Guidelines on Bioanalytical Method Validation in China

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11 September 2014, Berlin

Background

- Current guidelines for bioanalysis in China
  - Chinese Pharmacopoeia 2000-2010
  - Included in BA/BE guideline (1 page)
  - CFDA guidelines 2005
- Objectives of the new guidance in ChP2015
  - A separate guidance for bioanalysis
  - Harmonized with international guidelines (EMA, FDA)
  - Detailed information
  - Meet future demands in China

Background

- Process of drafting the guidance in ChP 2015
  - Pharmacopoeia Commission (2010)
  - Subcommittee for Drug Formulation (2010)
  - Drafting group (2010)

Background

- Process of drafting the guidance in ChP 2015
  - EMA and FDA guidelines for reference
  - Published on a journal (2011) and conferences for consultation (2012)
  - CBF discussion and revision (2013)
  - Approved in the Subcommittee (2014)
  - Released on website (July 2014) for consultation (#9012, 13 pages) http://www.chp.org.cn/cms/newscenter/publicity/000904.html

·专论·

生物样品定量分析方法指导原则（草案）

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摘　要：根据目前国际上对生物样品定量分析的相关指导原则，建议《中国药典》修订和扩充现有的的指导原则，以适应新药开发和仿制药开发的需求。内容包括：指导原则适用范围，生物分析方法确证，试验样品分析，配体结合分析，试验报告，以及生物分析相关定义。其中，对基质效应、已测样品再分析、稳定性考察等列出了详细的要求。

关键词：生物样品分析指导原则；生物分析方法确证；基质效应；已测样品再分析
中图分类号：R917　　文献标志码：A　　文章编号：1674-6376 (2011) 06-0409-07

Guidance on Bioanalysis: Method validation and analysis of study samples (Draft)

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Abstract: This is the draft version for the Guidance on Bioanalysis in China Pharmacopoeia, 2015 Edition. The recommendations are based on the current international guidelines and for adepting the requirements to the development of new drugs and generic drugs. It is composed of scope of the guidance, method validation, analysis of study samples, incurred samples reanalysis, ligand binding assays, reports, and definitions. Detailed requirements for matrix effect, incurred samples reanalysis, and stability investigation are introduced.

Key words: guidance on bioanalysis; method validation; matrix effect; incurred samples reanalysis

本指导原则是为中国药典 2015 年版附录准备的草案。其内容参考了中国药典 2010 年版指导原则（生物样品定量分析方法相关内容）[1]，美国 FDA 指导原则（2001）[2]，欧洲 EMA 指导原则（草案，2009）[3]，以及中国 SFDA 指导原则（2005，生物样品定量分析方法相关内容）[4-6]。目前，全球性的生物样品定量分析方法指导原则正在讨论中[7-8]。

1　范围

对于新药开发和仿制药开发，准确测定生物基质（全血、血浆、尿）中的药物浓度非常重要，这些数据可被用于资料申报。根据毒动学、药动学和生物等效性试验的结果做出关键性决定，以支持药品的安全性和有效性。因此，必须很好地表征、完整地确证和记录应用的生物分析方法。

本指导原则提供生物分析方法确证的要求，也涉及生物分析方法本身的特定方面，如临床前或临床试验样品的实际分析。还进一步指出，何时可能使用部分确证或交叉确证，替代一个生物分析方法的完整确证。

生物分析方法确证和试验样品分析应符合 GLP 原则。但是，由于临床生物分析试验处于 GLP 范围之外，所以开展临床试验的地点不需要作为国家 GLP 贯彻程序的一部分被监测。此外，对于在人体开展的临床试验，应该遵循 GCP 原则。

2　生物分析方法确证

2.1　分析方法的完整确证

对于任何分析方法，无论是新方法还是基于文献的方法，都应该进行完整的确证。

ChP Draft Guideline on Bioanalytical Method Validation

Contents

1. Scope
2. Bioanalytical Method Validation
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1. Scope

- It is very important for the development of drugs and formulations to accurately measure drug concentrations in biological matrix (e.g. blood, plasma, serum, or urine).
- These data could be used to support the safety and efficacy of drug products, or make critical decisions based on toxicokinetic, pharmacokinetic or bioequivalence studies. Therefore, the bioanalytical method should be fully validated and documented to obtain reliable results.
- This guidance provides the requirements for bioanalytical method validation, also involves requirements for analysis of nonclinical and clinical samples, as well as when partial validation or cross validation may be used instead of full validation.
- The bioanalytical method validation and study sample analysis should meet the requirements of this guidance. In respective bioanalytical analysis, GLP or GCP principles should be complied with.

