Rapid Analysis of Drugs

Anna Codina, Product Portfolio Manager, Pharma Market
Bruker BioSpin, France
30ème Réunion Utilisateurs
29- 30 Novembre 2016
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

Phase IV

High-throughput, Speed

Quality, Control, Compliance
# New Solutions

## Drug Discovery

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

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

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

### CMC-se
- 300-600 MHz
- RT or Prodigy

### CMC-sec
- 400-700 MHz
- 1.7 mm cryo

### CMC-sec
- 300-600 MHz
- RT or Prodigy

### Assure NMR Ascent
- Sample changer

### SmartFormula3D
- 300-600 MHz
- RT or Prodigy

### InsightMR
- Dynamics Center (off line)

### InsightXpress
- Potency by qNMR
- qSRC
- GxP
Fragment Based Screening

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

SamplePro Tube

30 fragments
blue = free
red = protein added

Courtesy of Dr. M. Blommers, Novartis Pharma, Switzerland
FBS Data Acquisition and Analysis
# FBS Data Acquisition and Analysis

New

---

### Table

<table>
<thead>
<tr>
<th>Cocktail</th>
<th>L1</th>
<th>L2</th>
<th>L3</th>
<th>L4</th>
<th>Date</th>
<th>Time</th>
<th>Molecular Formula</th>
<th>Molecular Mass (g/mol)</th>
<th>Concentration of Hit Stock Solution (nM)</th>
<th>User Comment</th>
<th>User Comment 2</th>
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<tbody>
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<td>1.35</td>
<td></td>
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</tr>
</tbody>
</table>

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**Note:** The table above shows a summary of the data acquired and analyzed using the FBS method. Each row represents a different compound, with details including the date and time of the hit identification, molecular formula, molecular mass, concentration of the hit stock solution, and user comments.

---

**Image Description:**

The image contains a screenshot of an Excel spreadsheet with data from a FBS experiment. The spreadsheet includes columns for cocktail, ligand, date, time, molecular formula, molecular mass, concentration of hit stock solution, and user comments. The data is part of a larger dataset related to the analysis of chemical compounds using the FBS method.
<table>
<thead>
<tr>
<th>Lead Discovery</th>
<th>Structure Verification</th>
<th>Structure Elucidation</th>
<th>Reaction Monitoring</th>
<th>Quantification, Impurity ID and QC</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBLD</td>
<td>SV</td>
<td>SE</td>
<td>RxM</td>
<td>CMC (F19)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SamplePro Tube</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>500-700 MHz</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT or Prodigy</td>
<td></td>
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</tr>
<tr>
<td>CMC-a / Smart Drive</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Sample changer</td>
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</tr>
<tr>
<td>or</td>
<td>Fusion-SV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300-600 MHz</td>
<td></td>
<td>400-700 MHz</td>
<td></td>
<td>Insur NMR</td>
</tr>
<tr>
<td>1.7 mm cryo</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CMC-se</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample changer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compact / Impact</td>
<td></td>
<td></td>
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<tr>
<td>Compact/ Impact</td>
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<tr>
<td>Dynamic Center (off line)</td>
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<tr>
<td>300 - 600 MHz</td>
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</tr>
<tr>
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<td></td>
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<tr>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>Potency by qNMR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>qSRC</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
### Drug Discovery

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead Discovery</td>
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<td>Reaction Monitoring</td>
<td>RxM</td>
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<td>Quantification, Impurity ID and QC</td>
<td></td>
</tr>
</tbody>
</table>

### Equipment Details

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Model/Technology</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-700 MHz</td>
<td>SamplePro Tube, SampleJet, QCI (F19), CMC-q, FBS TS</td>
</tr>
<tr>
<td>300-600 MHz</td>
<td>Sample changer, Smart Drive, Fusion-SV, CMC-se</td>
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<td>400-700 MHz</td>
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</tr>
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<td>300-600 MHz</td>
<td>RT or Prodigy, InsightMR, Dynamics Center (off line), InsightXpress, Assure NMR Ascent</td>
</tr>
<tr>
<td>300-600 MHz</td>
<td>RT or Prodigy, Potency by qNMR, qSRC</td>
</tr>
</tbody>
</table>
**InsightMR**

