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)

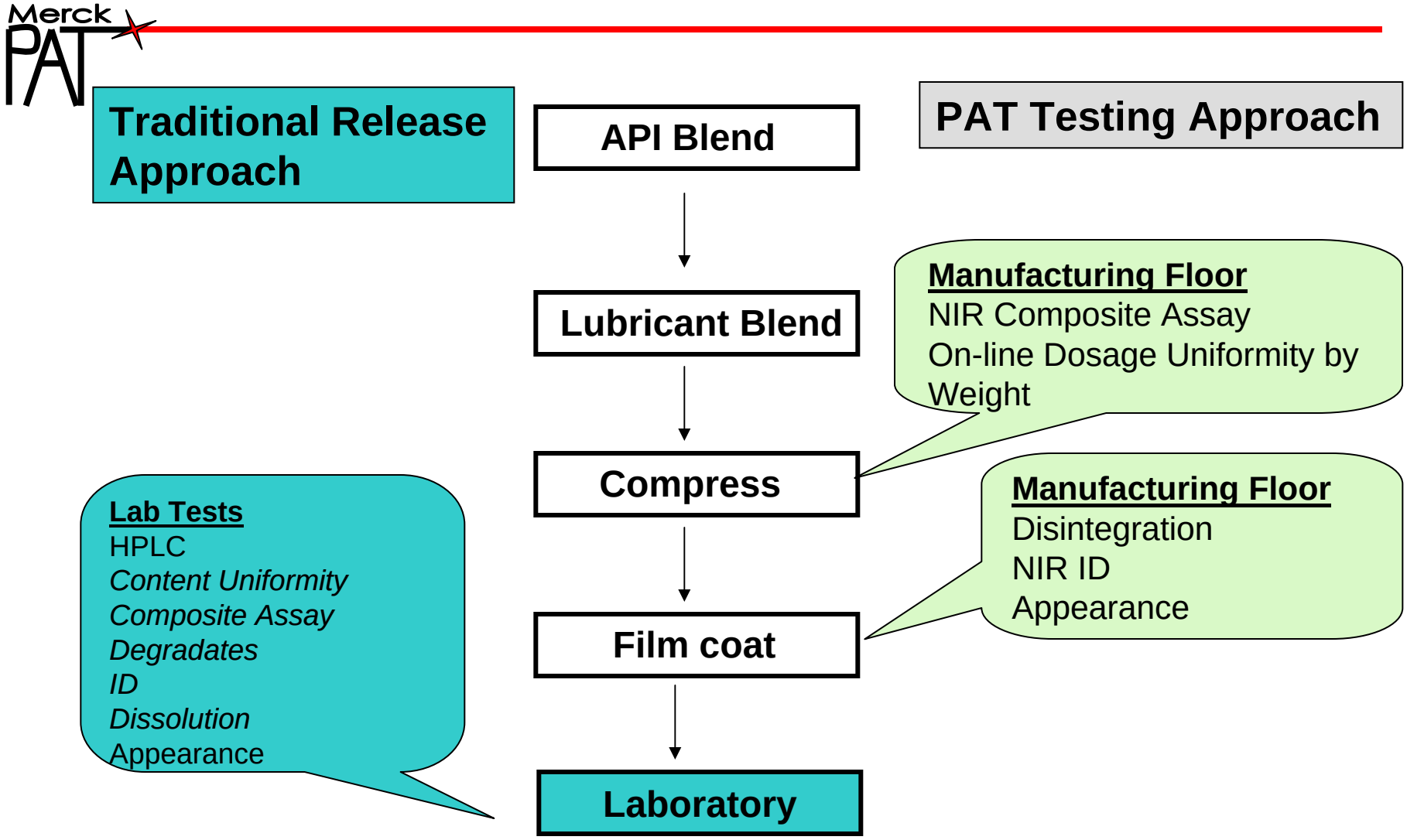
- Product attributes that support real-time release testing
  - Simple direct compression process with good development history of uniformity
    - Relatively high active content (~30%)
  - Very good stability*
  - No degradates*
  - BCS class I with well understood disintegration/dissolution behavior

* for approved stability window, under approved storage conditions and packaging

Merck 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

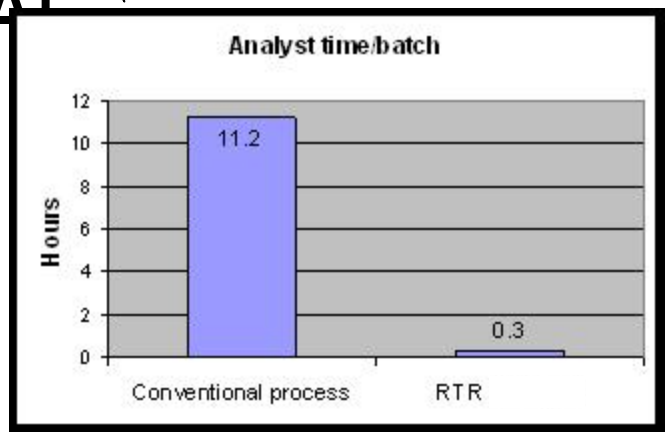
Control Strategy for Product – Real-Time Release Testing for Product Release

