Rapid Analysis of Drugs and Related Compounds

Anna Codina, Product Portfolio Manager, Pharma Market

Bruker UM, London, 17Nov16
Pharmaceutical Industry
From Drug Discovery to Market

Drug Discovery
- Target Discovery
- Compound Discovery

Drug Development
- Process Optimization and Scale Up
- Drug Safety, Formulation, Properties

Manufacturing
- Application/Approval
- Production
- Market!

Clinical Trials – Phase I, II and III
- I healthy voluntaries
- II small group of patients
- III big group of patients

High-throughput, Speed ≤ Quality, Control, Compliance
New Solutions

Drug Discovery

Lead Discovery
FBLD

Structure Verification
SV

Structure Elucidation
SE

Reaction Monitoring
RxM

QC

Drug Development

500-700 MHz
SamplePro Tube
SampleJet
QCI (F19)
CMC-q
FBS TS

300-600 MHz
RT or Prodigy
CMC-a / Smart Drive
Sample changer
or
Fusion-SV
Compact/ Impact

400-700 MHz
1.7 mm cryo
CMC-se
Sample changer
Compact / Impact
SmartFormula3D

300 - 600 MHz
RT or Prodigy
InsightMR
Dynamics Center (off line)

300 – 600 MHz
RT or Prodigy
Assure NMR Ascent
Sample changer

Potency by qNMR
qSRC
# New Solutions

## Drug Discovery

<table>
<thead>
<tr>
<th>Lead Discovery</th>
<th>Structure Verification</th>
<th>Structure Elucidation</th>
<th>Reaction Monitoring</th>
<th>QC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBLD</td>
<td>SV</td>
<td>SE</td>
<td>RxM</td>
<td></td>
</tr>
</tbody>
</table>

## Drug Development

<table>
<thead>
<tr>
<th>SamplePro Tube</th>
<th>SampleJet</th>
<th>QCI (F19)</th>
<th>CMC-q</th>
<th>FBS TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-700 MHz</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 500-700 MHz

- **SamplePro Tube**
- **SampleJet**
- **QCI (F19)**
- **CMC-q**

- **Sample changer**
- **CMC-a / Smart Drive**
- **Fusion-SV**
- **Compact/ Impact**

<table>
<thead>
<tr>
<th>300-600 MHz</th>
<th>400-700 MHz</th>
<th>300 - 600 MHz</th>
</tr>
</thead>
<tbody>
<tr>
<td>RT or Prodigy</td>
<td>1.7 mm cryo</td>
<td>RT or Prodigy</td>
</tr>
<tr>
<td>CMC-se</td>
<td></td>
<td>Assure NMR Ascent</td>
</tr>
<tr>
<td>Sample changer</td>
<td>Sample changer</td>
<td>Sample changer</td>
</tr>
<tr>
<td>Compact / Impact</td>
<td>InsightMR</td>
<td>InsightXpress</td>
</tr>
<tr>
<td>SmartFormula3D</td>
<td>Insights</td>
<td>Potency by qNMR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>qSRC</td>
</tr>
</tbody>
</table>

### 400-700 MHz

- **RT or Prodigy**
- **InsightMR**
- **InsightXpress**
- **Assure NMR Ascent**
- **Potency by qNMR**
- **qSRC**

### 300-600 MHz

- **RT or Prodigy**
- **InsightMR**
- **InsightXpress**
- **Assure NMR Ascent**
- **Potency by qNMR**
- **qSRC**
Fragment Based Screening

- **500-700 MHz**
- **QCI probe with F19**
- **Sample Jet, Te independent racks**
- **CMC-q**
- **New TS parsets & Analysis Tools**

SamplePro Tube

---

**Lead Discovery**

**Structure Verification**

**Structure Elucidation**

**Reaction Monitoring**

**Quality Control**

**GxP**

---

*Courtesy of Dr. M. Blommers, Novartis Pharma, Switzerland*
Screening Libraries

Our libraries had ca. 30% bad samples:

- 20% “no compound” → no compound in stock solution, or not soluble in buffer
- 10% decayed or wrong compound
- 50% concentration off by more than +/-30%

Not always what it says in the tin
FBS Data Acquisition and Analysis
FBS Data Acquisition and Analysis
SV & qNMR External Standard
User approaches instrument with question, sample description and restraints