- Online process monitoring in real-time under real conditions
- Process understanding: yield, mechanistic insights and reaction kinetics → 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
InsightMR Successful Stories – Pfizer Collaboration

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

Ulrich Hintermair, John Lowe, Andrew Hall

a) Change in Absorbance at 334 nm

b) Sample Hold-up

c) Flow Tube Bypassed vs. With Flow Tube

Relative Integral Area / %

- 1-Phenylethanol CH(OH)
- Isopropanol CH(OH)
- Trimethoxybenzene CH₃
- Acetophenone CH₃
- Acetone CH₂

Flow rate / mL min⁻¹
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
InsightXpress

- Rapid, streamlined process optimisation and understanding that can also monitor reaction in the time scale of seconds!
- 20 time increase of productivity when screening reaction conditions
- Ideal for pharma development (process chemistry), industry and academia. Specially suited for those academics studying fast reaction or developing / working with fast or UF experiments.

$t_{1/2} \approx 1 \text{ second}$

Monitoring the depletion of a reagent with a half life time of 1 second

InsightXpress mounted on the SampleXpress base.
## Quality Control

### Drug Discovery

<table>
<thead>
<tr>
<th>Stage</th>
<th>Equipment/Software</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lead Discovery</strong></td>
<td>FBLD</td>
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<td><strong>Quantification, Impurity ID and QC</strong></td>
<td>Assure NMR Ascent</td>
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</tbody>
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<table>
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<tr>
<th>Frequency Range</th>
<th>SamplePro Tube</th>
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</thead>
<tbody>
<tr>
<td>300-600 MHz</td>
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<td>RT or Prodigy</td>
</tr>
<tr>
<td></td>
<td>Dynamics Center (off line)</td>
</tr>
</tbody>
</table>

- **SamplePro Tube**
  - RT or Prodigy
  - CMC-se
  - Sample changer
  - SmartDrive
- **SampleJet**
  - Compact / Impact
  - Fusion-SV
  - CMC-q
  - FBS TS

- **Assure NMR Ascent**
  - RT or Prodigy
  - InsightMR
  - Sample changer
  - Potency by qNMR
  - qSRC
  - GxP

### Additional Notes

- **Drug Discovery**
  - **Fusion-SV**
  - **SmartDrive**
  - **CMC-se**
- **Drug Development**
  - **InsightXpress**
  - **InsightMR**
  - **Dynamics Center (off line)**
# Potency by qNMR

## Drug Discovery

<table>
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<th>Stage</th>
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<td>SV</td>
</tr>
<tr>
<td>StructureElucidation</td>
<td>SE</td>
</tr>
<tr>
<td>ReactionMonitoring</td>
<td>RxM</td>
</tr>
</tbody>
</table>

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

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

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

### Reaction Monitoring
- 300 - 600 MHz
- RT or Prodigy
- Assure NMR Ascent
- Sample changer
- Dynamics Center (off line)

## Drug Development

### Quantification, Impurity ID and QC
- 300 – 600 MHz
- RT or Prodigy
- Assure NMR Ascent
- Sample changer

### Potency by qNMR
- qSRC
- GxP
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 → LC-UV
- Process impurities → LC-UV
- Water → Karl Fisher
- Residual Solvents → GC
- Inorganic material → residue in ignition

Potency determination by qNMR has been shown to be a single point replacement for routine development testing which previously involved several experiments and techniques."

