

Industry Experiences in Launching,
Managing and
Transferring a Real-Time Release Testing
method globally from 2006 to today



Gert Thurau, Merck & Co., Inc.



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- Jeffrey Givand



Product and process introduction

- Indication diabetes
 - Solid oral dosage form
 - Tablet
 - 3 strengths which are weight-multiples
 - ~ 30% active by weight
 - Direct compression process with taste-masking overcoat

 - Initial approval 2006
 - FDA, EMEA
 - Subsequent approval in > 80 markets world-wide
 - Developed into high volume product (> 250 batches annually)
-
- Product attributes that support real-time release testing
 - Simple direct compression process with good development history of uniformity
 - Relatively high active content (~30%)
 - Very good stability*
 - No degradates*
 - BCS class I with well understood disintegration/dissolution behavior

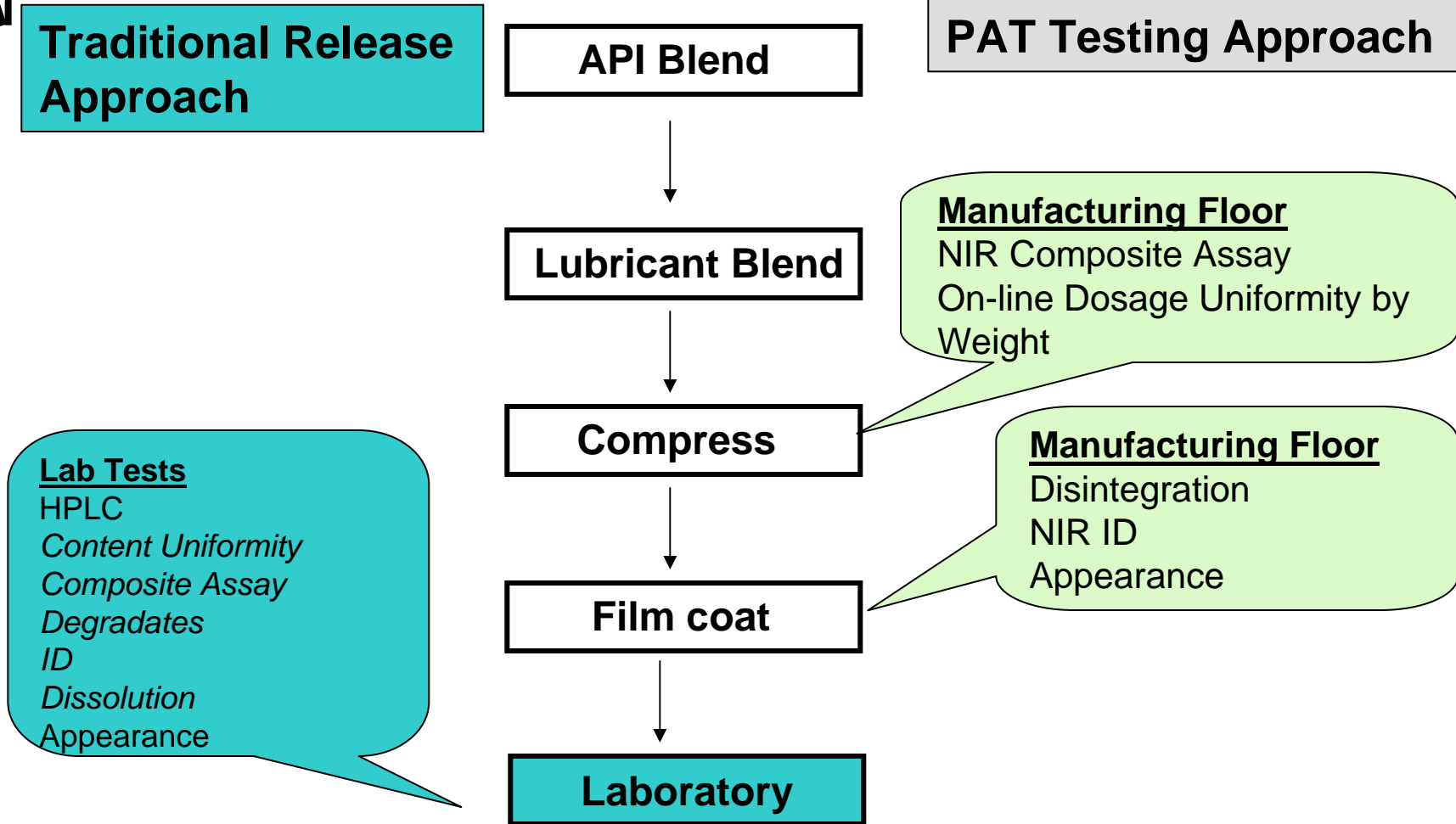
* for approved stability window, under approved storage conditions and packaging
Merck & Co., Inc./MSD 2012

Merck Fully Supports QbD



- Merck has embraced QbD as a strategic initiative on how we develop and manufacture products
 - QbD provides a consistent framework for developing high quality products that provide benefits to our patients and meet our customer's needs
 - QbD promotes systematic, scientific and risk-based approaches to product and process development
- Merck is executing a company-wide QbD strategy and playbook
- All of Merck's development programs now follow the QbD approach
 - Work processes are established to realize Merck's QbD strategy

