoftConnectors?	The installation procedure and initialization is explained here: https://pkanalix.lixoft.com/pkanalix-api/lixoftconnectors_installation/
The R scripts shown are not universal but tailored to PKanalix, correct?	Yes the R scripts shown are using PKanalix.
Can PKanalix perform deconvolution e.g. to assess in vivo dissolution?	No. This could be done in Monolix, but not in a straightforward way.
About the tranexamic acid case study, since the intended application of tranexamic acid is for females, should we also consider only the female subjects to see if there is a difference?	That could be a good idea, but out of the scope of this spring school.
Can we get the dataset please?	The dataset is available in the lecture materials on the Spring School website. https://lixoft.com/lixoft-university/pkanalix-spring-school-2022/
Is there any Lixoft application that can perform PBPK?	If you are ready to write all equations, you can use Monolix. If you are looking for an "out of the box" PBPK model, you can have a look at the GastroPlus software: https://www.simulations-plus.com/software/gastroplus/

Setting up the dataset & units

If I want to later use dose as covariate for stratification of the plot. However, only the first time point has dose and the rest of time points are NA. What should be a good way to select dose when reading the dataset? Should it be selected as continuous or categorical covariates?	Tag the column as Amount. In the Data tab, click on "add. covariates" and "First dose amount" to add automatically the corresponding categorical covariate.
Is it possible to correct the concentration data for fraction unbound, or do you need to do this in a separate dataset calculated manually using PPB results?	This needs to be done in a separate step.
My plot shows that the concentration for each ID goes up and down, not a smooth line, did I miss some settings on the dataset?	Probably. If you have several profiles per individual, you need an occasion column to distinguish them.
Is it possible to show units on graphs?	You can change the axis labels manually and add units this way.
In the PKanalix dataset, how does it handle multiple cycles of dosing in oncology? Is the cycle (28 days) converted to time or just classified as categorical or sort variable?	This depends on how you format your data set. The key concept is to have an OCCASION column and that each occasion will be considered as a separate profile to analyze. Monika will come back to it in a few minutes.
How will the application know how to handle the BLQ? Do we have to compute the value before importing the data into PKanalix?	You can choose in the GUI between missing, zero, LOQ or LOQ/2.
What are the abbreviations LOQ and BLQ standing for?	LOQ means limit of quantification, or the concentration below which the exact concentration of the drug cannot be quantified. BLQ means below limit of quantification and it refers to the data points for which the exact concentration is unknown, all it is known is that it is under the LOQ.

What happens if the lab reports a text as LLOQ instead of a value? Can we still use the censoring to set it to numerical 0 for example?	Currently, PKanalix requires only numerical values (or dots '.') in the observation column. We are working on a data formatting module for the next version. We also have an Excel macro available to download, that can transform your data by replacing the text by the LLOQ: https://pkanalix.lixoft.com/data-formatting-macro/
Is the LLOQ imputed in the dataset as half of BLQ?	You can choose in the GUI to impute the LLOQ as missing, zero, LOQ or LOQ/2.
What to enter for the dose for a metabolite?	The same as for the parent.
So the dose input for the metabolite occasion is the actual dose of the parent drug?	Yes
Is the re-scaling of the amount or concentration column also available in Monolix?	No, not yet.
Is it possible to use mg/kg for dose/amount instead of flat dose (mg)?	Monika is showing it now: it is not possible, thus you have to use mg and do the change yourself when reporting the results.
For unit conversions, does PKanalix also accommodate conversions from molar units to weight/volume?	Yes, you just need to give the molar mass in the "scaling" box.
Instead of rescaling mg to ng by dividing by 1000; I suppose we have ng and mg as units of measurement in the pkanalix? So that you just enter the value directly.	The "amount" part of the concentration (amount/time) and amount (amount) unit definition needs to be the same. So the scaling is necessary.
Is PKanalix able to handle replicate periods where you may have two occasions of reference and two occasions of test product?	Yes, we will show this on day 2.