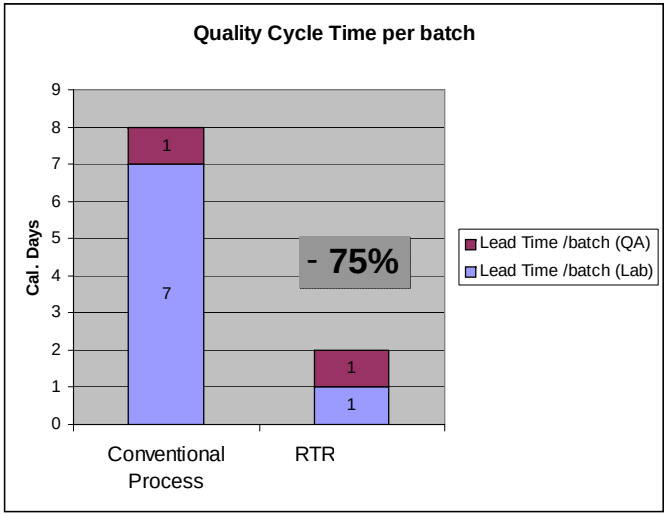


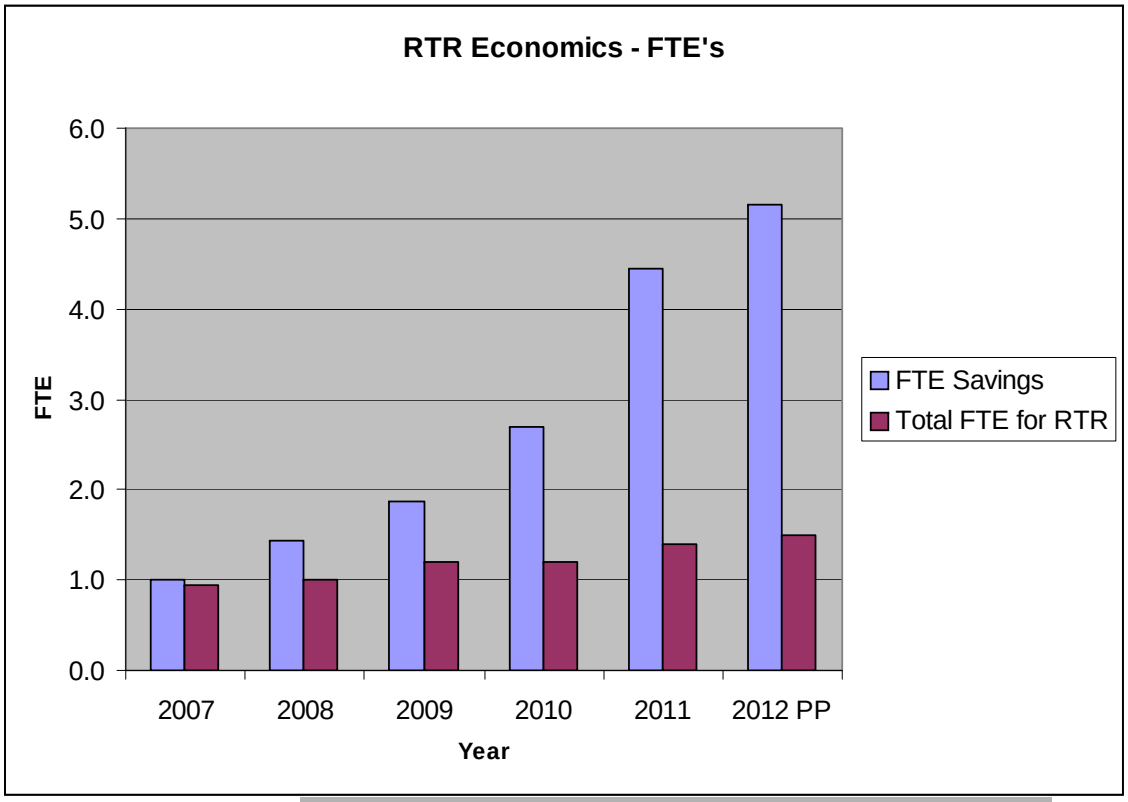
Near-Infrared Method Development and Initial Transfer