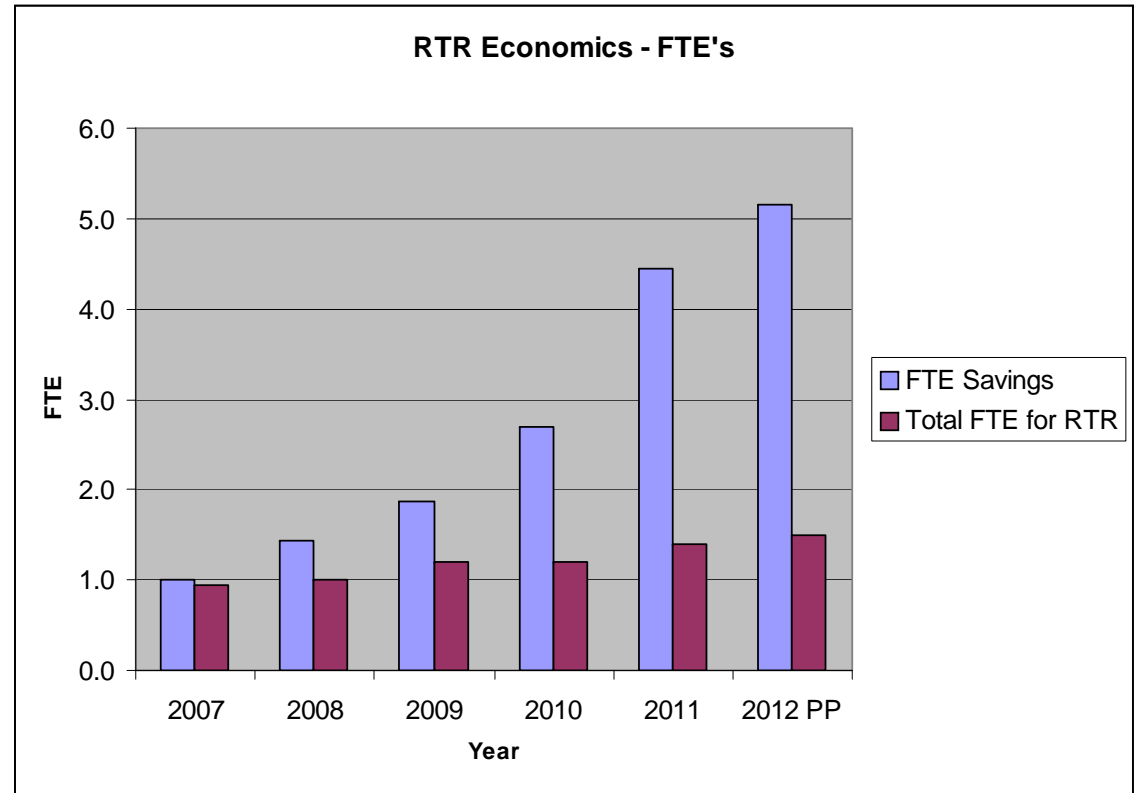
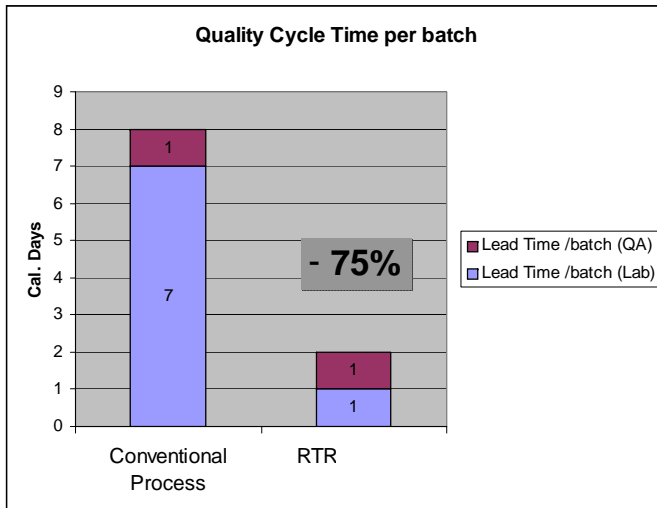
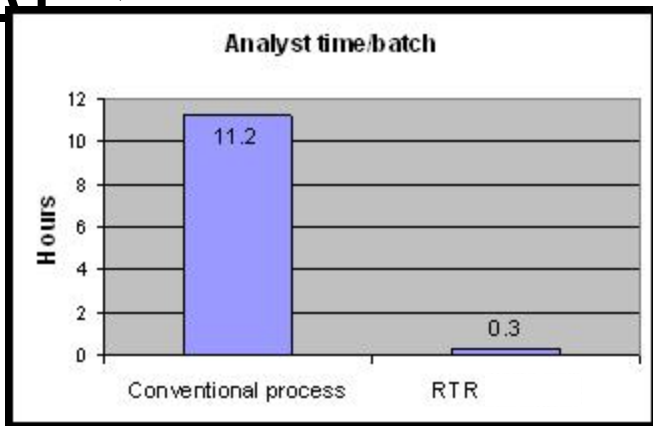
Control Strategy for Product – Real-Time Release Testing for Product Release



Near-Infrared Method Development and Initial Transfer



Real-Time Release Testing Business Assessment



- Additional business benefits in
 - Inventory Management Opportunities
 - Reduction in Waste

Requirements for NIR/RTTRT Method – The Production site's view

Merck
PAT

○ *Main requirement: Robust, manageable technology and methodology that delivers value*

No R&D
Not too complex
– no Ph.D. required
365 days a year

Hardware and software robust

Production has to run
=
Methods have to run

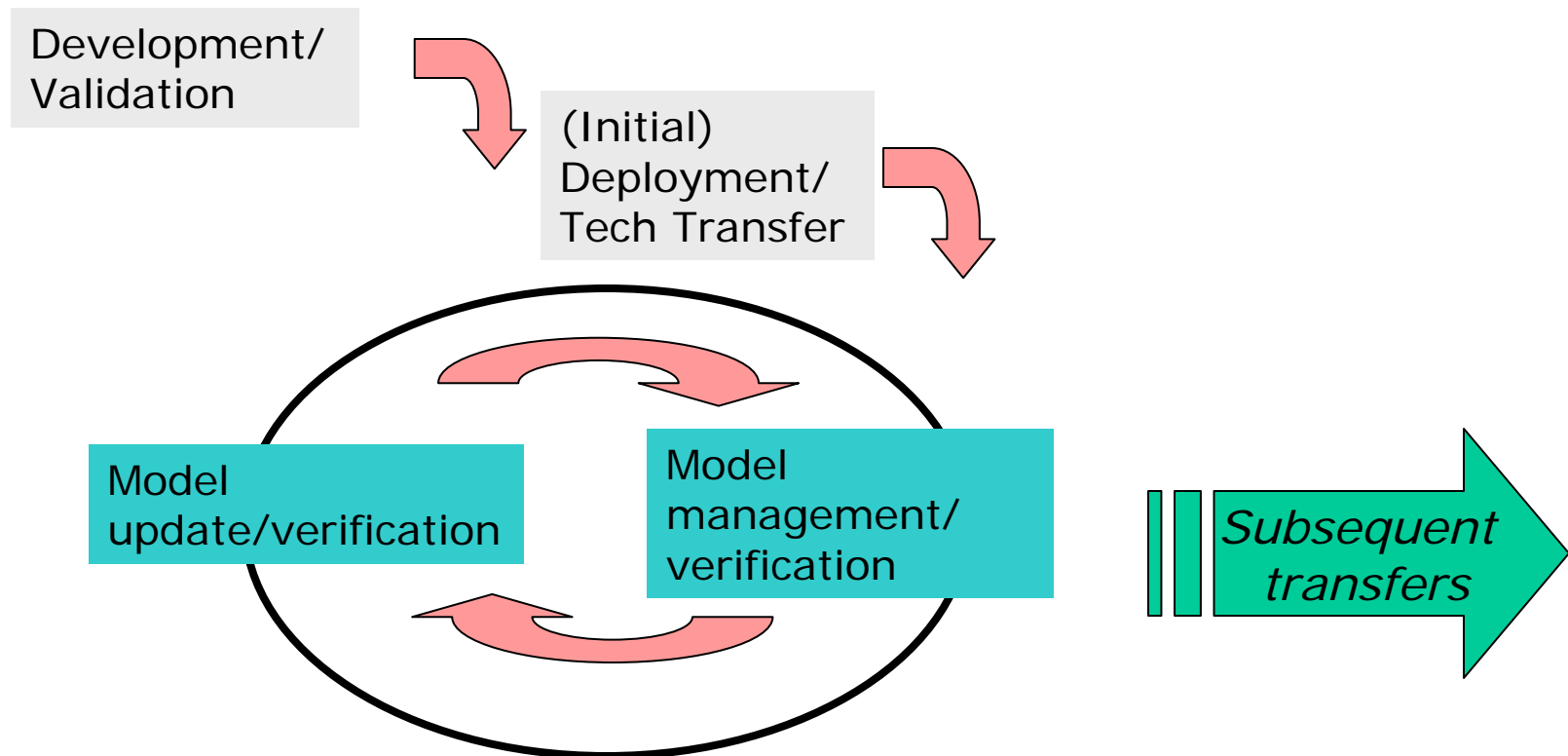
Throughout life of product:
Needs to be manageable by site resources
Needs to fit into existing (Quality) system