Is it possible to do baseline correction for post-dose levels using the average of the predose drug level?	Not for the moment.
In relation to the amount of dose, is it possible to normalize to mg/kg bw? In my case (veterinary pharmacology) it would be very useful for data processing (suggestion for future versions of PKanalix perhaps???)	We normalize by the value given in the dose column. If your dose is in mg/kg, we will normalize to mg/kg (even if you have indicated the unit as being mg instead of mg/kg).
Can one use EVID instead of Analyte to distinguish drug and metabolite?	You could use EVID to define occasions for the different analyte profiles. You still need the column Analyte to use as covariate to distinguish the occasions.
Going back to time units, if you had a sampling schedule that spanned minutes/hours/days/weeks/months, is there flexibility to plot the graphs based on several time units or do they all need to be converted to one unit?	They need to be converted to one unit. But you can use OCCASIONS to separate different profiles to analyze and "skip" all the time in between.
Is it possible to convert from ng or mg to molar units and see it in graphs too?	Yes, using the molar weight as scaling factor in the unit panel, but it won't be shown on the plots.
In which package is the function adaptDataPkx?	The adaptDataPkx function is the data formatting function from the upcoming RsPKanalix R package that will be released soon.
Could you please explain what the warning upon loading the dataset is all about?	You can click on the "yellow triangle" in the top right corner of the interface to see the warning message. They provide all the information.
Will you also have a dose by BSA (mg/m2) on the next update?	We will try to give more flexibility in the definition of units than in the current version.
I am not getting the option to add "sequence" in the covariates.	This option is new in the 2021R1 version. In addition, it appears only if different sequences are detected in the covariate column.

I have a question regarding preparing a dataset for both PKanalix and Monolix. For PKanalix I would add a time=0 conc=0 datapoint for each individual to calculate an accurate AUC. However, in Monolix, if I have pre-dose observations that are BLQ, and I change them to 0, will this affect the error model estimations? What is the recommended way to prepare such a dataset for use in PKanalix and Monolix, while not biasing the AUC calculation in PKanalix nor the error model estimation in Monolix?	You do not have to add conc=0 at time=0, it is actually done automatically by PKanalix for extravascular or infusion administrations. Although the dataset for the first hands-on included null concentration points at time 0, it is not recommended. The dataset without these points can be used in both PKanalix and Monolix.

Non-Compartmental analysis

Are values less than LLOQ (lower limit of quantification) excluded (ignored)?	You can choose how you want to process them (possibilities are as missing values, as zero, as LOQ values, as equal to LOQ/2). You can choose different possibilities, depending on if points are before or after Tmax.
Does NCA consider linear PK only, even if the drug disposition follows two- or more-compartments?	One, two and three compartment models are linear PK models. In opposition, drugs displaying target-mediated drug disposition are not linear.
How to calculate C0 with more points than the first 2 in IV administration?	This is not possible. C0 is always calculated using the two first points.
My question is about the number of points to choose to do the linear regression. Points just after the concentration peak can have great influence on the distribution process. Could these points be changing the values of lambda-z?	Several methods (including a manual choice) are available in PKanalix to select which points are used to calculate the lambda_Z. The value of the lambda_Z will depend on the choice of points and it is the user's responsibility to check that the choice is appropriate.
If the last points are LLOQ, how can I determine the terminal elimination phase?	You can choose how to handle the BLQ values (missing, LOQ, or LOQ/2 for instance). If you consider them as "missing", the terminal elimination phase will be calculated with the non-BLQ data