Merck PAT

Real-Time Release Testing Business Assessment







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

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

- *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

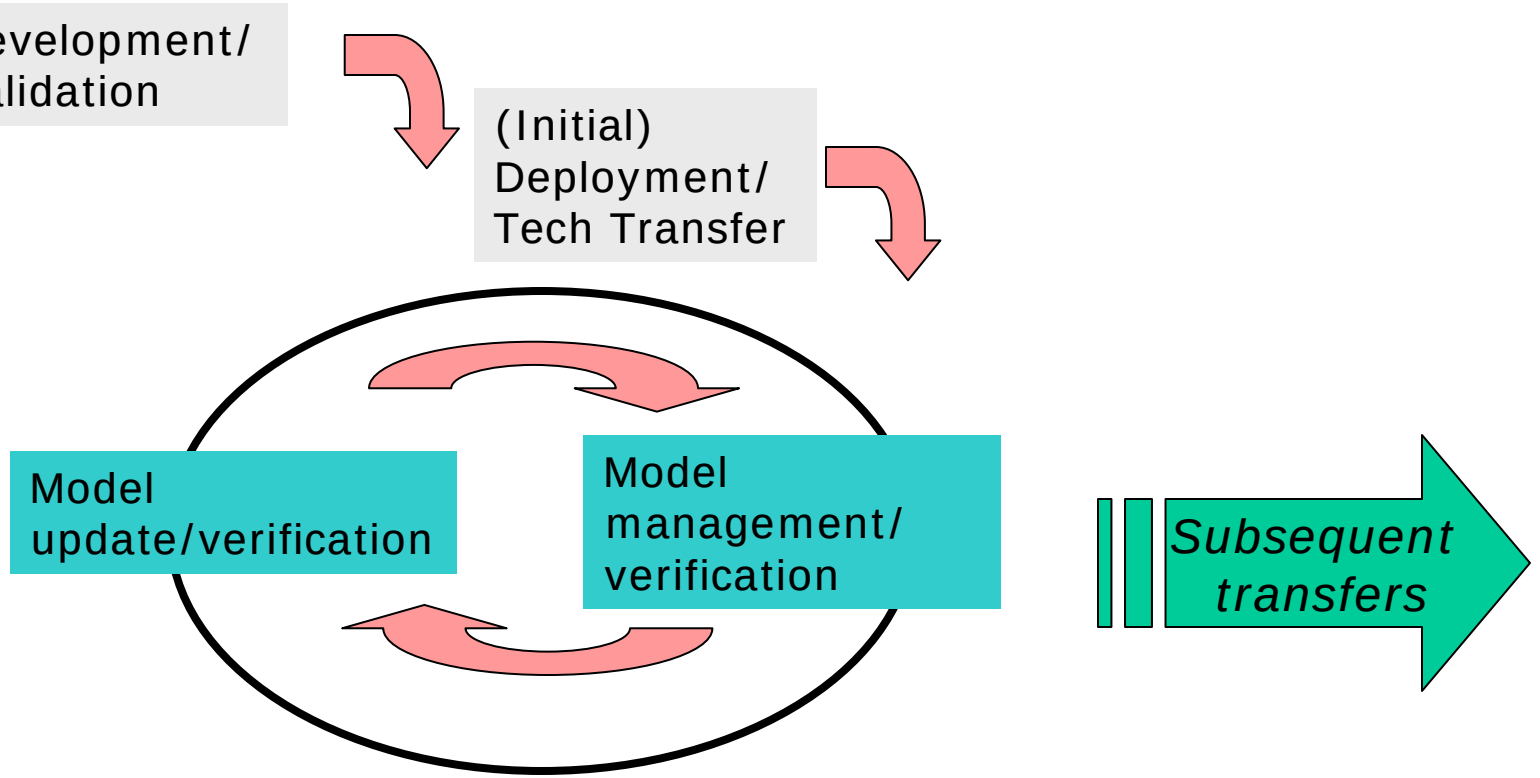
Production has to run
=
Methods have to run

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

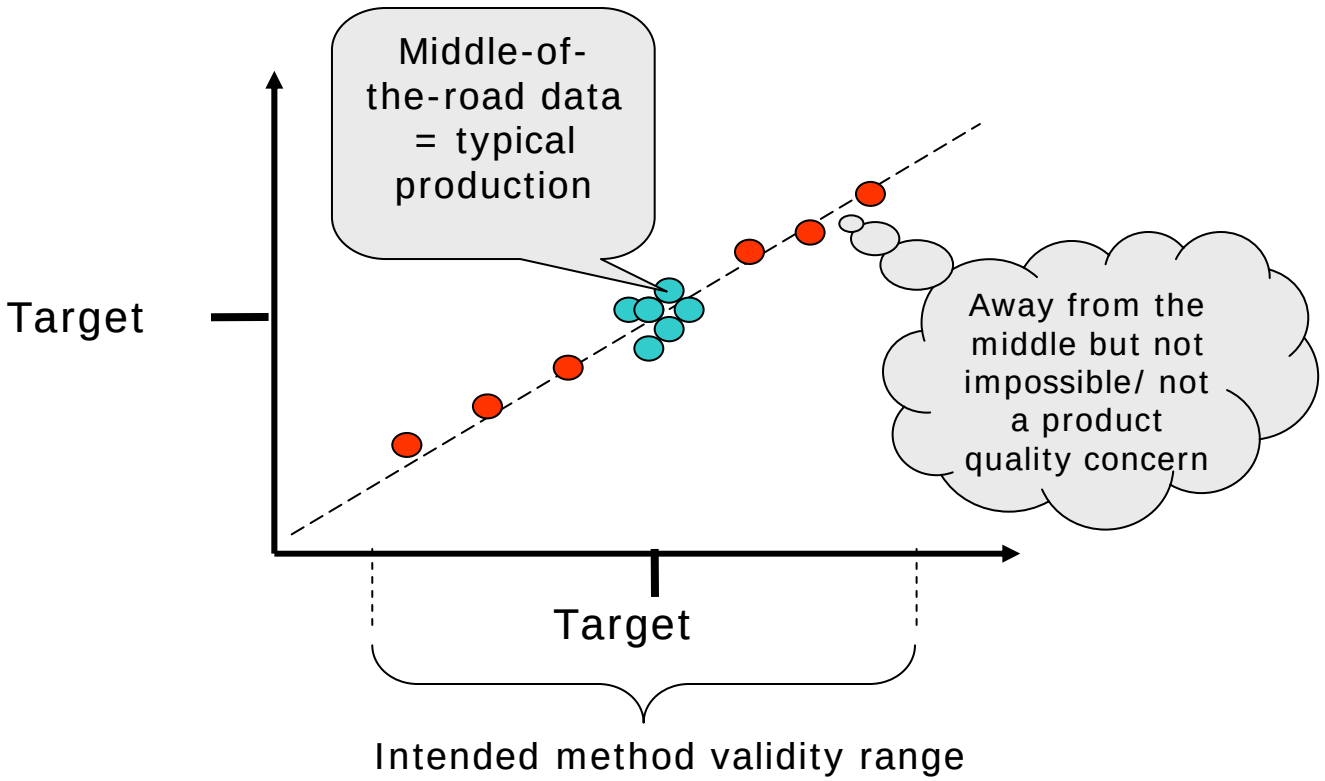
- Method validation
  - Use pre-established procedures and acceptance criteria
    - Applied for specific use of the method
    - Can be complex/highly statistical for true in-line methods
  - Documentation of what was done
    - Internal to company
    - Regulatory submission