2. Bioanalytical Method Validation

2.1 Full Validation

- Selectivity
- Carryover
- LLOQ
- Standard Curve
- Accuracy
- Precision
- Dilution Reliability
- Matrix Effect
- Stability

2.2 Partial Validation

2.3 Cross Validation

Selectivity

- The analytical method should be able to differentiate and quantify the intended analyte in the presence of other components in the sample.
- Analyses of blank samples of the appropriate biological matrix should be obtained from at least six sources. Each blank sample should be tested individually for interference.
- The result is generally acceptable If the interference is less than 20% of the analyte LLOQ, and less than 5% of the IS response.
- Potential interfering substances in a biological matrix include endogenous matrix components, metabolites, decomposition products, and concomitant medication. In some cases, the back inversion of drug metabolites to the parent drug should also be considered.

Carryover

- Carryover should be addressed and minimized during method development. Carryover should be assessed by injecting blank samples after a high concentration sample or calibration standard.
- Carry over in the blank sample following the high concentration standard should not be greater than 20% of the lower limit of quantification and 5% for the internal standard.
- Specific measures should be considered, tested during the validation and applied during the analysis of the study samples, so that it does not affect accuracy and precision. This could include the injection of blank samples after samples with high concentration, before the analysis of the next study sample.

Lower Limit of Quantification

- LLOQ is defined as the lowest analyte concentration that can be measured with acceptable accuracy and precision.
- LLOQ is the lowest concentration on the standard curve, which is suitable to the expected concentration range and the study aim.

Standard Curve (1)

- The instrumental response to the analyte should be evaluated in a given concentration range to obtain the standard curve. The calibration standards should be prepared in the same matrix as the matrix of the intended study samples by spiking the blank matrix with known concentrations of the analyte. There should be one calibration curve for each analyte studied in the method validation and for each analytical run.
- Before conducting the validation of the analytical method it is preferred to know the expected concentration range. This range should be covered by the calibration curve, defined by the lowest and the highest calibration standards. The range should be established to allow adequate description of the pharmacokinetics of the analyte.
- A minimum of six calibration concentration levels should be used, in addition to the blank sample (processed matrix sample without analyte and without IS) and a zero sample (processed matrix with IS). Each calibration standard can be analyzed in replicate.

Standard Curve (2)

- The simplest model that adequately describes the concentration-response relationship should be used. The blank and zero samples should not be taken into consideration to calculate the calibration curve parameters.
- The calibration curve parameters should be reported. The back calculated concentrations of the calibration standards should also be presented. A minimum of three calibration curves should be reported during method validation.
- The back-calculated concentrations of standards should not deviate by more than 15% of nominal concentrations, except at LLOQ where the standard should not deviate by more than 20%. At least 75% of standards, including 6 effective concentrations, should meet the above criteria. If the result of a standard does not meet the criteria, the standard should be rejected, and the standard curve reevaluated, including regression analysis.
- The calibration curve should preferably be prepared using freshly spiked samples. However, it is allowed to use previously prepared and stored calibration samples, if supported by appropriate stability data.