No
Uncertainty:
• Quality
• Technical
• Regulatory

NIR Methodology Life Cycle



- Simplified sequence
 - Variations possible



Method Development and Validation

- Use of all available tools for robust method development
 - Risk assessment and management (fishbone, FMEA)
 - Include all elements contributing to methods performance, such as hardware, software, sample, process etc.
 - Design of Experiments/Modeling
 - (If applicable) analysis of the reference method
 - => "QbD" approach for method development

- Method validation
 - Use pre-established procedures and acceptance criteria
 - Applied for specific use of the method
 - Can be complex/highly statistical for true in-line methods
 - Documentation of what was done
 - Internal to company
 - Regulatory submission

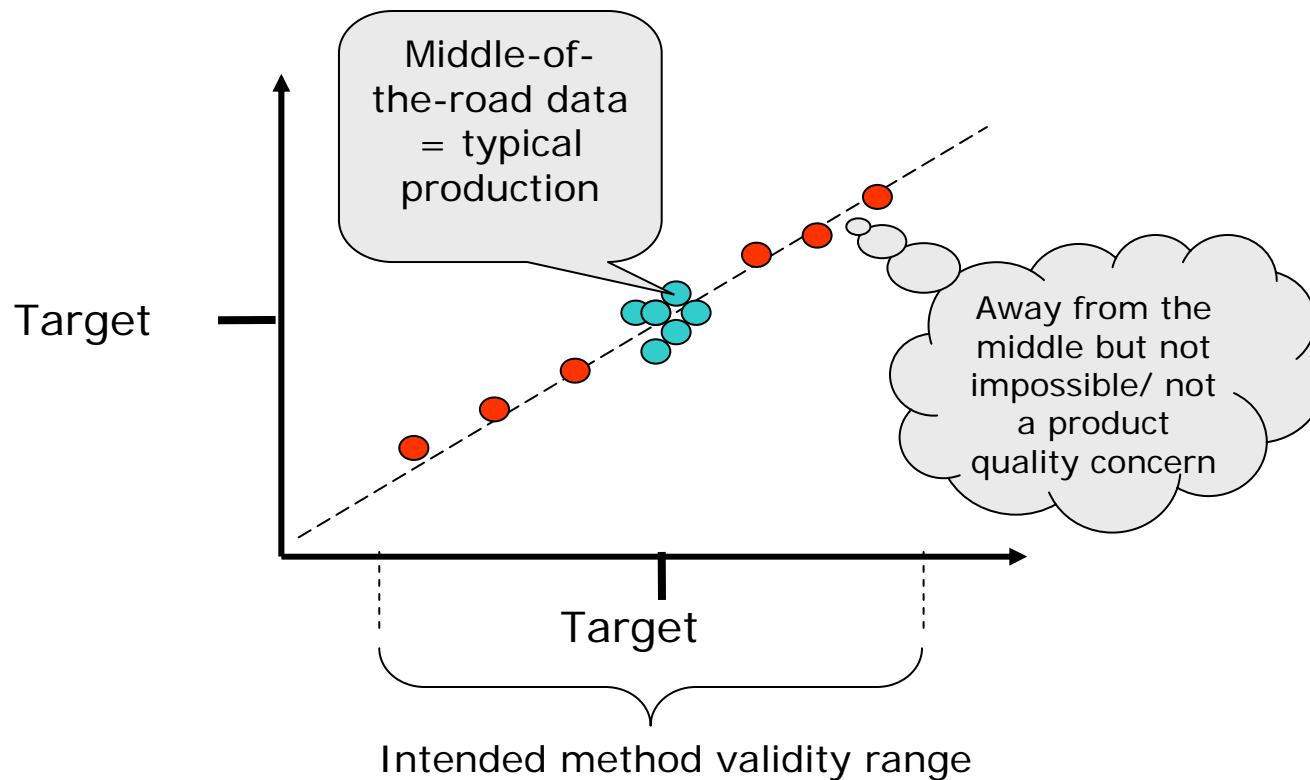
Now let's take a closer look at "Model robustness design"

- Composition of calibration sample
 - Balance of samples to challenge method with "typical performance" samples

NIR Robustness Design for New and Existing Products



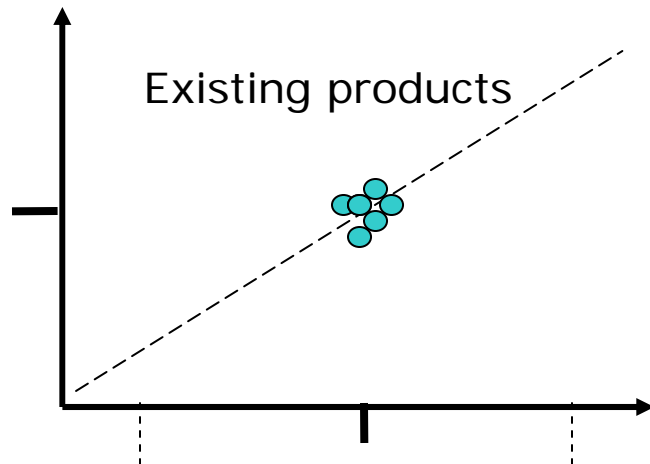
- You ideally want both:



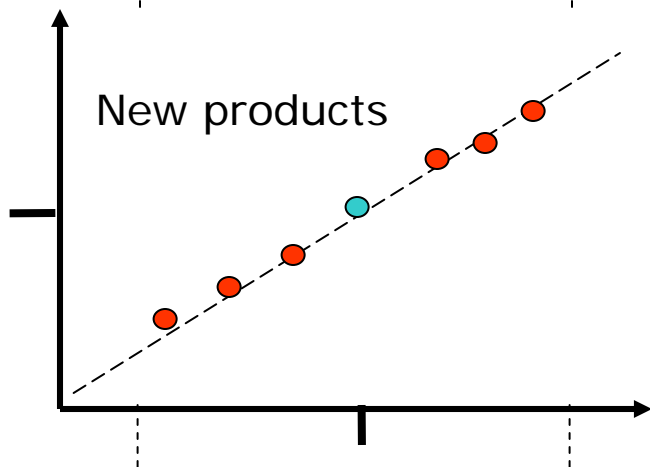
NIR Robustness Design for New and Existing Products



○ ...but you typically have these:



- Lot's of "at target" values => limited value for correlation/calibration
- Very little desire to create off-target value (product cost/risk)
- No desire to generate additional variation in processing conditions



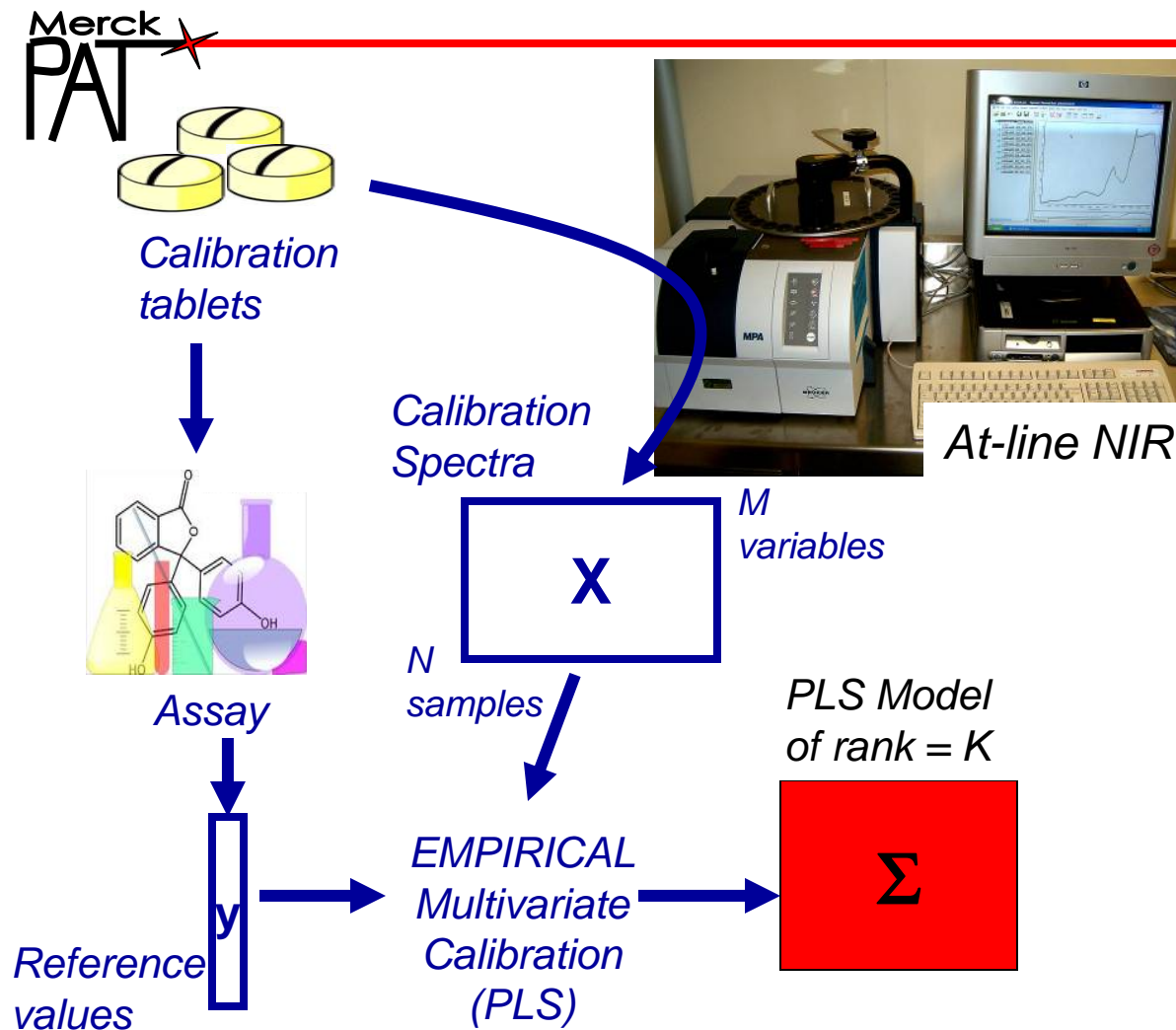
- Often significant variations (intentional, sometimes unintentional) at various scales (pilot and full scale) = good to use for robustness challenges
- Limited development runs at target values = fine-tuning of model at target can be challenging

Approach to and Results of Method Validation and Transfer for *this* Method



- Approach
 - Pre-determined acceptance criteria
 - In this at-line method based on reference method (linearity, accuracy, specificity etc.)
 - Performance acceptance criteria should not change
 - NIR **method** should not change – **the NIR model may**
 - Independent calibration and validation set
 - Independent batches except for 'designed samples'
 - Considered wide range of chemometric algorithms
 - Balance between performance and practical implementation requirements
 - Method transfer based on protocols
- Result:
 - Near-Infrared Method passed all pre-determined validation criteria
 - Method transfer passed all criteria
 - Use of method in process validation

Near-Infrared Method for Concentration of Active in Tablets



NIR Method:

- Samples are whole tablets
- Measured in transmission
- At-line method
- Overall spectral range (i.e. NIR)...

NIR Model:

- Specific samples used in cal/val
- PLS model rank
- pre-treatments
- specific wavelength range
- ...

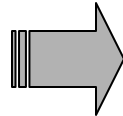
Last (and repeated) step: Model management/maintenance



- NIR methods/models can be influenced by several factors
 - Physical and chemical effects
 - Initial method development will attempt to cover most aspects, but can unlikely cover all future life-cycle events
 - Method verification, and possible update, is needed

In cases where calibration to reference methods are used:

- Decide if reference method is "gold standard"
- Define correlation between reference and NIR method well