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

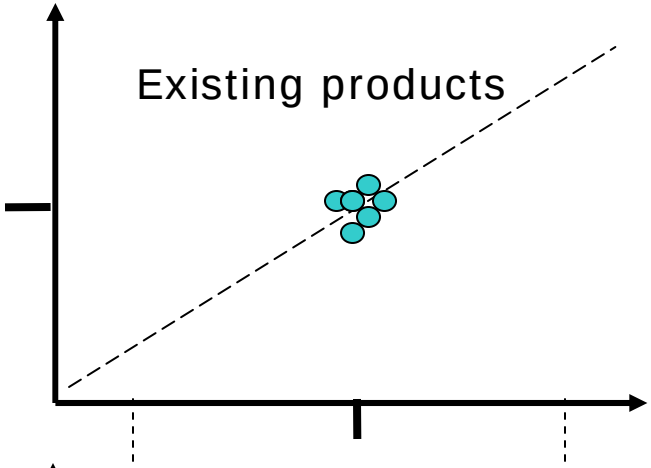
NIR Robustness Design for New and Existing Products

- You ideally want both:

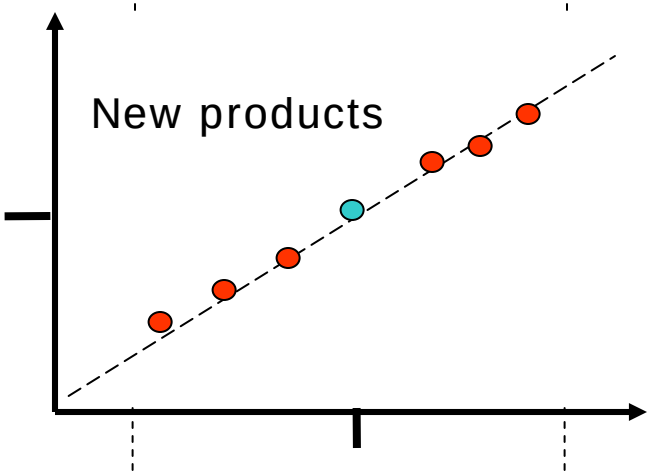


NIR Robustness Design for New and Existing Products

- …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



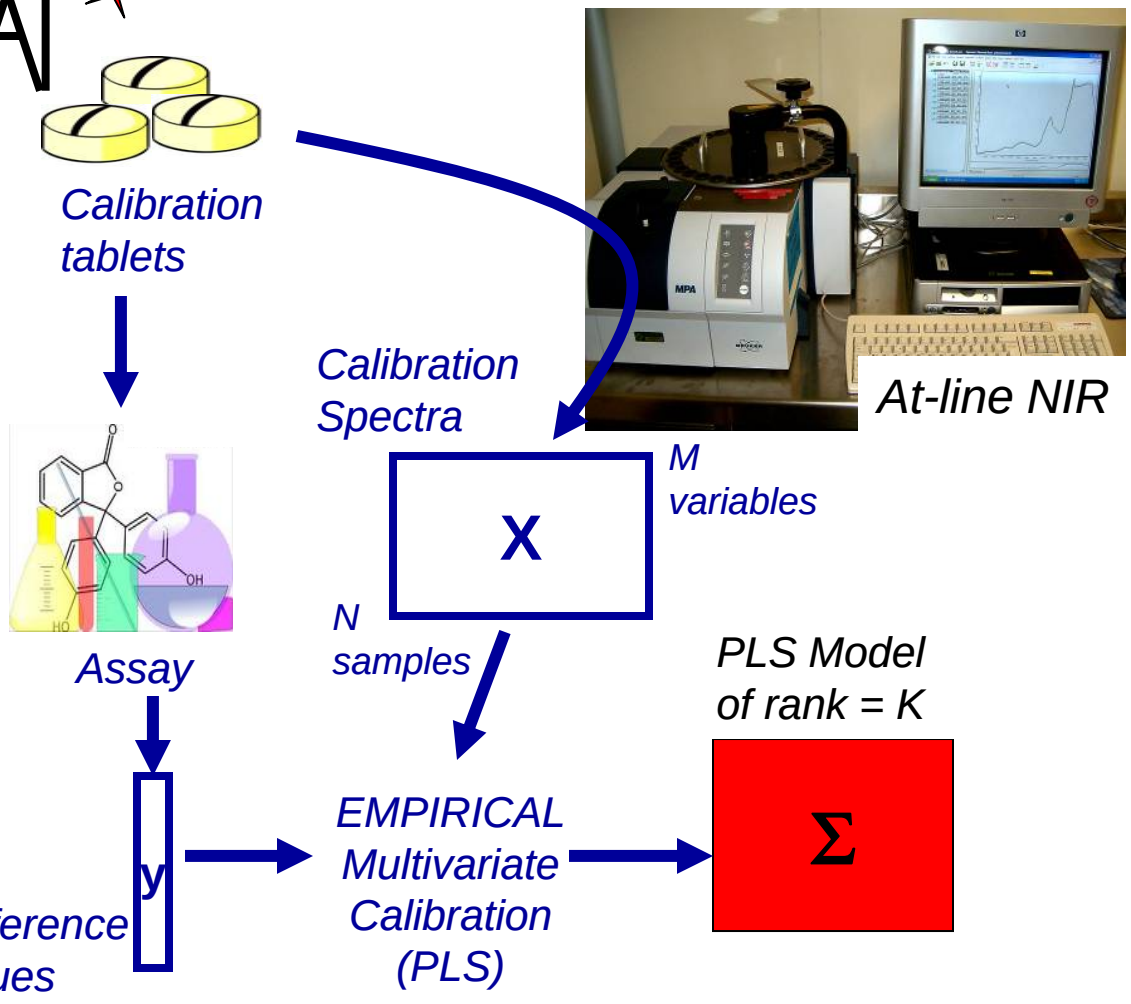
- Often significant variations (intentional, sometimes unintentional) at various scales (pilot and full scale) = good to use for robustness challenges
- Limited development runs at target values = fine-tuning of model at target can be challenging