Accuracy

- The accuracy of an analytical method describes the closeness of mean test results obtained by the method to the actual concentration of the analyte. It is calculated as: (measured value – actual value)   100%. Accuracy is determined by replicate analysis of samples containing known amounts of the analyte (i.e., QCs). The QC samples should be spiked independently from the calibration standards, using separately prepared stock solutions.
- The QC samples are analyzed against the calibration curve, and the obtained concentrations are compared with the nominal value. The accuracy should be reported as percent of the nominal value. Accuracy should be evaluated for the values of the QC samples obtained within a single run (the within run accuracy) and in different runs (the between-run accuracy).
- To enable evaluation of any trends over time within one run, it is recommended to demonstrate accuracy and precision of QC samples over one or more runs in a size not less than a prospective analytical run of study samples.
- Within-run accuracy should be determined by analyzing in a single run a minimum of 5 samples per concentration at a minimum of 4 concentrations. They should cover the calibration curve range: the LLOQ, within three times the LLOQ (low QC), near midrange of the calibration curve (medium QC), and at about 75% of the upper calibration curve range (high QC). The mean value should be within 15% of the nominal value except at LLOQ, where it should be within 20%.
- For the validation of the between-run accuracy, LLOQ, low, medium and high QC samples from at least three runs analyzed on at least two different days should be evaluated. The mean value should be within 15% of the nominal value except at LLOQ, where it should be within 20%.
- Reported method validation data and the determination of accuracy and precision should include all results obtained except those cases where errors are obvious and documented.

Precision

- The precision of an analytical method describes the closeness of repeated individual measures of analyte, expressed as the coefficient of variation (CV). Precision should be demonstrated for the LLOQ, low, medium and high QC samples, within a single run and between different runs, using the same runs and data as for the demonstration of accuracy.
- For the validation of the within-run precision, there should be a minimum of five samples per concentration at LLOQ, low, medium and high QC samples in a single run. The within-run CV value should not exceed 15% for the QC samples, except for the LLOQ which should not exceed 20%.
- For the validation of the between-run precision, LLOQ, low, medium and high QC samples from at least three runs analyzed on at least two different days should be evaluated. The between-run CV value should not exceed 15% for the QC samples, except for the LLOQ which should not exceed 20%.

Dilution Reliability

- Dilution of samples should not interfere with the accuracy and precision.
- Dilution reliability should be demonstrated by spiking the matrix with an analyte concentration above the ULOQ and dilution of this sample with blank matrix (at least five determinations per dilution factor).
- Accuracy and precision should be within ±15%. Dilution reliability should cover the applied dilution of the study samples.

Matrix Effect

- Matrix effects should be investigated when using mass spectrometric methods, using at least 6 lots of blank matrix from individual donors. Pooled matrix should not be used. For rare matrix, using less than 6 lots of blank matrix is acceptable, but should be justified.
- For each analyte and the IS, the matrix factor (MF) should be calculated for each lot of matrix, by calculating the ratio of the peak area in the presence of matrix (measured by analyzing blank matrix spiked after extraction with analyte), to the peak area in absence of matrix (pure solution of the analyte). The IS normalized MF should further be calculated by dividing the MF of the analyte by the MF of the IS. The CV of the IS-normalized MF calculated from the 6 lots of matrix should not be greater than 15 %. This determination should be done at a low and at a high level of concentration.
- If this approach cannot be used, for instance in the case of on-line sample preparation, the variability of the response from lot to lot should be assessed by analyzing at least 6 lots of matrix, spiked at a low and at a high level of concentration (maximum of 3 times the LLOQ and close to the ULOQ). The validation report should include the peak areas of the analyte and of the IS and the calculated concentration for each individual sample. The overall CV calculated for the concentration should not be greater than 15 %.
- In addition to the normal matrix it is recommended to investigate matrix effects on other samples e.g. haemolyzed and hyperlipidaemic plasma samples.

Stability (1)

- Stability should be ensured for every step in the analytical method. The conditions applied to the stability tests, such as sample matrix, anticoagulant, container materials, storage and analytical conditions should be similar to those used for the actual study samples. Reference to data published in the literature is not considered sufficient.
- Stability of the analyte in the studied matrix is evaluated using low and high QC samples (blank matrix spiked with analyte at a concentration of a maximum of 3 times the LLOQ and close to the ULOQ) which are analyzed immediately after preparation and after the applied storage conditions that are to be evaluated.
- The QC samples are analyzed against a calibration curve, obtained from freshly spiked calibration standards, and the obtained concentrations are compared to the nominal concentrations. The mean concentration at each level should be within ±15% of the nominal concentration.
- Stability of the stock and working solutions should be tested with an appropriate dilution, taking into consideration the linearity and measuring range of the detector.