- Instrument decides which experiments to run with which parameters
- Automatic data analysis
- Yields result with confidence level (🌟🌟🌟🌟🌟 - 🌟🌟🌟🌟🌟)
- Decides if- and which other experiments are required to achieve user desired confidence level
- If user allotted time permits, system sets up runs follow up experiments

Decision Making -> Time Saver
Adding MS to SV = Confidence
600 MHz 1.7 mm CryoProbe
Resurrecting insensitive experiments
Adding Confidence

Molecular Formula
CMC-se

1,1-adequate 1 mg 23 h

Codina, A.; Bruker NMR User Meeting, Coventry, U.K., Nov 2010 // Poster and UM talk @ ENC 2011.
With Lab2Lab, chemists in mid-size to large-size pharma and CRO facilities will always have the ideal spectrometer sitting right there on your lab-bench!

- It can be a 400 MHz PRODIGY system for a structure verification sample or
- It can be 600 MHz DCH CryoProbe for an elucidation sample ON THE SAME BENCH
### Drug Discovery

<table>
<thead>
<tr>
<th>Lead Discovery</th>
<th>Structure Verification</th>
<th>Structure Elucidation</th>
<th>Reaction Monitoring</th>
<th>QC &amp; Impurity profiling</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBLD</td>
<td>SV</td>
<td>SE</td>
<td>RxM</td>
<td>QC &amp; Impurity profiling</td>
</tr>
</tbody>
</table>

#### Lead Discovery
- 500-700 MHz
  - SamplePro Tube
  - SampleJet
  - QCI (F19)
  - CMC-q
  - FBS TS
- 300-600 MHz
  - RT or Prodigy
  - CMC-a / Smart Drive
  - Sample changer
  - Fusion-SV
  - Compact / Impact

#### Structure Verification
- 400-700 MHz
  - 1.7 mm cryo
  - CMC-se
  - Sample changer
  - Compact / Impact

#### Structure Elucidation
- 300 - 600 MHz
  - RT or Prodigy
  - InsightMR
  - Dynamics Center (off line)

#### Reaction Monitoring
- 300 - 600 MHz
  - RT or Prodigy

#### QC & Impurity profiling
- Assure NMR
  - Ascent
  - Sample changer
- Potency by qNMR
  - qSRC

InsightMR

**InsightMR flow tube**

- Online process monitoring in real-time under real conditions
- Process understanding: yield, mechanistic insights and reaction kinetics $\Rightarrow$ Savings
- Intuitive workflow making NMR an accessible PAT tool
New

**InsightMR Accessories**

- Lead Discovery
- Structure Verification
- Structure Elucidation
- Reaction Monitoring
- Quality Control
- GxP

**Bruker: InsightMR + pump + chiller**

With full package, optional installation

NMR system 300-950 MHz

www.bruker.com/InsightMR
**InsightMR** Successful Stories – Pfizer Collaboration

- Dunn A.L. et. al, MRC, DOI: 10.1002/mrc.4317
InsightMR Flow Tube

Flow Behaviour

Ulrich Hintermair, John Lowe, Andrew Hall

Hall A. et.al., Catalysis Science & Technology, 2016, DOI: 10.1039/C6CY01754A
Reaction Monitoring by EPR – EMXnano

- Making research-grade data accessible to a larger audience
- Analyse all EPR species - transition metals, antioxidants and free radicals
- Valuable information and insights to biological and chemical reactions
- Novel permanent magnet and an efficient new microwave resonator for unmatched sensitivity and stability
- Analyse short-lived radicals using ‘spin trapping’
- Enables quantitative EPR with the inclusion of Bruker’s patented spin counting module
Drug Discovery

- Lead Discovery (FBLD)
- Structure Verification (SV)
- Structure Elucidation (SE)
- Reaction Monitoring (RxM)

Drug Development

- QC
- 300 – 600 MHz
  - RT or Prodigy
  - Assure NMR
    - Ascent
      - Dynamics Center (off line)
      - Sample changer
  - InsightMR
    - RT or Prodigy
  - Sample changer

SamplePro Tube
- 500-700 MHz
- SampleJet
- QCI (F19)
- CMC-q
- FBS TS

SampleJet
- 300-600 MHz
  - RT or Prodigy
  - Smart Drive
    - CMC-a
    - Sample changer
  - Fusion-SV
    - Compact/ Impact

CMC-q
- 400-700 MHz
  - 1.7 mm cryo
  - CMC-se
    - Sample changer
  - SmartFormula3D

InsightXpress
- 300 - 600 MHz
  - RT or Prodigy

Potency by qNMR
- qSRC
Quantification

- Liquids: Potency Determination
- Solids: Quantification of Components
Potency of Drugs Definition

- Needed before administrating the drug to determine the correct dose based on the amount of active drug in the preparation.