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:*

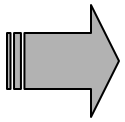
- Specific samples used in cal/val
- PLS model rank
- pre-treatments
- specific wavelength range
- …

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:

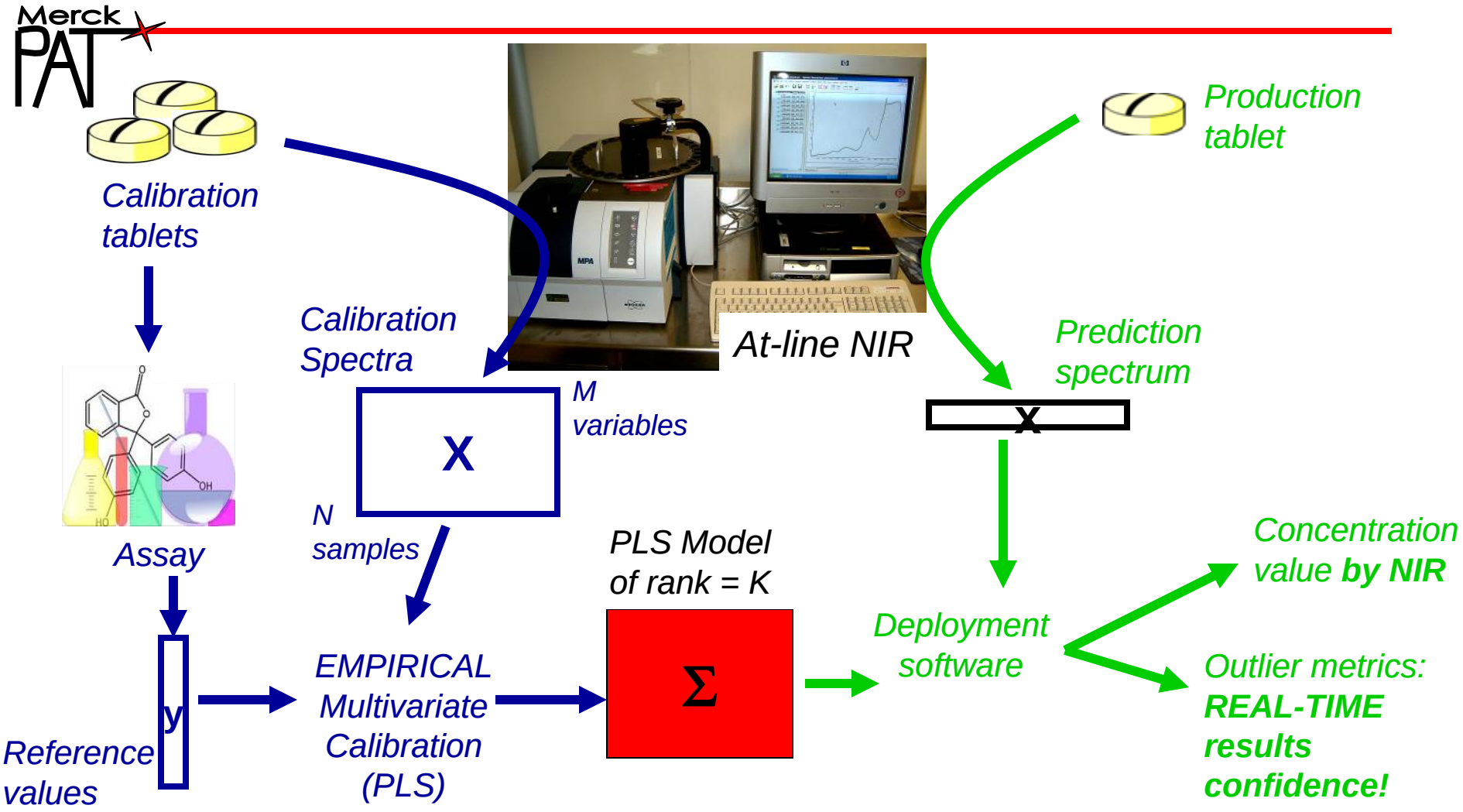
- Decide if reference method is “gold standard”
- Define correlation between reference and NIR method well