Stability (2)

- Stability studies should investigate the different storage conditions over time periods that not less than those applied to the actual study samples.
- The following stability tests should be evaluated:
  - stability of the stock solution and working solutions of the analyte and internal standard,
  - freeze and thaw stability of the analyte in the matrix from freezer storage conditions to room temperature or sample processing temperature,
  - long term stability of the analyte in matrix stored in the freezer,
  - In addition the following tests should be performed if applicable:
  - stability of the processed sample at room temperature or under the storage conditions to be used during the study,
  - stability of the processed sample at the autosampler temperature.
- In case of a multi-analyte study and specific for bioequivalence studies, attention should be paid to stability of the analytes in the matrix containing all the analytes.
- Sufficient attention should be paid to the stability of the analyte in the sampled matrix directly after blood sampling of subjects and further preparation before storage, to ensure that the obtained concentrations by the analytical method reflect the concentrations of the analyte in the subject at the moment of sampling. A demonstration of this stability may be needed on a case-by-case basis, depending on the structure of the analyte.

Partial Validation

- In case of minor changes of an analytical method, a partial validation may be needed, depending on the nature of the applied changes.
- Possible changes include transfer of the bioanalytical method to another laboratory, change in equipment, calibration concentration range, limited sample volume, another matrix or species, change in anticoagulant, sample processing procedure, storage conditions etc.
- All modifications should be reported and the scope of revalidation or partial validation justified.

Cross Validation

- Where data are obtained from different methods within and across studies or when data are obtained within a study from different sites, applying the same method, comparison of those data is needed and a cross validation of the applied analytical methods should be carried out.
- Cross validation should be performed in advance of study samples being analyzed if possible. For the cross validation, the same set of QC samples or study samples should be analysed by both analytical methods.
- For QC samples, the obtained mean accuracy by the different methods should be within 15% and may be wider, if justified. For study samples, the difference between the two values obtained should be within 20% of the mean for at least 67% of the repeats.

3. Analysis of Study Samples

3.1 Analytical Run

3.2 Acceptance Criteria for an Analytical Run

3.3 Calibration Range

3.4 Reanalysis of Study Samples and Selection of Reporting Value

3.5 Integration

3.6 Incurred Sample Reanalysis for Estimation of Method Reproducibility

Analytical Run

- An analytical run includes a blank matrix sample (matrix sample processed without analyte or internal standard), a zero sample (matrix sample processed without analyte but with internal standard), at least 6 non-zero calibration standards, at least 3 levels of QC samples (duplicates for each level or at least 5% of the total study samples, whichever is higher), and study samples.
- All samples in the same run including calibration standards, QC samples, and study samples should be processed and extracted in the order of sample submission or analysis.
- Samples in one run need to be processed without interruption in time by the same analyst using identical reagents under consistent conditions. To ensure the accuracy and precision of the whole analytical run, QC samples should be spread over the run.
- To minimize the variation of data, it is preferred that all samples from the same subject should be analyzed in the same analytical run for bioequivalence study.

Acceptance Criteria for an Analytical Run (1)

- The acceptance or rejection criteria for an analytical run should be described in a study protocol or a SOP. If a single run includes multiple batches, then the acceptance criteria apply to the whole run and to the individual batches. The acceptance criteria are as follows:
  - Calibration standards should not deviate by more than 15% of nominal concentration, except that LLOQ should not deviate by more than 20%.
  - For a calibration curve, at least 75% of non-zero standards, with a minimum of 6, must meet this criterion. If one of the calibration standards does not meet this criterion, this standard should be rejected. Then the calibration curve should be recalculated and regressed excluding this failed standard.