- Typically measured by HPLC. Characterised reference standard of the drug itself is needed. Otherwise it is determined by difference:

\[ P(Drug) = Drug - \sum \text{Inactive Compounds} \]

**Inactive Compounds:**
- Degradation substances \(\rightarrow\) LC-UV
- Process impurities \(\rightarrow\) LC-UV
- Water \(\rightarrow\) Karl Fisher
- Residual Solvents \(\rightarrow\) GC
- Inorganic material \(\rightarrow\) residue in ignition

NMR ‘One-Stop Shop’

- potency determination
- purity assessment
- relative response factor calculation
- residual solvent
- moisture analysis
- identity testing

‘Potency determination by qNMR has been shown to be a single point replacement for routine development testing because of the following reasons. The synthesis of natural compound is not so easy in most cases. Therefore the targeted compound is separated from natural materials with a great deal of effort requiring high economical cost. 2) Karl Fischer method is necessary to determine water contents precisely, and consequently the valuable separated compounds are consumed for the determination of water content and this also leads to high economical cost. Considering these difficulties, JP utilizes many chemical reagents commercially available as reference standards for quantitative analyses instead of JP-CRS. However, there is no information on their absolute purity. In order to solve the issues, in 2009 the JP experimental group started the joint research for utilizing quantitative NMR (qNMR) to determine the absolute purity of chemical reagents used for assay of herbal medicines. As a result, in 2013, four reference standards (geniposide, magnolol, paenol and magnoflorine) having absolute purity values determined by qNMR in a reagent company are available in the markets and the quantitative HPLC assays by using these reference standards will appear in several monographs in JP16 supplement 2.

## Rapid and Flexible Workflow

### Sample Preparation
Weighing of analyte and internal standard, dissolution and transfer to the NMR tube

### Sample Submission
Experiment and internal standard selection, weights input

### Results
Spectra, potency, Excel table and PDF Report

### Raw Data

<table>
<thead>
<tr>
<th>Prep.</th>
<th>Wt a. [mg]</th>
<th>Wt IS [mg]</th>
<th>CH</th>
<th>Region 1</th>
<th>Region 2</th>
<th>Region 3</th>
<th>Averaged Area a.</th>
<th>SD Area a.</th>
<th>Potency [%]</th>
<th>RSD Potency [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10.30</td>
<td>5.10</td>
<td></td>
<td>1.03</td>
<td>0.99</td>
<td>0.98</td>
<td>0.99</td>
<td>0.01</td>
<td>99.11</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>13.10</td>
<td>5.60</td>
<td></td>
<td>0.88</td>
<td>1.00</td>
<td>0.97</td>
<td>0.98</td>
<td>0.01</td>
<td>99.19</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>12.40</td>
<td>17.80</td>
<td></td>
<td>2.93</td>
<td>0.98</td>
<td>0.82</td>
<td>0.94</td>
<td>0.08</td>
<td>95.42</td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>97.91</strong></td>
<td></td>
<td></td>
<td><strong>1.80</strong></td>
</tr>
</tbody>
</table>

### qNMR Potency = 98 %

Analyte: 23.70 mg, Reference: 21.30 mg

Analyte Integral Regions:
- 14_s_Q1 [2.21 ppm to 2.32 ppm]
- 13_m_Q2 [2.92 ppm to 3.21 ppm]
- 7,9,10_m_Q3 [7.22 ppm to 7.42 ppm]

Reference Integral Region:
- CH [6.14 ppm to 6.41 ppm]
Quantification

- Liquids: Potency Determination
- Solids: Quantification of Components
Physical API form plays crucial role
Choose “best” API form for development
80% of API molecules exhibit polymorphism
Very wide range of physical and chemical properties
Criteria: bioavailability, thermodynamic stability, processability, ...