10.3. Marker Compounds for Assay and Reference Substances for Quantitative Analysis of Crude Drugs and Extracts of Kampo Formulations in the JP

If it is possible to price a reagent used as a quantitative index component in a crude medicine with a correct content using qNMR based on the above-mentioned principle, it also becomes possible to use the reagent as a reference substance for analysis with assured metrological traceability. According to a result of a validation experiment, in case of a compound with molecular mass of around 300 to be measured, it is possible to perform pricing at an ordinary laboratory level by using about 10 mg of the compound for the measurement while ensuring two significant figures even if including errors between used devices. As content of quantitative index component in a crude medicine is just a few percent at most in general and the minimum unit of regulation value is 0.1%, two significant figures is believed to be enough to ensure accuracy of content of reference substance for quantitative analysis in consideration of variation for each crude medicine as a natural substance.

Such reagents priced with SI traceable quantitative value (degree of purity) by qNMR that have been defined in a paragraph for reagent and test solution are available as Japanese Pharmacopoeia reagents for quantitative analysis. Further, in cases where a reagent priced by qNMR is used as a reference substance for quantitative analysis such as HPLC and involved in a calculation of quantitative value of subject compound after converting degree of purity (%) of the priced reagent, it becomes possible to use the resulting quantitative value as a SI traceable value. In addition, in cases where a reagent priced by qNMR is used as a reference material for a quantitative analysis based on HPLC, condition of the quantitative analysis is based on an assumption that no impurity is recognized at any peak of a component of the reagent to be quantified, which is required to be confirmed separately by a device such as photodiode array detector or mass spectrometer.
Introduction of qNMR to the Japanese Pharmacopoeia (JP) for specification of marker compounds used for standardization of herbal medicines

Goda Y
National Institute of Health Sciences, Japan

In Japan, standardization of herbal medicines is mostly controlled by the Japanese Pharmacopoeia (JP). JP16 contains the monographs of 217 crude drugs including powders, 22 Kampo extracts and 32 crude drug preparations other than Kampo extracts. The specific marker compound for quantification is very important for standardization of herbal medicines. Therefore, JP has prepared several marker compounds as JP Certified Reference Standards (JP-CRS), which are highly purified and of which the water contents are known. But, it is difficult to prepare them because of the following reason. 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 [1] 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 using these reference standards will appear in several monographs in JP16 supplement 2. References: [1] Hosoe J. et al., Pharmaceutical and Medical Device Regulatory Science, 41, 960 – 970 (2010); [2] Hosoe J. et al., ibid., 43, 182 – 193 (2012); JP16 Supplement 1: http://www.mhlw.go.jp/topics/bukyoku/iyaku/yakkyoku/english.html

Planta Med 2013; 79 - SL79
DOI: 10.1055/s-0033-1351904

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

<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>1.03</td>
<td>1.00</td>
<td>0.99</td>
<td>0.98</td>
<td>0.99</td>
<td>0.01</td>
<td>99.11</td>
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</tr>
<tr>
<td>2</td>
<td>13.10</td>
<td>5.60</td>
<td>0.88</td>
<td>1.00</td>
<td>0.98</td>
<td>0.97</td>
<td>0.98</td>
<td>0.01</td>
<td>99.19</td>
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</tr>
<tr>
<td>3</td>
<td>12.40</td>
<td>17.80</td>
<td>2.93</td>
<td>1.00</td>
<td>0.98</td>
<td>0.82</td>
<td>0.94</td>
<td>0.08</td>
<td>95.42</td>
<td></td>
</tr>
</tbody>
</table>

Average 97.91 1.80

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]
<table>
<thead>
<tr>
<th>Drug Discovery</th>
<th>Drug Development</th>
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<tr>
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| 500-700 MHz                                       |                                         |
| **SamplePro Tube**                               | **Assure NMR Ascent**                   |
| SampleJet                                        |                                         |
| QCI (F19)                                        |                                         |
| CMC-q                                            |                                         |
| **SampleJet**                                    |                                         |
| Sample changer                                   | **Potency by qNMR**                     |
| **PCNI**                                         |                                         |
| **InsightXpress**                                |                                         |
| **Potency by qNMR**                              |                                         |
| **Assure NMR Ascent**                            |                                         |
| **Potency by qNMR**                              |                                         |
| **InsightXpress**                                |                                         |