Acceptance Criteria for an Analytical Run (2)

- The accuracy of QC samples should be within 15% of their respective nominal concentrations. At least 67% of the QC samples and at least 50% of QC samples at each level should meet this criterion. If the analytical run fails to meet this criterion, then the run should be rejected and the study samples should be re-extracted and analyzed.
- With regard to an assay involving multiple analytes, a calibration curve is required for each analyte. If one analyte in the assay meets the batch acceptance criteria and another analyte fails to meet the acceptance criteria, then the data from the accepted analyte can be used. However, the study samples should be re-extracted and analyzed to determine the rejected analyte.
- For a run with replicate calibration standards, the calibration range does not change if only one of the LLOQ or ULOQ standards fails.
- The overall mean accuracy and precision of each level of QC samples should be calculated and reported. Additional investigation should be performed and the cause for deviation should be described if the overall mean accuracy and precision of one level of QC samples deviate more than 15%. Under the circumstance of bioequivalence studies, this deviation may result in the rejection of the data.

Calibration Range

- If a narrow range of analyte concentrations of the study samples is known or anticipated prior to the start of sample analysis, it is recommended to narrow the dynamic range of standard curve, adjust the concentration of QC samples or add additional QC samples at new concentration in order to sufficiently reflect the concentration of study samples.
- If the concentration of a large number of study samples appears to be above ULOQ, the dynamic range of calibration curve should be extended, additional QC samples should be added or the concentrations of QC samples should be modified.
- At least two QC samples levels should be within the concentration range of study samples.
- In order to verify the response function and ensure accuracy and precision, the bioanalytical method should be re-validated or partially validated if the calibration curve range is changed.

Reanalysis of Study Samples (1)

The reasons for sample reanalysis could be the following:

- An analytical run fails to meet acceptance criteria in terms of accuracy and precision for calibration standards or QC samples.
- The responses of internal standards for study samples differ significantly from those for the calibration standards and QCs samples.
- Improper sample injection or malfunction of instruments.
- The measured concentrations are either above ULOQ or below LLOQ where the lowest calibration standard is rejected from standard curve, causing the LLOQ of the run higher than other runs.
- There are measured concentrations in pre-dose or placebo samples.
- Abnormal chromatography

Reanalysis of Study Samples (2)

- For bioequivalent studies, the reanalysis of study samples typically is not acceptable due to pharmacokinetic reasons.
- For the reanalysis due to the measurable concentrations in pre-dose samples or due to pharmacokinetic reasons, the identifications of the reanalyzed samples, original values, the reasons for reanalysis, values from reanalysis, the final accepted values as well as the reason for acceptance need to be provided.
- When the analytical runs stop due to instrument failure, the processed samples can be re-injected if the reinjection reproducibility and autosampler stability have been demonstrated during method validation. For the runs that fail to pass the acceptance criteria, all study samples need to be re-extracted and re-analyzed in this case.

Integration

- Chromatogram integration or re-integration should be described in the SOP. Any deviation from SOP should be discussed in the analytical report.
- All integration parameters need to be recorded in the laboratory. In the case of re-integration, all initial and final integration data will be documented and provided upon request.

Incurred Sample Reanalysis (1)

- The calibration standards and QC samples might not be able to mimic the actual samples. For example, factors such as the protein binding, back-conversion of known or unknown metabolites, sample inhomogeneity or concomitant medication can affect the precision and accuracy of the samples during sample storage and processing.
- As a result, it is recommended that reanalysis of study samples in separate runs at different days to assess the accuracy of the data for incurred samples. The extent of the test will be based on the analytes, the study samples as well as the understanding of the analytical method and analytes.
- It is recommended the samples around C_{max} and in the elimination phase be chosen. Generally 10% of samples are reanalyzed in the case of less than 1,000 samples. If sample number is more than 1,000, additional 5% of the samples over 1,000 will be reanalyzed.

Incurred Sample Reanalysis (2)

- The acceptance criteria of incurred sample reanalysis is that at least 67% of the reanalysis concentrations is within ±20% of their mean of original and repeat concentrations.
- If the results fail to meet the acceptance criteria, investigations need to be initiated and necessary steps to improve the analytical method might be required.
- Incurred sample reanalysis should be conducted at least in the following situations:
  - Once per species in toxicokinetic studies
  - All pivotal bioequivalent studies
  - First-in-human studies
  - First-in-patient studies
  - First-in-human impaired hepatic and/or renal function.
- For animal experiments, it is recommended to conduct incurred sample reanalysis only during early phase representative pivotal studies such as those to establish the relationship between dose administered and resulting drug concentrations.