	only.
Which parameter should we trust more? R2 or adjusted R2?	The community consensus is to use the adjusted R2.
I believe the last concentration point for lambda estimation should be the detectable concentration, right? I mean if the last time point concentration is less than LLOQ but higher than LOD, we can not use LOD for the last time concentration?	Using values between LOQ and LLOQ to calculate the lambda_Z may bias the lambda_Z regression. We recommend setting BLQ after Tmax as "missing" (i.e ignored).
For partial AUC, is the assumption to always use the partial nominal time point or would partial AUC consider the actual sampling time point? So if subjects did not have an exact time point collected at 24 hrs, then an extrapolation method would be used to calculate partial AUC?	The times between which the partial AUC are calculated are given by the user in the GUI and they are the same for all individuals. So they usually are nominal times. If some individuals do not have a measurement at this time, an extrapolation method is used.
How can we select the number of data points in the elimination phase for NCA? What is the lowest number of data points required for NCA?	There are several options available, you can use four different rules (R2, adjusted R2, time interval or number of points) or you can manually select the number of points, with the minimum being 2.
Is it common to use the NCA output from Monolix and embed it in the CSR?	NCA parameters calculated by PKanalix are commonly included in the CSR. The full PKanalix output can also be added.
If the concentration value at 0.00 hr is missing due to haemolysis or any other reason, which value is considered for AUC estimation for extravascular and intravascular administration?	For plasma data, if an individual has no observation at dose time, a value is added: Extravascular and Infusion data: For single dose data, a concentration of zero. For steady-state, the minimum value observed during the dosing interval. IV Bolus data: the concentration at dose time (C0) is extrapolated using a log-linear regression (i.e log(concentration) versus time) with uniform weight of first two data points. In the following cases, C0 is taken to be the first observed measurement instead (can be zero or negative): - one of the two observations is zero - the regression yields a slope >= 0 See https://pkanalix.lixoft.com/calculation-rules/

So is there an option to calculate the partial AUCs individually for each subject according to the actual time point collected in PKanalix?	No, the partial AUC is defined for all individuals simultaneously.
With single oral dose data for a drug and its primary and secondary active metabolites, how can you predict Css for the active secondary metabolite?	This seems somewhat challenging. Non-parametric superposition to extrapolate single dose data to multiple-dose data is currently not possible in PKanalix.
Which AUC calculation method is the best to use for NCA?	There is no consensus. Linear up log down is quite popular.
Why is BLQ calculated as LOQ/2 after Tmax?	This is only one of the possible choices. It assumes that the "most probably" value is the middle between 0 and LOQ, so LOQ/2. But this is questionable. We rather recommend to set the BLQ data as missing after Tmax.
For microdialysis data do we have to select extravascular or intravascular administration? The administration occurs on femoral vein for example and the collection on the probe inserted on the liver. In WinNonlin we set extravascular administration. Do we have to use the time of the sampling or the midpoint between the times of sampling?	It depends on what your data looks like, but you would probably need to select extravascular administration. For NCA analysis, it would probably make more sense to use the midpoint. If you have some microdialysis data that you can share, you can contact us on springschool@lixoft.com and we can discuss this further.
Can you refine the BLQ rule? e.g ignore data that are BLQ at the same time points for all animals, but if one animal at least shows a quantifiable concentrations then use 1/2*LLOQ?	No, the rule needs to be the same for all individuals. If you need a more refined BLQ rule, you can do it in the data set directly (outside of PKanalix).
In your opinion, what should be the minimum value cut-off of adjusted R2 to be considered reliable ?	It really depends on your data. If the data is very noisy and the threshold leads to ignoring 3/4 of your individuals, it does not make sense.
As in the example showed, if R2 is less than 0.98 due to data quality, what should we do?	It depends, if it happens for only a few individuals, you can filter them out using the flag. If it happens for many individuals, I recommend checking the choice of points for the lambda_Z regression and possibly

	adjusting the choice of points manually.
Is lambda z equivalent to the elimination rate constant (Ke)?	It is related to it, yes.
Is there any method available to assess attainment of steady state?	No, not for the moment.
Are the PK parameter names aligned with CDISC standards?	Not the names displayed in the interface, but the table of parameters outputted in the results folder have a second header line with the CDISC codes for the parameters.
What is the nominal time point you are referring to?	Depending on your dataset, the time in the dataset can be the exact time, or the nominal time, that is the time at which the measurement should have been done, if the exact time is unknown. But there is actually no distinction in PKanalix, they are handled the same. If you have several individuals measured at the same nominal time, you need to average these values before loading the data into PKanalix.
Is there an option to rename NCA parameters before running NCA?	There is no option to rename the parameters.
Does this NCA model work for analyzing PK of animal data?	Yes it works also for animal data.
What is the difference between R2 and adjusted R2?	Adjusted R2 adjusts R2 value, so that it prefers more points. The exact formula of how adjusted R2 is calculated is: 1 - (1-R2)*(n-1)/(n-2)
Is there any minimum limit for the number of samples to be used for NCA?	There is no clear cut-off number of samples. To estimate the lambda_Z regression, you need at least 3.
Can you make templates on the NCA workflow?	No, but the workflow is so straightforward that you don't need to. Some of the settings (such as units) can be set in the Settings > Preferences for instance.