Techniques must be available to monitor and quantify physical API forms in solid samples
API form ID and Quantification

- Common techniques for physical characterization:
  - X-ray powder diffraction (other X-ray techniques)
  - Optical + vibrational spectroscopy (Raman, IR, NIR, ...)
  - Thermometric methods like Differential Scanning Calorimetry (DSC) and Thermogravimetry (TG)
  - Solid State NMR (*state of the art*)

- General issues:
  - High LOD, not accurate enough, intricate calibration necessary, not enough specificity, time consuming

- New Approach:
  - Relaxation TD-NMR data to be used for API form identification and quantification
Sample Preparation
Place 200-300 mg of analyte and reference components in 10 ml glass tubes

Calibration
Acquisition of $T_1$ SRC data of the reference components

Data Acquisition
Acquisition of $T_1$ SRC data of the analyte sample

Data Analysis
Dynamics Center

Results
$T_1$ SRC curves, quantification, PDF Report,
Excellent correlation btw prepared and predicted blend compositions

Slopes and intercepts close to theoretical values, high $R^2$ and low rms

<table>
<thead>
<tr>
<th>Prepared m% lbu</th>
<th>qSRC – 4 scans m% lbu / rms</th>
<th>qSRC – 32 scans m% lbu / rms</th>
</tr>
</thead>
<tbody>
<tr>
<td>50.2</td>
<td>50.6 / 0.0082</td>
<td>49.8 / 0.0022</td>
</tr>
<tr>
<td>39.9</td>
<td>40.3 / 0.0081</td>
<td>40.9 / 0.0037</td>
</tr>
<tr>
<td>30.1</td>
<td>30.8 / 0.0097</td>
<td>31.2 / 0.0030</td>
</tr>
<tr>
<td>20.1</td>
<td>20.2 / 0.0116</td>
<td>21.0 / 0.0045</td>
</tr>
<tr>
<td>9.9</td>
<td>9.3 / 0.0135</td>
<td>9.5 / 0.0042</td>
</tr>
<tr>
<td>5.0</td>
<td>4.6 / 0.0120</td>
<td>4.7 / 0.0048</td>
</tr>
</tbody>
</table>

No increase in accuracy of qSRC for data with higher SNR
## Summary

### Tools to increase productivity and speed

<table>
<thead>
<tr>
<th></th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>InsightMR</td>
<td>Available now</td>
</tr>
<tr>
<td>InsightXpress</td>
<td>Demos @ Uni. of Edinburgh // Coventry 1Q 17</td>
</tr>
<tr>
<td>Potency Determination</td>
<td>$\beta$ -&gt; Release TS3.5.pl7</td>
</tr>
<tr>
<td>Quantification of solids</td>
<td>Demos @ Billerica, US and Fallanden, CH</td>
</tr>
<tr>
<td>Drug discovery (FBS)</td>
<td>$\beta$ -&gt; Release RS3.5.pl7</td>
</tr>
</tbody>
</table>
Acknowledgments

### Potency by NMR

<table>
<thead>
<tr>
<th>Company</th>
<th>Contributors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck</td>
<td>Thomas Williamson</td>
</tr>
<tr>
<td></td>
<td>Kevin O'Sullivan</td>
</tr>
<tr>
<td></td>
<td>Ian Sherlock</td>
</tr>
<tr>
<td>Lilly</td>
<td>Mark Zell</td>
</tr>
<tr>
<td></td>
<td>Ruth Boetzel</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Steve Coombes</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Francesca Benevelli</td>
</tr>
<tr>
<td></td>
<td>Till Kuehn</td>
</tr>
<tr>
<td></td>
<td>Fabrice Moriaud</td>
</tr>
<tr>
<td></td>
<td>Martin Wyser</td>
</tr>
<tr>
<td></td>
<td>Jochen Klages</td>
</tr>
<tr>
<td></td>
<td>Christine Bolliger</td>
</tr>
<tr>
<td></td>
<td>Markus Lang</td>
</tr>
<tr>
<td></td>
<td>Oliver Horlacher</td>
</tr>
<tr>
<td></td>
<td>Patrick Amsler</td>
</tr>
<tr>
<td></td>
<td>Thomas Williamson</td>
</tr>
<tr>
<td>InsightMR</td>
<td>Prof. G. Lloyd-Jones</td>
</tr>
<tr>
<td></td>
<td>Ted King</td>
</tr>
<tr>
<td></td>
<td>Ruth Dooley</td>
</tr>
<tr>
<td></td>
<td>Ariana Jones</td>
</tr>
<tr>
<td></td>
<td>Dusan Uhrin</td>
</tr>
<tr>
<td></td>
<td>Matteo Pennestri</td>
</tr>
<tr>
<td></td>
<td>Mark Garvey</td>
</tr>
<tr>
<td></td>
<td>Peter Neidig</td>
</tr>
<tr>
<td></td>
<td>Martin Hofmann</td>
</tr>
<tr>
<td></td>
<td>Ulrich Braumann</td>
</tr>
<tr>
<td>FBS</td>
<td>Alavar Gossert, Wolfgang Jahnke, Marcel Blomers, Cesar Fernandez, Paul Erbel</td>
</tr>
<tr>
<td></td>
<td>Daniel Wyss, Hugh Eaton</td>
</tr>
<tr>
<td></td>
<td>Bettina Elshorst</td>
</tr>
<tr>
<td></td>
<td>Markus Schade</td>
</tr>
</tbody>
</table>