4. Ligand Binding Assays

4.1 Considerations before Method Validation

- Reference Standards Selection
- Matrix Selection
- Minimum Dilution
- Reagents

4.2 Method Validation

- Full Validation
- Partial Validation and Cross Validation

4.3 Analysis of Study Samples

- Analytical Run
- Acceptance Criteria for an Analytical Run
- Incurred Sample Reanalysis

Full Validation of Ligand Binding Assays

- Calibration Curve and Calibration Range
- Specificity
- Selectivity
- Accuracy and Precision
- Dilution Linearity
- Parallelism
- Stability
- Commercial Kits

5. Documentation

Method Validation Report

- All raw data should be kept in original format and be available upon request.
- Any study deviation from method validation protocol should be documented.
- All measured and back-calculated concentrations should be presented in method validation report.

Method Validation Report

- Overall summary of method validation results
- Detailed information in analytical procedure. Source of origin of analytical method should be provided if a reference method is used.
- Brief description of analytical procedures
- Reference standards
- Calibration standards and quality control samples
- Acceptance criteria for analytical runs
- Analytical run: table summary of all analytical run including calibration range, regression parameters, back-calculated concentrations and accuracy; table summary of QC samples from all accepted runs; storage stability results for stock solution, working solution and QC samples; assessment results on selectivity, LLOQ, carryover, matrix effect and dilution integrity.
- Sufficient justification on any action taken to address unexpected results during method validation
- Any deviations from analytical method and/or SOP

Sample Analysis Report (1)

- The sample analysis report should provide a reference to method validation report and it should also include the detailed description of study samples.
- All raw data should be kept in original format and be available upon request.
- The report should include the discussion on any deviations from analysis protocol, analytical procedure and/or SOPs.
- Results from incurred sample reanalysis may be presented in method validation report, analytical report or a seprate report.
- For studies such as bioequivalence study, the report should include all chromatograms from analytical runs containing subject samples and the associated calibration standards and QC samples.

Sample Analysis Report (2)

- Reference standards
- Storage conditions of calibration standards and QC samples
- Brief description on acceptance criteria of analytical runs, reference to the relevant study protocol and/or SOPs.
- Study sample tracking record (date of sample receipt, contents, sample status, storage location and conditions)
- Study sample analysis: table summary of all analytical runs and study sample analyzed including date of analysis and results, table summary of calibration curves and QC samples from all analytical runs, any values outside of acceptable range should be clearly marked.
- All failed analytical runs
- Any deviations from analytical method and/or SOP
- Results from reanalysis

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Introduction of Shanghai Institute of Materia Medica, Chinese Academy of Sciences

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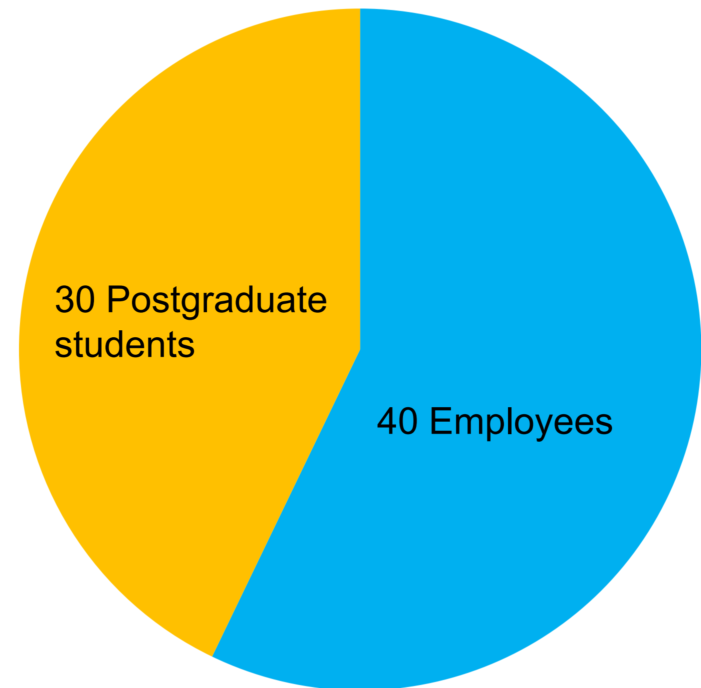
DMPK Research Platform: Personnel