Is the distribution of the individual parameters (Cmax, tmax) supposed to be normal or lognormal (like clearance, Vd)?	It depends on the parameters, most of them are supposed to be log-normal, but Tmax is usually considered as normal.
What about weighing in NCA?	Several weighting options are available in the "check lambda_z" tab.
What is the difference between _obs and _pred (e.g., AUCINF_obs vs AUCINF_pred)?	The difference is in the extrapolation to infinity, it is based on the lambda_z estimated but also the last time point considered, with _obs the last time point is observed (AUCINF_obs = AUClast + Clast/Lambda_z), with _pred it is predicted, i.e. it is the concentration at the final observation time estimated using the linear regression performed to estimate lambda_z (AUCINF_pred = AUClast + Clast_pred/Lambda_z).
For lambda_z estimation, is it possible to manually select the terminal phase?	Yes, you can select points used in the calculation manually for each individual either by selecting/removing each point individually or with the time slider. Check the video lecture for more details.
How can we calculate Ctrough or Ctrough_ss?	It will be the observed concentration at the end of the dosing interval. If the observed concentration does not exist, the value is interpolated or extrapolated. Information about all parameters is here: https://pkanalix.lixoft.com/nca-parameters/
In the dataset for NCA we put zero concentration at zero time. It is not really correct when modeling (should be rather BQL). I guess it is done in the NCA to have a good starting point for trapezoid calculation, isn't it?	Yes, it is actually optional because PKanalix automatically adds 0 at the dosing time to compute NCA parameters for extravascular or infusion administration..
You said that PKanalix automatically adds a point with conc=0, time=0 for NCA. Is it also the case for intravascular administrations, for example IV bolus?	For IV bolus a point is added with extrapolation, it is explained here: https://pkanalix.lixoft.com/calculation-rules/#additional
Do the equations in the NCA model apply to animal models as well?	The equations to calculate lambda-z, AUC, interpolation and extrapolation are based

	only on the observed data, not on the species they come from.
Is there a place where the differences between trapezoidal / log trapezoidal / up down are described ?	The differences were covered in the first session, but you can also find them in this Feature of the Week video: https://www.youtube.com/watch?v=rmRH8SCuPP4
Would it have made any difference to compare the two treatment groups using the AUCs of the 2 groups or AUC/Dose since the calculation of AUC has the Dose (AUC =Dose/Cl)factored in?	It would make a difference, if doses are different in treatment groups. Since AUC will be larger for larger doses, to compare different doses you would need to correct AUC by dose. Comparing Cl values should not depend on the dose, since they are calculated through the equation you have given, which means that they are actually equal to the inverse of dose corrected AUCs.
In which situation will the calculation of partial AUC be necessary/required?	It depends on the regulatory guidelines and the question you want to answer. For example, in a bioequivalence study, the requirement might be that the partial AUC between week 3 and 4 are equivalent.
Let's assume that AUClast for the majority of subjects is computed over 3 weeks, and some subjects missed the Visit on week 3, so their AUClast is up to 18 days (for example) and AUClast of these subjects is less than AUClast of other subjects in general. Should such AUClast be ignored/excluded or pooled with all the available AUClast estimations?	It would make more sense to ignore them. If you have a categorical covariate column in the dataset to distinguish these ids (it is possible to add automatically the number of observations as covariate) you can use it to filter out these ids in the summary table of NCA parameters.
Will the AUClast/AUCinf<0.8 be highlighted?	This is not highlighted in PKanalix and won't be discussed during the spring school.
When AUC is mentioned, is it AUCinfinity or AUCt that is implied?	Usually we mean AUCinfinity but it depends on the case.
Can NCA fits be used to simulate new dosing scenarios?	No, non-parametric superposition is not available yet in PKanalix.