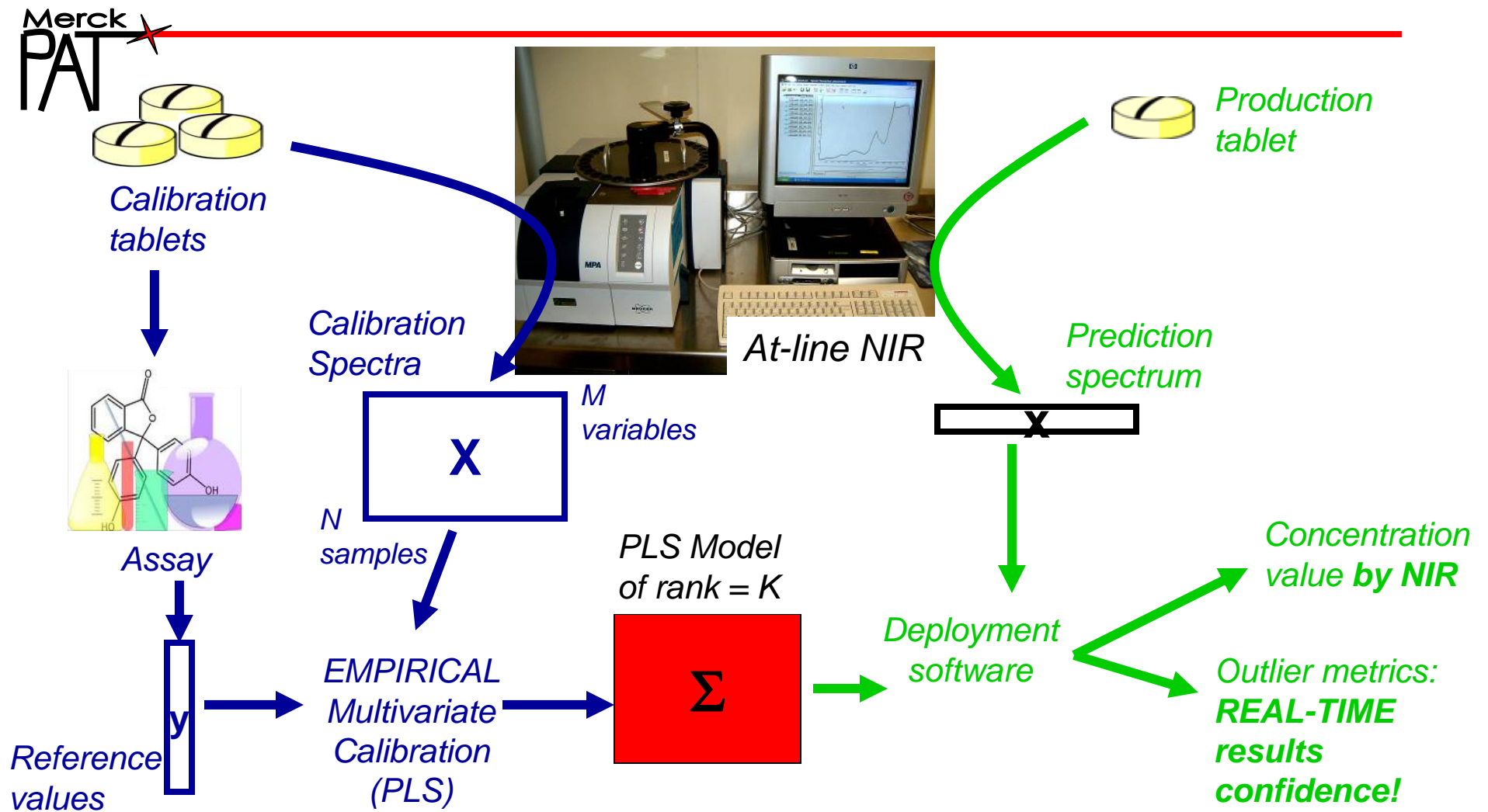


If so, then ultimate verification is comparison to reference method

- Often called "parallel testing" (can be misnomer as one might not test all samples with reference method)
- However not practical in production => use the power of chemometrics instead

○ *"The model will give you more than just the quantitative result"*

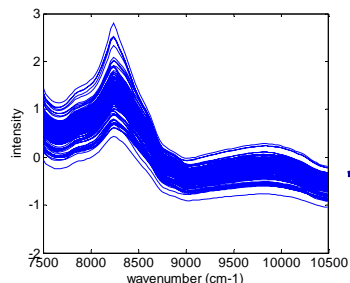
Basis for use of Spectral Outlier Statistics



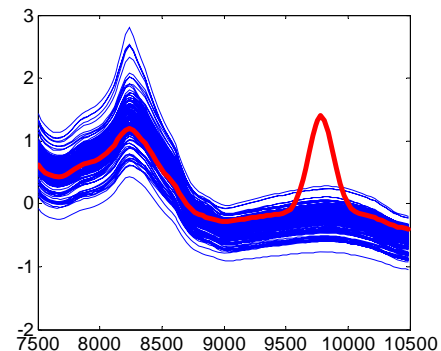
Multivariate Outlier Metrics



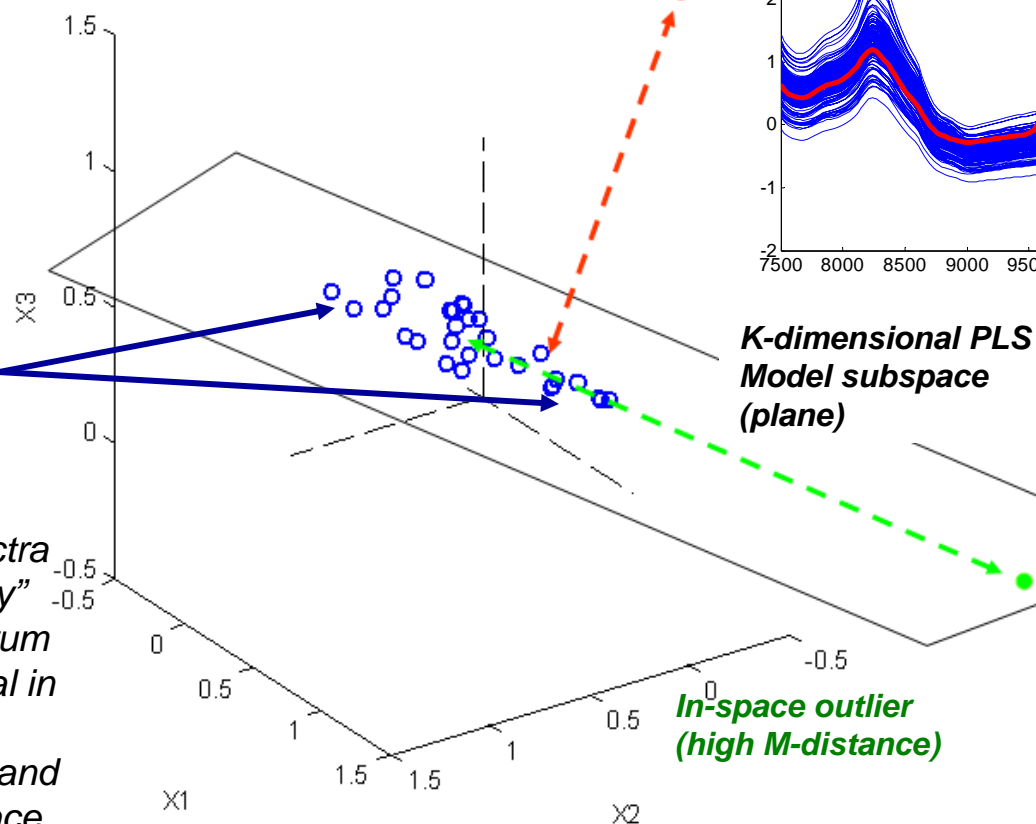
N NIR spectra
(M variables
each) used to
build model