If so, then ultimate verification is comparison to reference method

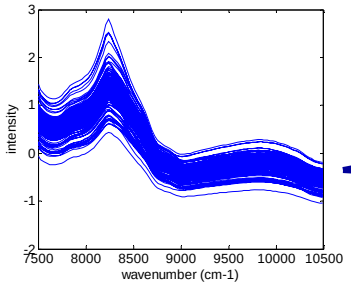
- Often called “parallel testing” (can be misnomer as one might not test all samples with reference method)
- However not practical in production => use the power of chemometrics instead
  - *“The model will give you more than just the quantitative result”*

Basis for use of Spectral Outlier Statistics

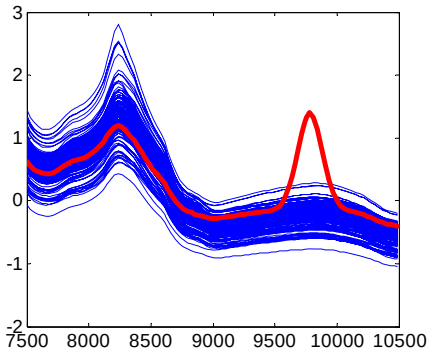


Multivariate Outlier Metrics

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

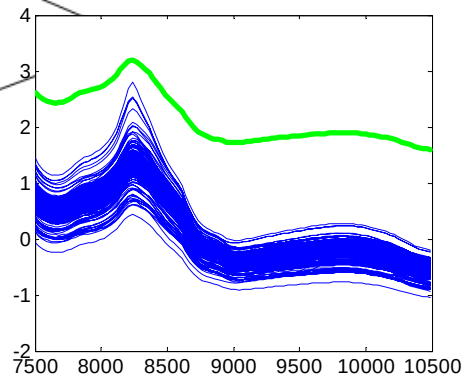


Out-of-space outlier (high F-value)



K-dimensional PLS Model subspace (plane)

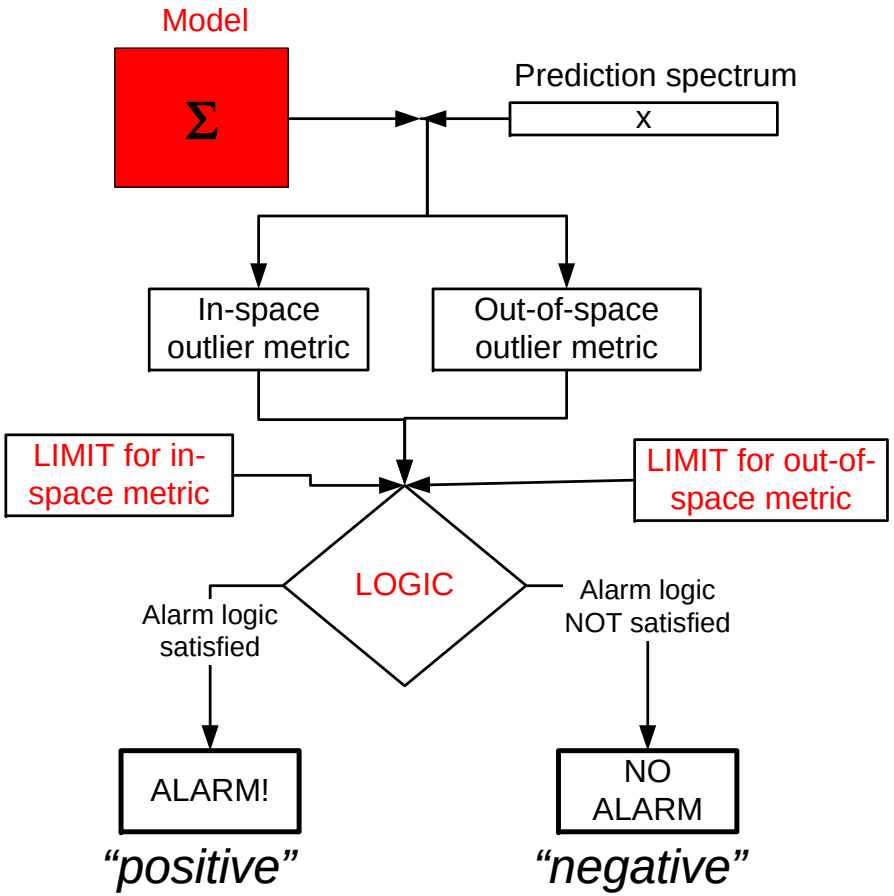
In-space outlier (high M-distance)