Is it feasible to calculate AUC between the baseline and observed value (i.e., AUC between two plots). Without calculating it individually and estimating the difference?	You could correct the points in the dataset by the baseline values and then calculate AUC.
Is the dose used for metabolite PK calculation?	Some parameters use the dose. You can find the entire list here: https://pkanalix.lixoft.com/nca-parameters/
Is there a presentation of the different weighing options and their implications?	You can check: https://pkanalix.lixoft.com/check-lambda_z/
Is it possible to perform Dose escalation studies (1,10&100mg/kg) and find the NCS PK parameters in PKanalix?	Yes.
Can we get the AUC for each patient as output?	Yes!
Is it more common to run NCA for PK parameters for CSR of clinical studies than popPK?	Yes, NCA is more common than popPK.

Compartmental analysis

If I understand it correctly, the compartmental analysis in PKanalix uses a stochastic approximation expectation method to generate general initial estimates. For WinNonlin, it uses curve stripping to generate individual initial estimates. What is the difference between both methods? and is it possible to do curve stripping to generate individual initial estimates in PKanalix ?	PKanalix does NOT use SAEM to generate initial values for compartmental analysis. It uses a fit on the pooled data using the Nelder-Mead deterministic algorithm. It is not possible to use the exact same algorithm as in WinNonLin.

Is it possible to use both NCA and CA for a drug?	Yes, you will see NCA today and CA on Thursday.
Is it possible to calculate individual and population parameters such as Cl, V and T1/2?	This rather seems a population approach (with non-linear mixed effects models). Monolix (not PKanalix) is the appropriate tool for this. Check the Spring School from last week: https://lixoft.com/lixoft-university/spring-school-2022/
How to choose the right weighing?	The default option is the best.
For me as a user, a key weak point in the MonolixSuite package is missing model diagnostics in PKanalix CA (classical PK), as only basic goodness-of-fit plots are available here. Could you show some tricks to do the diagnostics manually, for example calculation of R2, AIC, BIC? Maybe expansion of the source code or helpful references? Are you planning to provide model diagnostics in GUI in the next versions of PKanalix? I would welcome more diagnostics plots like obs vs pred, res vs time, res vs obs, res vs pred, histogram of residuals - so just typical graphs just are most common.	Thank you for your feedback. Calculation of AIC and BIC is something we will consider for the next version, as well as more diagnostic plots.
Isn't CA the same as population PK in Monolix?	In compartmental modeling in PKanalix, each individual is fitted independently of the others. In a population PK approach in Monolix, all individuals are considered at the same time and a population distribution is estimated.

Are the PK models in PKanalix same as those in Monolix?	Yes, the PK model libraries are the same.
What does lag time mean in bolus administration ?	It can be used as a "trick" in some situations (taking into account doses wrongly coded in the dataset) but is very rare in practice.
Could the infusion option be used for long acting IM with constant absorption rate ?	If you mean infusion followed by first-order absorption, from the 2021 version on, yes.
Is there a convenient way to know when a drug should be modeled with zero order or first order absorption?	This is hard to guess in advance. Best is to try. First-order is more common.
When should we use transit compartments to replace tlag?	When you have dense data in the absorption phase that show a progressive increase, which cannot be captured by a Tlag.
Q refers to Clearance and not blood flow?	Q refers to intercompartmental clearance. It is a typical parameter name for PK models (although it might be confusing for the PBPK community which uses Q as blood flow).
If a drug is intended for intramuscular administration but the drug is in depot with constant release rate, can we use the infusion model considering the constant release as well as absorption rate are constant exactly as the infusion rate?	Constant release can be modeled by a zero-order absorption (i.e transfer from depot to central). The equations for zero-order absorption or infusion rate are the same, except that the infusion rate (or duration) is defined in the data set while the zero-order absorption duration can be estimated.
In the result of the model parameters, we have Cl and at the same time Q1, Q2. Kindly clarify please.	If you refer to the slide with the individual and pooled fit, the used model actually has three compartments, so Cl is the elimination clearance and Q2 and Q3 are intercompartmental clearances.
My PhD data has one point sampling time whereby all samples were drawn 14 hours after oral dose administration. Can I use Monolix for compartmental analysis using this data with one time point sampling time?	If all samples are drawn at 14hours, it seems challenging to me to do a NCA analysis in PKanalix or popPK in Monolix.
Will it be possible in a future version to use iteratively reweighted LS, i.e., have the weights modeled based on the data?	This is not on our short-term roadmap.