- Prof. Dafang Zhong, P.I.
  - DMPK research of innovative drugs
- Prof. Xiaoyan Chen, P.I.
  - DMPK research of innovative drugs
- Prof. Chuan Li, P.I.
  - DMPK research of TCM
- Dr. Jia Liu, SIMM-Servier Joint Laboratory
  - Early evaluation of drug-like properties of hit compounds

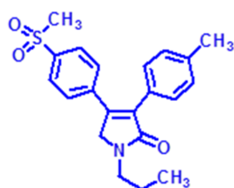


DMPK Research Platform in SIMM: Instrumentation and Facilities

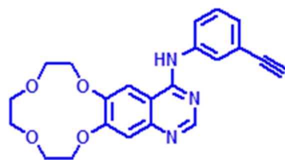
- 16 LC-MS systems installed
  - LC-QqQ MS for PK biosample analysis
  - UPLC/Q-TOF MS for metabolite ID
- Radioactivity facilities for metabolite profiling, mass balance, and tissue distribution studies
- Animal facilities and in vitro models
- QA system for bioanalysis
- Watson LIMS

Summary of DMPK Studies

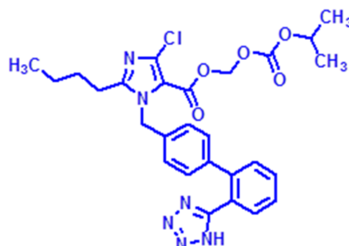
- Since 2009, preclinical ADME evaluation for 65 INDs (30% in China)
- In collaboration with hospitals, conducted over 30 clinical DMPK studies
- Among them, 31 INDs approved for clinical trial in China, 5 INDs approved in USA
- Five innovative drugs approved for marketing in China
- Conducted over 60 BA/BE studies



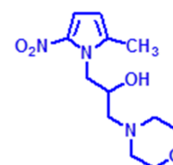
Imrecoxib (2011)



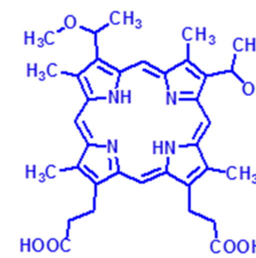
Icotinib (2011)



Allisartan Isoproxil (2012)



Morinidazole (2013)



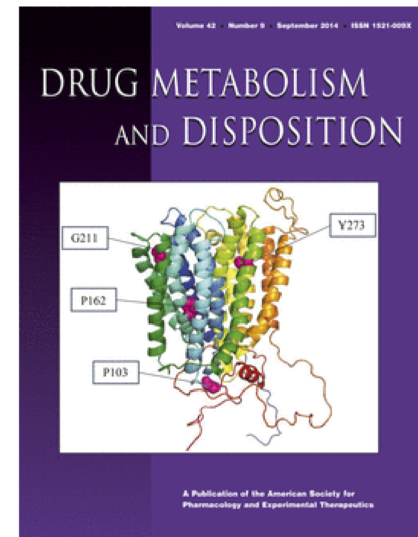
Hemprofin (2013)

Publications: Bioanalytical Methods using LC-MS/MS

Journal	Papers
• J Chromatogr B	21
• J Pharm Biomed Anal	7
• Bioanalyisis	6
• Anal Chim Acta	2
• Biomed Chromatogr	2
• J Liq Chromatogr	1
• Anal Bioanal Chem	1

Publications: Research of Drug Metabolism

Journal	Papers
Drug Metab Dispos	13
Chem Res Toxicol	4
Antimicrob Agents Chemother	3
Acta Pharmacol Sin	3
Brit J Pharmacol	1
J Pharmacol Exp Ther	1
J Agric Food Chem	1
Rapid Comm Mass Spectrom	1
Eur J Med Chem	1
Cancer Chemother Pharmacol	1



Thanks for your attention!