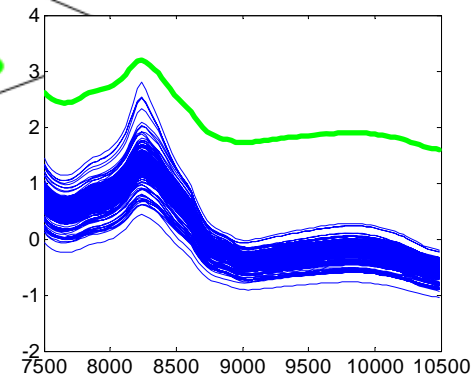
*Out-of-space outlier
(high F-value)*



*K-dimensional PLS
Model subspace
(plane)*



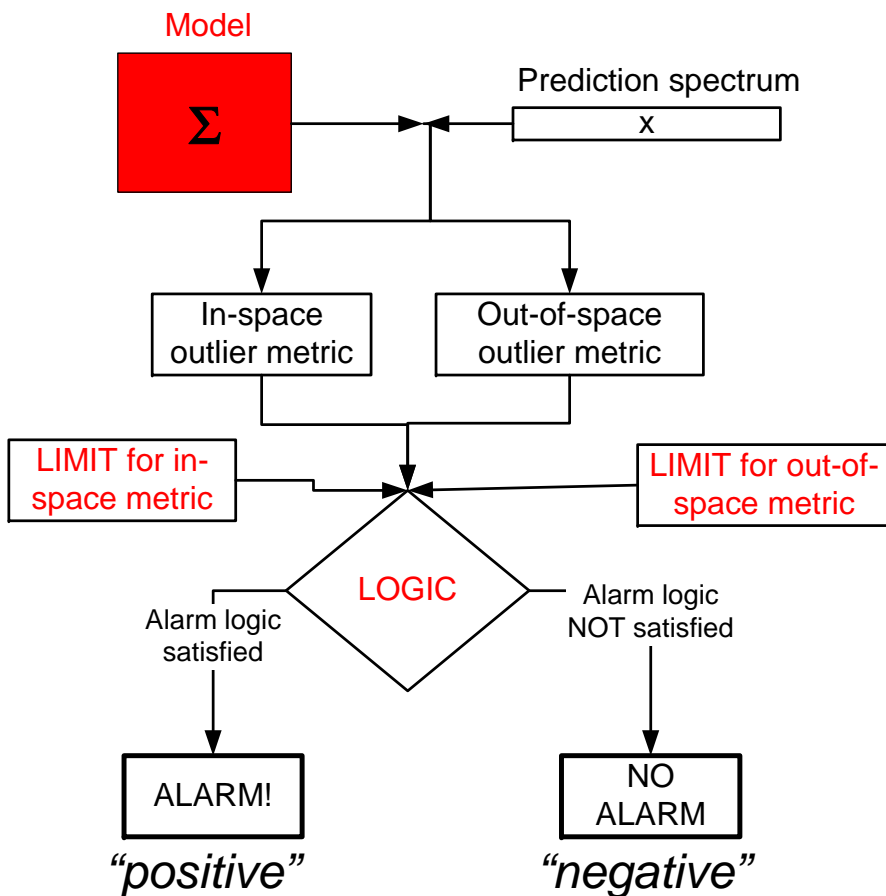
*In-space outlier
(high M-distance)*



- Calibration spectra define “normality”
- Any **new** spectrum can be abnormal in 2 ways:
 1. *in-space*, and
 2. *out-of-space*

• Monitoring of metrics is imperative: **REAL-TIME** NIR results confidence !
 • Two metrics reflect **different** NIR failure modes → both must be monitored!

Basic Elements of Spectral Outlier Alarm System and Limits



Metrics are the central element of a larger “Outlier alarm system”

Other critical elements:

- **Model:** is often the same PLS model that is used to generate assay results (does **not** need to be)
- **Limits:** the primary means to adjust **sensitivity and specificity** of the alarm
- **Logic:** how the results are used to determine “alarm” vs. “no alarm”

Sensitivity: ability to alarm when presented with true defective case (bad measurement or sample)

Specificity: ability to correctly not alarm when presented with good measurement



When is a NIR method “ready” for production? When to do “parallel testing”?

- NIR method readiness is based on method validation criteria
 - Including robustness ... and it's detection
 - Method verification scheme must be ready, too.

- “Parallel testing” could refer to testing of product with 2 methods (NIR and reference method)
 - Need to be sure which one is used for release of product
 - Need to define up front what happens if results of two methods don't agree

- “Parallel testing” should not replace sound method development
 - I.e. to deploy preliminary method

- “Parallel testing” (and how to get in, and out of it) should not inhibit eventual PAT method implementation
 - Operational aspects
 - Quality system aspects
 - Regulatory (approval) aspects
 - Do we need two approvals for the method?

Considerations for NIR model introduction for *new products*

(if alternate/reference method is available for use)



- Use all available development data for now to assess method capability/validation
- Develop transition plan/implementation plan with defined criteria
 - Should be results oriented, data driven
 - Not ideal: x number of batches

Subject to review in submission

- Use reference method for control
- or*
- Implement model verification/ management to have real-time assessment of performance of method

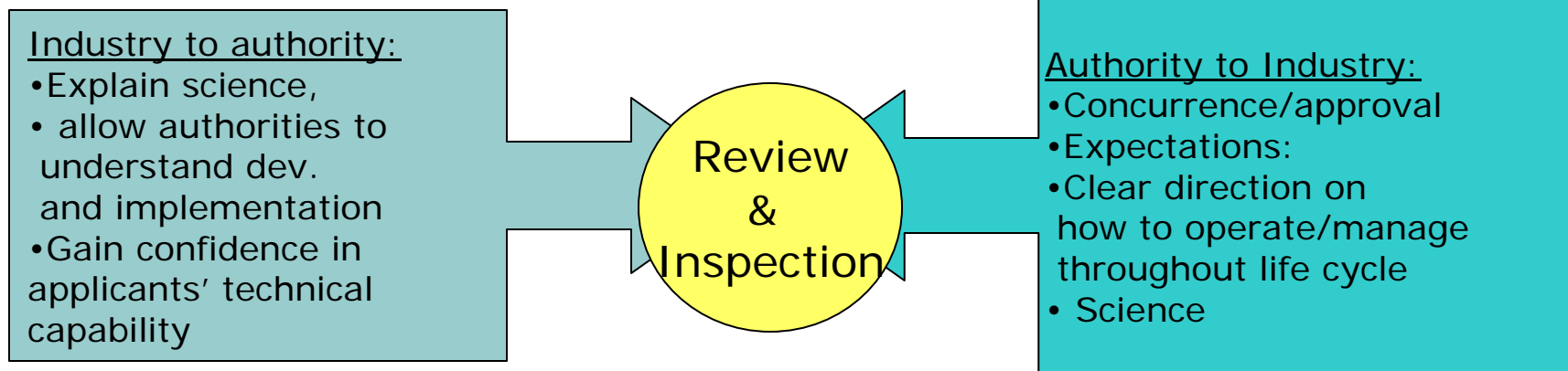
Element of site quality system (inspection) incl. transition to NIR method