Any notes/tips when working with plasma data from an intranasal administration?	We only have a small experience with intranasal administration and have no specific tips to give.
If I have intense sampling data, which of the 2 options will give better fit; doing CA modeling in PKanalix or do popPK modeling directly?	Usually a popPK approach is more powerful.
In the latest version of PKanalix/Monolix, is it possible to auto-init the initial values for a compartmental model with double absorptions to fit the concentration-time profiles which have a double-peak phenomenon?	Yes, this is possible with the 2021 version
What is/are the benefit(s) of performing the individual fit based on a compartment model in PKanalix while we can perform more sophisticated analyses based on the population model in Monolix?	The advantage of the CA in PKanalix is its simplicity. Doing popPK modeling in Monolix requires understanding at least some theory on the population approach.
I just missed that part, how can we add covariates to the CA model and adjust for them? And does CA in PKanalix provide a predictive equation for CL?	It is not possible to add covariates in the CA in PKanalix. This is only possible in Monolix.
Can CA modeling in PKanalix be used for longitudinal data (i.e, repeated measures)?	Yes, CA requires longitudinal data (i.e several measures per individual over time).
How can I calculate AUC using CA modeling in PKanalix?	You can export the CA model to Simulx and use the 'additional lines in the model" to add the AUC calculation. See https://www.youtube.com/watch?v=SCdGbscupyU and
Thanks Frano, I was thinking about Iteratively reweighted least squares (ILS) which assigns different weights for each parameter. But it looks like that question was answered previously.	This is currently not possible in PKanalix.
Is it possible to use sparse data combined with intensive sampling data in PKanalix? (in the same form of monolix), or is it more relevant to use sparse data in monolix?	You can use sparse data combined with intensive sampling data in both PKanalix and Monolix, however one of the benefits of the population approach (which is used in Monolix) is that the information contained in intensive sampling data will impact the

	estimation of individual parameters on the subjects with sparse data, so the individual estimates will be more precise.
Does PKanalix have a PD library? If not, do you plan to include it and when?	PKanalix does not have a PD library. For the next version, custom models (user-defined) will be possible in PKanalix and we might also add the PD library.
If I have a PK dataset and would like to perform PK modeling, would you recommend using PKanalix to get the initial parameters or using previously reported PK parameters in the literature?	Both are possible!

Bioequivalence

Do we need to demonstrate bioequivalence when bridging IV to SC?	It would depend on regulatory guidelines.
Would PopBE and IndivBE analysis be discussed in more detail in today's course?	No. In the next few weeks we will provide Feature of the week videos to explain the concepts in more detail.
Do examples with EndPoint data exist?	There are examples of bioequivalence analyses in the demos tab of PKanalix.
Is the 90% confidence interval predetermined by the regulatory guidelines or is it the standard?	In PKanalix, in the Bioequivalence settings, you can specify the values. The 9% confidence interval is the standard for most common studies but the regulatory guidelines change depending on the study.
Why is it the 125% upper limit since there is a 5% risk of true ratio without the range?	If confidence intervals are 90% and need to be inside some range, then there is in the worst case 5% risk of true ratio outside that range, independently of the range values. The 125% range was chosen by regulatory agencies as an acceptable higher bound of that range for most of the drugs.
What is the use of Repeated crossover design?	The goal is to have a study with more statistical power.
Can ISV be calculated as a standard 2x2x2 crossover BE design ?	Yes.