- 300-600 MHz
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- **InsightXpress**
- **qSRC**
- **GxP**
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,
qSRC Method Approach

- Approach: Superposition fits of saturation recovery curves
  \[ \text{Int}(mix, \tau) = c_1 \times \text{Int}(C1, \tau) + c_2 \times \text{Int}(C2, \tau) + b \]
- Curves are scaled with respect to molecular masses and number of nuclei

For Example two-component system:
- C1 and C2 in a 1:1 ratio
- Point at \( \tau = 5.0 \) s (gray line):
  \[ \text{Int}(\text{mix}, 5.0s) = 0.5 \text{Int}(C1, 5.0s) + 0.5 \text{Int}(C2, 5.0s) \]
- Linear-combination fit of SRCs to obtain relative concentrations
qSRC Results System 1

- Excellent correlation btw prepared and predicted blend compositions
- Slopes and intercepts close to theoretical values, high $R^2$ and low rms

---

### Ibuprofen–Indomethacin Binary Blends

- 4 scans: $R^2 = 0.99972$, BestFit: $-0.502653 + 1.0233 \times$
- 32 scans: $R^2 = 0.998307$, BestFit: $0.0392816 + 1.01072 \times$

<table>
<thead>
<tr>
<th>Prepared m% Ibu</th>
<th>qSRC – 4 scans m% Ibu / rms</th>
<th>qSRC – 32 scans m% Ibu / 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
qSRC Results System 2

- *Ibuprofen/Itraconazole*, binary blends with 50 – 5 m% ibuprofen
- $^1\text{H} \ T_1$: Ibu = 640 ms, Itra = 690 ms (1.1x !)
- SRCs for 40.1% Ibu blend with 4sc/inc, 32sc/inc, and 64 sc/inc
- qSRC quantification works for close $^1\text{H} \ T_1$s with high-SNR data

Fit → 55.0%

rms = 0.0123

Fit → 43.1%

rms = 0.0036

Fit → 40.5%

rms = 0.0025
qSRC Results System 2

- Correlations for $^1$H $T_1$ data with different number of scans/inc
- qSRC fails with low-SNR data
- qSRC becomes increasingly accurate with increasing SNR of $^1$H $T_1$ data
- Same accuracy as for model system 1 is observed when high-SNR $^1$H $T_1$ data is used (128 scans/inc)
## Regulatory GxP

### Drug Discovery

<table>
<thead>
<tr>
<th>Activity</th>
<th>Frequency</th>
<th>Equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lead Discovery (FBLD)</td>
<td>500-700 MHz</td>
<td>SamplePro Tube</td>
</tr>
<tr>
<td>Structure Verification (SV)</td>
<td>300-600 MHz</td>
<td>RT or Prodigy</td>
</tr>
<tr>
<td>Structure Elucidation (SE)</td>
<td>400-700 MHz</td>
<td>CMC-a / Smart Drive</td>
</tr>
<tr>
<td>Reaction Monitoring (RxM)</td>
<td>300-600 MHz</td>
<td>RT or Prodigy</td>
</tr>
<tr>
<td>Quantification, Impurity ID and QC</td>
<td>300 - 600 MHz</td>
<td>Assure NMR Ascent</td>
</tr>
</tbody>
</table>