- Then*
- Update model as needed based on previously established criteria
 - Start/continue using NIR method as control element

Regulatory Submissions and Inspections



Regulatory Submissions and Inspection of this NIR Method – Give and Take



There are differences, but also many similarities to conventional methods:

Differences:

- Technical/scientific

Similarities/Commonalities:

- Quality System overall (=interpretation of different science)
- Operational requirements

Experiences with Submissions and Inspections



○ Submissions

- Details on method development/validation
- Clarity on use of method vs. reference method
- Strategy of life cycle management (i.e. model changes)

○ Inspections (PAI was QbD-like inspection, reviewer and inspector jointly)

- Some method development
- Method execution/operational aspects
- Change management procedures and internal quality system
- Review of investigations

Significant Events in the Life of a NIR method



NIR RTRT Implementations – Looking down the road



- Typical pharmaceutical products will experience many changes throughout life cycle
 - Transfer/expansion to new manufacturing sites (incl. contract manufacturing)
 - Changes in suppliers
 - Additional formulations/doses

- NIR/PAT methods need to be able to “go with the flow” on all other aspects of products
 - Robust
 - Flexible
 - Transferable/implementable

• Translates into requirements for:
Technology/Science

- Skills/capabilities
- Regulatory/Quality

A cyan speech bubble with a black outline and a tail pointing towards the top-left, containing the text above.


Life of *this* NIR Method

1. Changes within a model in one method application
 - Model verification, spectral outliers, model updates

2. Changes beyond one application instance
 - Second analyzer
 - Second site, ...
 - More doses/formulations

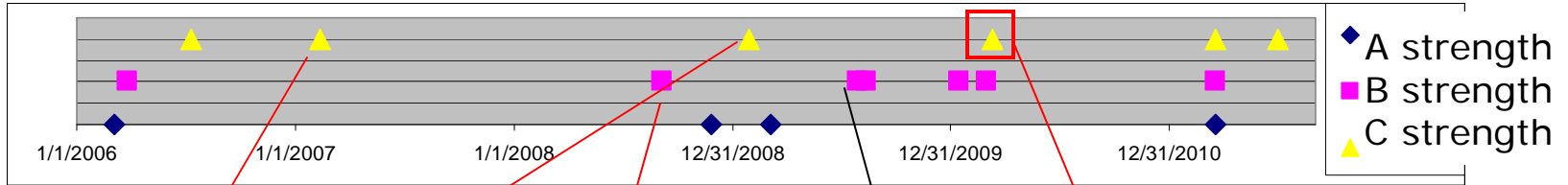


*Manage
locally*



*Then go
global*

PAT Method Events over several years



MAR, JUL 06: 3 NIR models put into service

A and B model updates

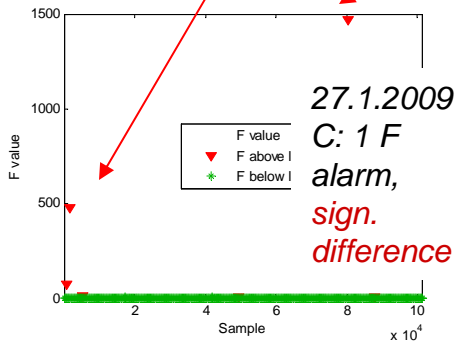
29.7.2009 B: 6 MD alarms over 2 weeks, *no sign difference*

B: 3 separate MD alarms, *sign. difference*

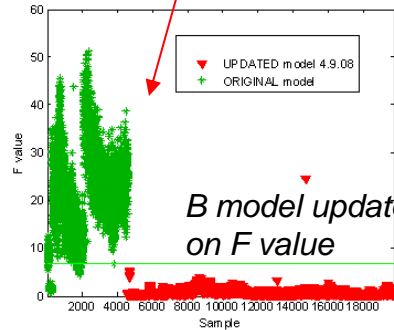
18.3.2011 (all): new MD limits set using 95% CL

30.6.2011 C: model update

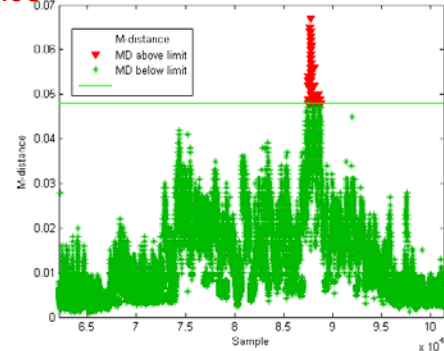
12.2.2007 C: 2 F alarms, *sign. difference*



27.1.2009 C: 1 F alarm, *sign. difference*



B model update effect on F value



10.3.2010 C 132 MD alarms over 8 batches! *No sign differences*

→ Investigation of outlier metric limits (too "tight"???)