For biologics the rules are slightly different. Is that reflected also in PKanalix?	There is no way to distinguish biologics in PKanalix, you have to change the settings yourself.
In the example of the parallel design you are showing, the CV is called "intrasubject CV": should it be "inter" instead?	Yes for parallel design it is between-subject variability.
How to determine the sample size (subject no) for BE studies?	For this goal you can use Simulx - an application for clinical trial simulations. We will show how it works tomorrow.
Is it possible to perform a BE analysis using PD endpoint as mentioned in orlistat FDA product specific guidance using PKanalix?	PKanalix can only handle PK data for now, not PD endpoints.
Is it possible for PKanalix to test if period/sequence/formulation effects exist (big enough to contribute to the difference between R and T formulations) and give a p-value for it?	This is what is done in the ANOVA tab of the BE results.
Is ANCOVA available for BE analysis? (I have seen it in some articles, not guidelines; may be reasonable if the dosage is per kilogram and there is an imbalance in weights between groups)	Thank you for the suggestion. It is not available in PKanalix, we will have a look to maybe consider it for future versions.
Is it possible to conduct a simulation in Simulx based on a pilot study data of x subjects for a much higher number of subjects y in a higher scenario like 5000 or 10000 times to have an idea regarding the pivotal study performance, in case of a study conducted on the same formulation? And also post processing the simulated data to assess in which cases the BE is met?	Yes, that is possible to do. It is actually described in this Feature of the Week video: https://www.youtube.com/watch?v=W6mqDqR64Xw
Can you also compute some ratios (e.g. day ratios, sex ratios)?	BE can be used to compute ratios of means between the categories of any covariate. Individual ratios cannot be computed in PKanalix, but the R package that will be released for reporting will include an option to output tables of ratios.
You mentioned something about DDI in the introduction, how could this be assessed	You can use the BE module to compare groups of individuals with/without DDI, the

using PKanalix?	same way you compare groups with test/ref formulations.
Using only complete data is fine in a 2×2×2 crossover but discards information in a higher-order crossover or a replicate design.	In the current version, PKanalix ignores individuals with incomplete data. For a 2x2x2 crossover design, excluding these individuals or not does not matter. For higher order, excluding these individuals or nor changes the results. We will add the option to choose in the next version.
PROC Mixed ANOVA is not available as of today for BE evaluation in PKanalix, correct?	For the moment, PKanalix provides only fixed effect modeling, so the equivalent of "proc glm" in SAS, but no random effects.
95% upper bound scaled ANOVA for typical FDA submission for high variability molecules is not not available in PKanalix at the moment, correct?	Correct
Where do you see applicability of modeling on BE analysis? You gave a great presentation on long acting in a workshop on complex generics. Is the model/project used in this workshop available for reference?	The presentation on long acting injectables was using a pop PK model that is described in the following publication: Population Pharmacokinetics of a Monthly Buprenorphine Depot Injection for the Treatment of Opioid Use Disorder: A Combined Analysis of Phase II and Phase III Trials.
You mention Tmax. Is there an analysis needed for Tmax?	Tmax is usually not required in the BE analysis, as per regulatory guidance.
What conclusions should we draw if Cmax passes the BE but AUC does not?	BE can be concluded only if all three NCA metrics pass the BE criteria.
To meet the BE standard (80-150), could we approximate the lower and upper boundary to meet the standard (e.g 79.65 - 149.89)?	No, rounding is not allowed per regulatory guidelines. That means that if your lower value is 79.65, the test formulation is not bioequivalent. Note that PKanalix allows you to change the BE limits in the advanced BE settings if the default 80-125% is not appropriate to your situation.
In a BE trial subjects are uniquely coded. If there is subject 1 in sequence RT, there is not ‘another’ subject 1 in subject TR. Hence, the nested model (though stated in all guidelines) is bogus. You can remove	I agree that removing sequence does not change the ratio and CI values. Specifying that ID is nested in SEQ (although the subjects are uniquely coded) changes the least-squares means but not the point