### Drug Development

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<thead>
<tr>
<th>Activity</th>
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</tr>
</thead>
<tbody>
<tr>
<td>SampleJet</td>
<td></td>
<td>CMC-se</td>
</tr>
<tr>
<td>QCI (F19)</td>
<td></td>
<td>Sample changer</td>
</tr>
<tr>
<td>CMC-q</td>
<td></td>
<td>Compact / Impact</td>
</tr>
<tr>
<td>Fusion-SV</td>
<td></td>
<td>SmartFormula3D</td>
</tr>
<tr>
<td>Compact/ Impact</td>
<td></td>
<td>Dynamics Center (off line)</td>
</tr>
<tr>
<td>SmartFormula3D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>InsightMR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>InsightXpress</td>
<td></td>
<td></td>
</tr>
<tr>
<td>qSRC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GxP</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- CMC-a / Smart Drive can also use Sample changer or Fusion-SV.
- CMC-se can be used with Sample changer Compact / Impact or SmartFormula3D.
- Assure NMR Ascent supports Dynamics Center (off line) for InsightMR or InsightXpress.
‘Regulatory authorities are getting tougher. Best efforts will soon not be good enough’
## Audit trail (continued)

If no audit trail is available, a paper-based audit trail will be permitted until a fully audit-trail system becomes available. These hybrid systems are currently permitted, where they achieve equivalence to an audit trail described in Annex 11 of the GMP Guide. If such equivalence cannot be demonstrated, it is expected that facilities should upgrade to an audit-trail system by the end of 2017.

## Data Review

There should be a procedure which describes the process for the review and approval of data, including raw data. Data review must also include a review of relevant metadata, including audit trail.

Data review must be documented.

A procedure should describe the actions to be taken if data review identifies an error or omission. This procedure should enable data corrections or clarifications to be made in a GMP compliant manner, providing visibility of the original record, and audit-trail traceability of the correction, using ALCOA principles (see 'data' definition).
| Computerised system user access / system administrator roles | Full use should be made of access controls to ensure that people have access only to functionality that is appropriate for their job role, and that actions are attributable to a specific individual. Companies must be able to demonstrate the access levels granted to individual staff members and ensure that historical information regarding user access level is available.

Shared logins or generic user access should not be used. Where the computerised system design supports individual user access, this function must be used. This may require the purchase of additional licences.

It is acknowledged that some computerised systems support only a single user login or limited numbers of user logins. Where alternative computerised systems have the ability to provide the required number of unique logins, facilities should upgrade to an appropriate system by the end of 2017. Where no suitable alternative computerised system is available, a paper based method of providing traceability will be permitted. The lack of suitability of alternative systems should be justified based on a review of system design, and documented.

System administrator access should be restricted to the minimum number of people possible taking account of the size and nature of the organisation. The generic system administrator account should not be available for use. Personnel with system administrator access should log in under unique log-ins that allow actions in the audit trail(s) to be attributed to a specific individual. |
Topspin 3.5.pl6 New GxP Functionality

Data Integrity

✓ Audit trail
✓ Lockdataset
✓ Editing Restrictions in the Plot Editor
Login Auditing

- The file `login.txt` keeps the log of TopSpin startups/stops and also the log of „internal user login/logoff“ events.

- This log can be evaluated for processes in **in regulated environments (GxP)**. The log entries are now protected with checksums.

- With every new entry added to this log, TopSpin checks the existing entries against their checksums to get a proof of consistency.

- **Third-party modifications** of content will be detected by TopSpin and documented with a **warning message** (which gets a checksum added by itself).
**lockdataset**

- **lockdataset** will modify the file access permissions of the currently active dataset.

- Available from menu selection
  
  Manage → Security → Lock Data Set Against Changes

- Or in command line:

- Command **lockdataset** can be included in processing AU programs as well (think of AUNMP).
**lockdataset**

- The content of **EXPNO** and **PROCNO** directories becomes protected against further overwrite/append/delete operations.

- In other words, the directory becomes „frozen“. It is still possible to add new **PROCNOs** for the same raw data and to process there. The initial **PROCNO** remains protected then.