- *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

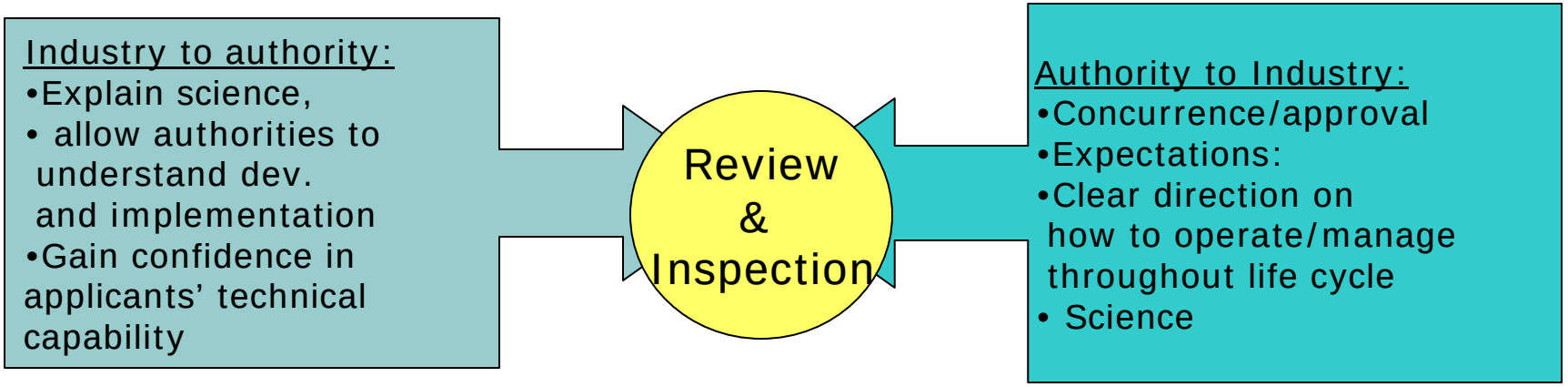
Then

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

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

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

Merck PAT

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

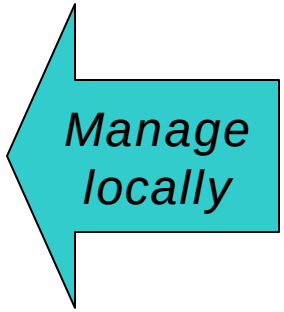
- NIR/PAT methods need to be able to "go with the flow" on all other aspects of products
  - Robust
  - Flexible
  - Transferable/implementable

•Translates into requirements for:
Technology/Science
•Skills/capabilities
•Regulatory/Quality

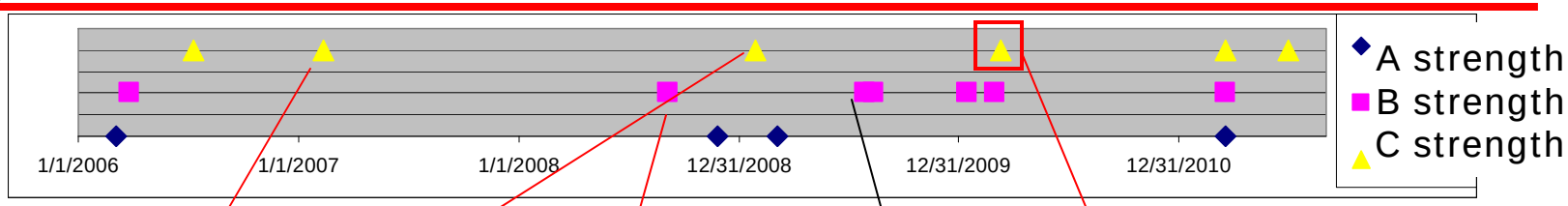
Life of *this* NIR Method

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



PAT Method Events over several years



MAR, JUL 06: 3 NIR models put into service

A and B model updates

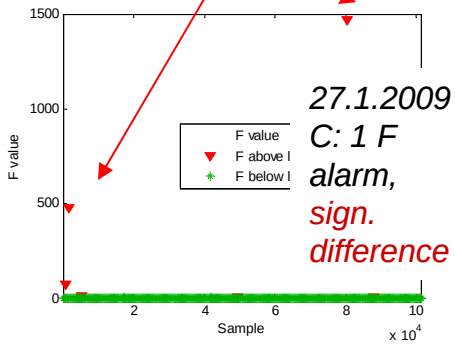
29.7.2009 B: 6 MD alarms over 2 weeks, no sign difference

B: 3 separate MD alarms, sign. difference

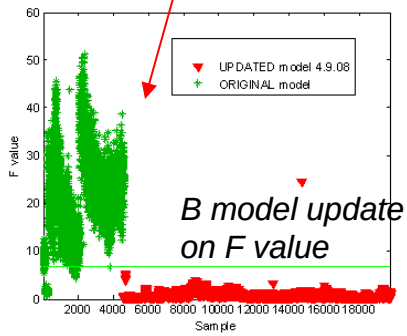
18.3.2011 (all): new MD limits set using 95% CL