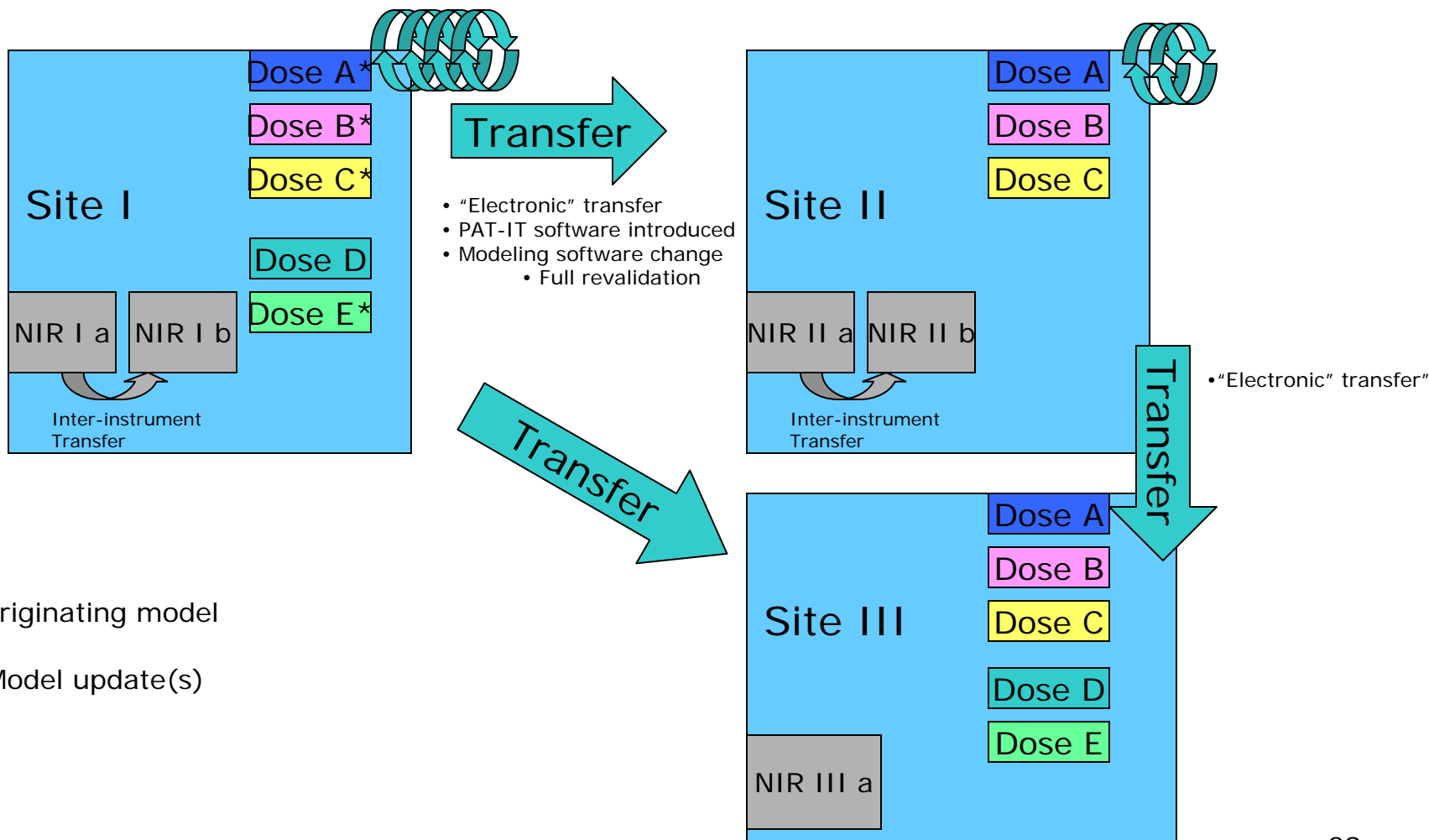
- C model generated useful metrics right away; A and B models did so after a model update
- Since 2006, only 6 confirmed tablets with sign. differences (out of >120k!)
 - *all of which* were flagged by the outlier detector!
 - *none of which* were confirmed as product quality issues!
- However, *132 false alarms* for C model in 2010



Notes on Model Verification/Updates

- All spectral outlier values were investigated
 - Cause and impact
 - *"Unmodeled variability"* as a root cause
- In cases where model was updated
 - In all cases the original method validation criteria were used (and passed)
 - Internal independent Quality organization review of results
- Data/justifications reviewed during subsequent inspections
 - Positive feedback on internal quality system

Global Life of *this* RTRT NIR method



*: originating model



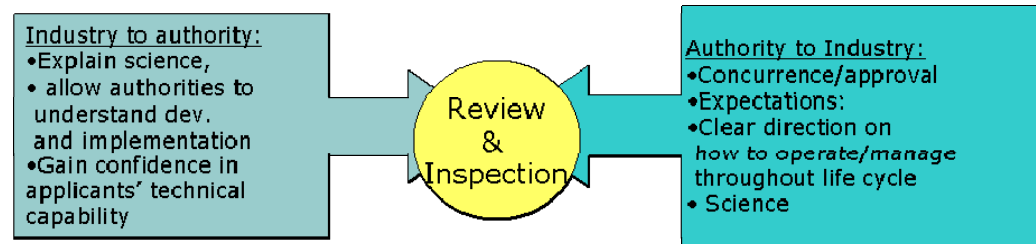
Model update(s)

Notes on Method Life Cycle events – “Global expansion”



- In all cases (updates, transfers) original method validation criteria were used
- Method did not change - models did (sometimes) change
 - Sometimes necessity (would not pass criteria otherwise)
 - Sometimes business decisions (continuous improvement)
- Significant changes were risk-assessed and identified risks mitigated
 - Expl. Introduction of PAT-IT system software
- In the end, method(s) continue to perform well in all sites

Discussion points on Regulation of NIR Methods



- Regulation of NIR methods vs. conventional analytical methods
 - Level of prescription – do we need more familiarity/scientific understanding or do we want to limit the options by regulation
 - Method transfer (to other instruments, to other sites)
- Consider overall control strategy and use of NIR method
 - Not all NIR methods are real-time release testing – expectations should be different (ICH QbD Q&A documents)
- Life Cycle Mgmt/Change control of NIR models:
 - Needs to be scientifically and quality-system sound but also manageable and efficient – role of the regulator?
 - Do we need different approach to other conventional method change control?
 - *Can we update and implement a model within 1 week?*

Also...not every NIR method is for Real-Time Release Testing



- RTRT methods get much visibility but are not the only types of method used
- For expl. Merck/MSD implemented and filed a number of in-process NIR methods that are not final determination of product quality (i.e. still release testing) – chemical & formulation process control strategies

FDA U.S. Food and Drug Administration
Protecting and Promoting Public Health www.fda.gov

Considerations for Submission of Models

- **Level of detail in submission should depend on the importance of the model to the overall control strategy**
- **Low Impact Model** (e.g., Models for development)
 - General discussion of how model was used to make decisions during process development
- **Medium Impact Model** (e.g., Design space models)
 - More detailed information about model building, summary of results and statistical analysis
 - Discussion of how the model fits into the control strategy
- **High Impact Model** (e.g., RTRT models)
 - Full description of data collection, pretreatment and analysis
 - Justification of model building approach
 - Statistical summary of results
 - Verification using data external to calibration set
 - Discussion of approaches for model maintenance and update

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See also recent FDA re-issuance of ICH QbD Q&A “Use of Models”



Conclusions

- NIR is very established technology in many industries, continuing to gain rapid acceptance in regulated industry
- Pharmaceutical Quality (and regulatory) system can be adapted to support NIR as well as other PAT tools
- Real-time release method has been
 - in use with high volume product for 6+ years, undergone several changes
 - without impact to performance of method or quality assurance of product
- Regulatory interpretation is evolving in dialogue between authorities and industry