- This is useful within **GxP environments** and e.g. allows the following procedure:
  - ➔ Automatic acquisition and processing of data in **PROCNO 1**.
  - ➔ Apply digital signature to data by command **esign**.
  - ➔ Execute **lockdataset** in order to protect against modification
  - ➔ With command **wrp 2** create a new **PROCNO**
  - ➔ with **rep 2** switch to new **PROCNO**
  - ➔ Do further processing interactively
Editing Restrictions in Plot Editor

- **TopSpin** Plot Editor offers interactive editing of Text and Parameter objects (including its text contents).
  - **In GxP regulated environment** this may be seen as undesired option.

- A new configuration option allows preventing users from modifying text objects. (Object remains selectable, but options for editing the content are removed.)

- Adaption/change of spectral ranges is still possible.

- The restriction is configured in file **globals.prop** (in user’s personal configuration directory). Add the following line:
  
  ```
  GLP_RESTRICTIONS_ACTIVE=1
  ```

- Personal configuration directory is found at:
  - `%HOMEDRIVE%`%HOMEPATH%\topspin-
  - `%COMPUTERNAME%`\prop
  - e.g.: C: Users\nmr\topspin-SpectrometerPC\pro
Summary GxP

Working on enhancing our offering to facilitate compliance.

- Data integrity and audit trail improvements in TopSpin => TS3.5.pl6
- +1 dedicated FTE
- More in TS3.5.pl7
- 21CFR part 11 TS manual upgrade
- DQ, IQ, OQ, PQ
- Involvement in meeting with users and regulatory authorities

We are looking forward to hearing your feedback and learning from you!
# Quality Control  Future Outlook

## Drug Discovery

<table>
<thead>
<tr>
<th>Lead Discovery</th>
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<th>Structure Elucidation</th>
<th>Reaction Monitoring</th>
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<tbody>
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<td>RxM</td>
</tr>
</tbody>
</table>

### 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

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

## Drug Development

<table>
<thead>
<tr>
<th>QC</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 – 600 MHz</td>
</tr>
<tr>
<td>RT or Prodigy</td>
</tr>
</tbody>
</table>

### Assure NMR Ascent
- **Potency by qNMR**
- **qSRC**
- **GxP**

### Dynamics Center (off line)
- InsightMR
- Sample changer

### InsightXpress
- **GxP**
Many are talking about it:

- Abbreviated pathways for approval of ‘biosimilars’
- Structure Fingerprint for assessment of biological function
- Using NMR’s unique ability to evaluate higher order structure

AssureNMR

- 1D PROFILE\(^1\)
- 2D HSQC automated analysis

---

\(^1\) L. Poppe et al., Anal. Chem. 2013, 85, 9623–9629; L. Poppe et al., Anal.Chem. 2015, 87, 5539-5524
## 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**
- Thomas Williamson
- Kevin O’Sullivan
- Ian Sherlock
- Mark Zell
- Ruth Boetzel
- Steve Coombes
- Francesca Benevelli
- Till Kuehn
- Fabrice Moriaud
- Martin Wyser
- Jochen Klages
- Christine Bolliger
- Markus Lang
- Oliver Horlacher
- Patrick Amsler

**In-situ Fast RxM**
- Prof. G. Lloyd-Jones
- Ted King
- Ruth Dooley
- Ariana Jones
- Dusan Uhrin
- Matteo Pennestri
- Mark Garvey
- Peter Neidig
- Martin Hofmann
- Ulrich Braumann

**FBS**
- Novartis
- Alavar Gossert, Wolfgang Jahnke, Marcel Blommers, Cesar Fernandez, Paul Erbel
- Daniel Wyss
- Hugh Eaton
- Bettina Elshorst
- Markus Schade
- Stefan Jehle
- Pavel Kessler
- Fabrice Moriaud, Matteo Pennestri
- Till Khuehn

**Quant. Solid Mixtures**
- Dirk Stueber
- Thomas Williamson
- Stefan Jehle
- Peter Neidig
- Jochem Struppe

**InsightMR**
- David Foley
- Mark Zell
- Ulrich Hintermair
- Andrew Hall
- John Lowe

**GxP and Biologics**
- Peter-Rene Steiner
- Sven Augner
- Kim Colson

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