### Quant. Solid Mixtures

<table>
<thead>
<tr>
<th>Company</th>
<th>Contributors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck</td>
<td>Dirk Stueber</td>
</tr>
<tr>
<td></td>
<td>Thomas Williamson</td>
</tr>
<tr>
<td>Bruker</td>
<td>Stefan Jehle</td>
</tr>
<tr>
<td></td>
<td>Peter Neidig</td>
</tr>
<tr>
<td></td>
<td>Jochem Struppe</td>
</tr>
<tr>
<td></td>
<td>Ulrich Hintermair</td>
</tr>
<tr>
<td></td>
<td>Andrew Hall</td>
</tr>
<tr>
<td></td>
<td>John Lowe</td>
</tr>
<tr>
<td>UoB</td>
<td></td>
</tr>
</tbody>
</table>

### In-situ Fast RxM

<table>
<thead>
<tr>
<th>Company</th>
<th>Contributors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brueker</td>
<td>Prof. G. Lloyd-Jones</td>
</tr>
<tr>
<td>ERC</td>
<td>Ted King</td>
</tr>
<tr>
<td>TgK</td>
<td>Ruth Dooley</td>
</tr>
<tr>
<td></td>
<td>Ariana Jones</td>
</tr>
<tr>
<td></td>
<td>Dusan Uhrin</td>
</tr>
<tr>
<td>Brueker</td>
<td>Matteo Pennestri</td>
</tr>
<tr>
<td></td>
<td>Mark Garvey</td>
</tr>
<tr>
<td></td>
<td>Peter Neidig</td>
</tr>
<tr>
<td></td>
<td>Martin Hofmann</td>
</tr>
<tr>
<td></td>
<td>Ulrich Braumann</td>
</tr>
<tr>
<td>InsightMR</td>
<td>David Foley</td>
</tr>
<tr>
<td></td>
<td>Mark Zell</td>
</tr>
<tr>
<td>Pfizer</td>
<td></td>
</tr>
<tr>
<td>UoB</td>
<td>Ulrich Hintermair</td>
</tr>
<tr>
<td></td>
<td>Andrew Hall</td>
</tr>
<tr>
<td></td>
<td>John Lowe</td>
</tr>
<tr>
<td>FBS</td>
<td>Alavar Gossert, Wolfgang Jahnke, Marcel Blomers, Cesar Fernandez, Paul Erbel</td>
</tr>
<tr>
<td></td>
<td>Daniel Wyss, Hugh Eaton</td>
</tr>
<tr>
<td></td>
<td>Bettina Elshorst</td>
</tr>
<tr>
<td></td>
<td>Markus Schade</td>
</tr>
<tr>
<td></td>
<td>Stefan Jehle</td>
</tr>
<tr>
<td></td>
<td>Pavel Kessler</td>
</tr>
<tr>
<td></td>
<td>Fabrice Moriaud, Matteo Pennestri</td>
</tr>
<tr>
<td></td>
<td>Till Kuehn</td>
</tr>
</tbody>
</table>

Thanks!
‘Partnering with scientists to shorten time-to-market with confidence, by gaining qualitative and quantitative insights into molecular structure and dynamics.’