even sequence from the model (not period) and will get exactly the same result.	estimate and ratio.
Is it possible to perform a RSABE analysis in PKanalix?	No, this is not possible yet
For a full replicate design for EMA regulation, can PKanalix calculate the wider acceptance interval?	You can widen the BE limits but the calculation of the new BE limits need to be done outside PKanalix.
F >100% is possible indeed. An oral solution of theophylline is an example. In the IV route we have first-pass metabolism in the lung, which is bypassed in the oral route.	Yes, I agree. To our knowledge, it is not the case for this drug (and we didn't want to confuse the audience with going too much into the details).
Is there some guidelines in the case you also have an active metabolite for BE ? Or is it the same than the parent drug ? Shall we consider an active metabolite as a "new" investigation when using PKanalix ?	Some product-specific guidelines do require measuring plasma concentrations and report NCA parameters for metabolites, but we do not know if there are product specific guidelines requiring that bioequivalence should be based on both parent and metabolite.
What are in a simple explanation the pros and cons between NCA and CA for BE? I usually prefer compartmental analysis. Is it a question of the number of sampling times?	The regulatory agencies request NCA for calculating the PK parameters for BE.
What is your opinion on the emerging interest in MBBE (model-based bioequivalence)? As far as I could understand from some posters and slides it is a mixture of popPK for AUC/Cmax evaluation and then ANOVA for confidence interval assessment.	My personal opinion is that model-based estimation of Cmax and AUC is more powerful than NCA. But it requires developing a model that is appropriate for the data and this may be challenging in some cases (and less easy to review for regulatory agencies).
'@Lixoft @Helmut : It seems a bit outdated to still use NCA instead of CA for regulatory approval. When you see the creation of a pharmacometrics division by the FDA and the fact that an awesome understanding of the inherent drug mechanism is usually required for a new drug approval etc... Do you know if we can expect some changes about the regulatory process in a few years ?	Lixoft: I am not very optimistic in this regard. Helmut: I agree with Géraldine. No way. If you – really – have nothing better to do, attend the Conference on The Global Bioequivalence Harmonisation Initiative (Amsterdam) or BioBridges (Prague), both in later September. You will be surprised how little progress we had in the last four (!!) decades.

Ok thanks for your feedback! Let's stay in the stone age!	

Monolix

Can Monolix run a meta-analysis using a PD model that is not built-in? like an operational model of agonist.	Yes, you can code your own models. Meta-analysis is also possible. Check our case study: https://monolix.lixoft.com/case-studies/longitudinal-model-based-meta-analysis-mbma-monolix/
Sometimes for custom written models (described as stiff ODE with no error in the model after checking with Mlxtran), Auto-init yields a message "NaNs produced during simulation". What can be the issue? When auto-init fails, it also does not allow to manually toggle the parameter values in the check initial estimates. Any suggestions?	Autoinit may go towards extreme parameter values that lead to a failure to the ODE solver (for instance tumor size going to infinitely large values). When running 'autoinit', it creates a "reference curve" with the previous parameter set and you can restore these values by clicking on the small downward arrow at the top right where the reference is stored.
Is it possible to share the link to syntax/macros used to specify the Weighing scheme in the user-defined models in Mlxtran?	Weighting is not used in population modeling, but you can choose different error models in the Statistical models & Tasks tab. If this doesn't answer your question, can you be more specific?
In the Individual Estimates in the Monolix Results tab we have conditional mean and conditional mode results. Do the former correspond to the EBEs task, and the latter to the Conditional task?	The conditional mean is calculated during the Conditional distribution task as a mean of sampled individual parameters and conditional mode is calculated during the EBEs task.
I just realized that Tlag was assumed to be lognormal. Is it possible to use a truncated normal (what I generally use in my models in R)?	You can use a logit distribution with custom bounds but not truncated normal.
Is there any specific way to formulate our decision to arrive at the choice of the best fit (vs other fits) for our data in popPK?	There is no unique decision path (otherwise we would have automatized everything already ;-)). It depends on your modeling goal also.