30.6.2011 C: model update

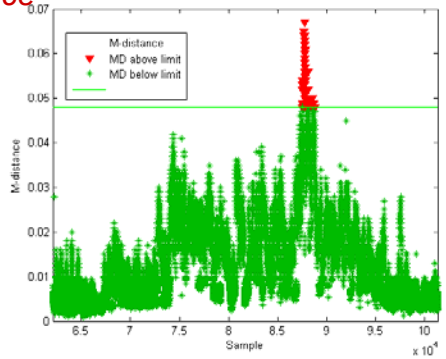
12.2.2007 C: 2 F alarms, sign. difference



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

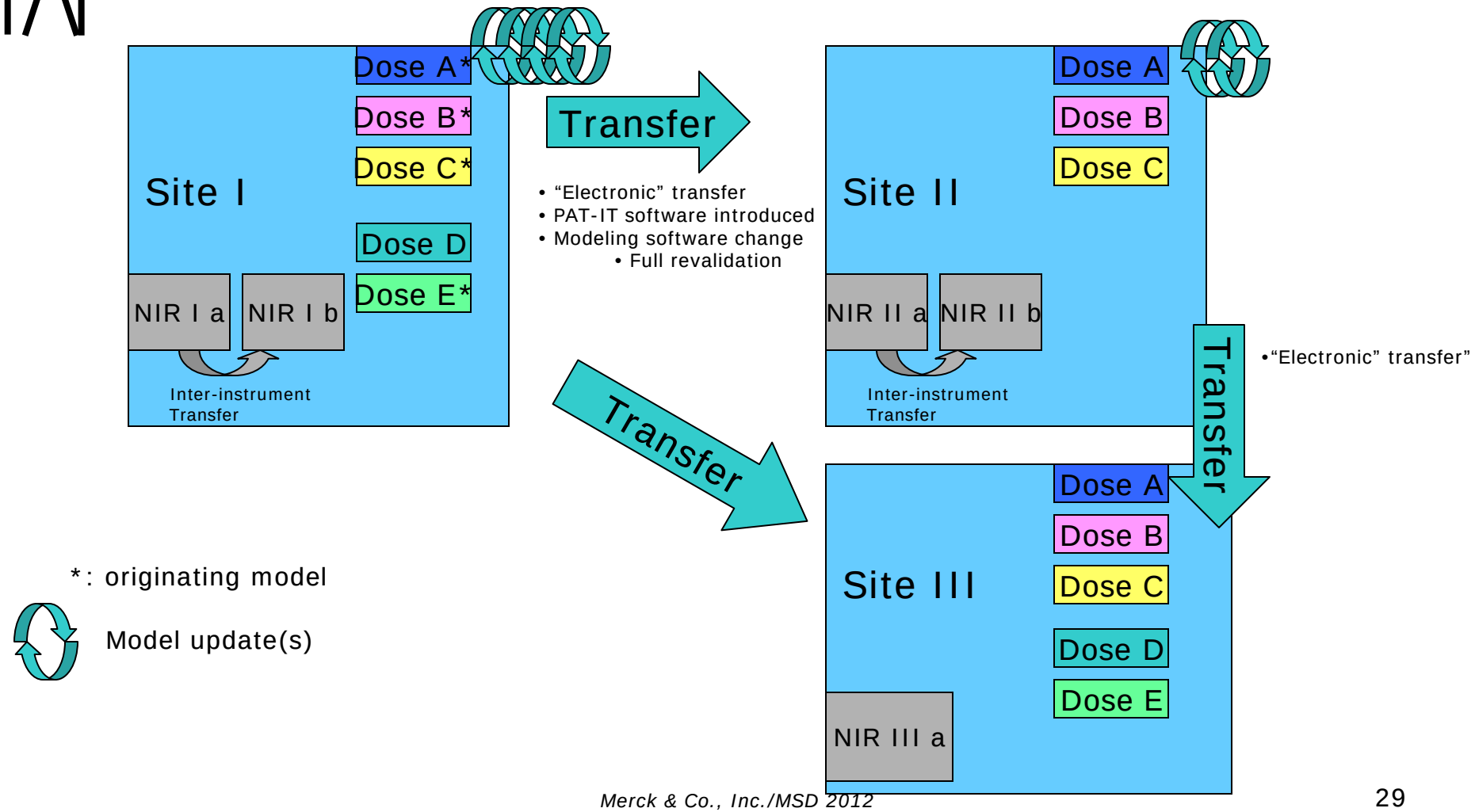
→ Investigation of outlier metric limits (too "tight"???)

- *Cmodel 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

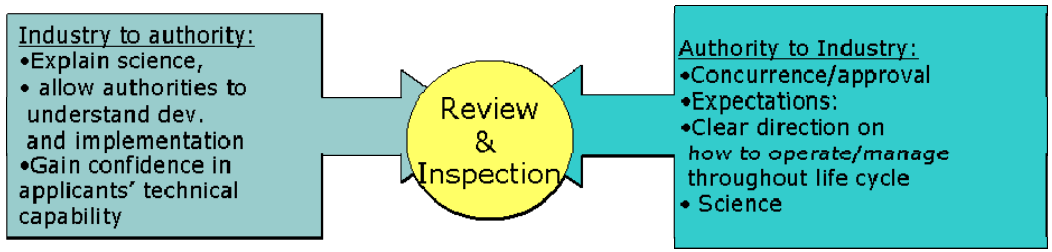
Global Life of *this* RTRT NIR method



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

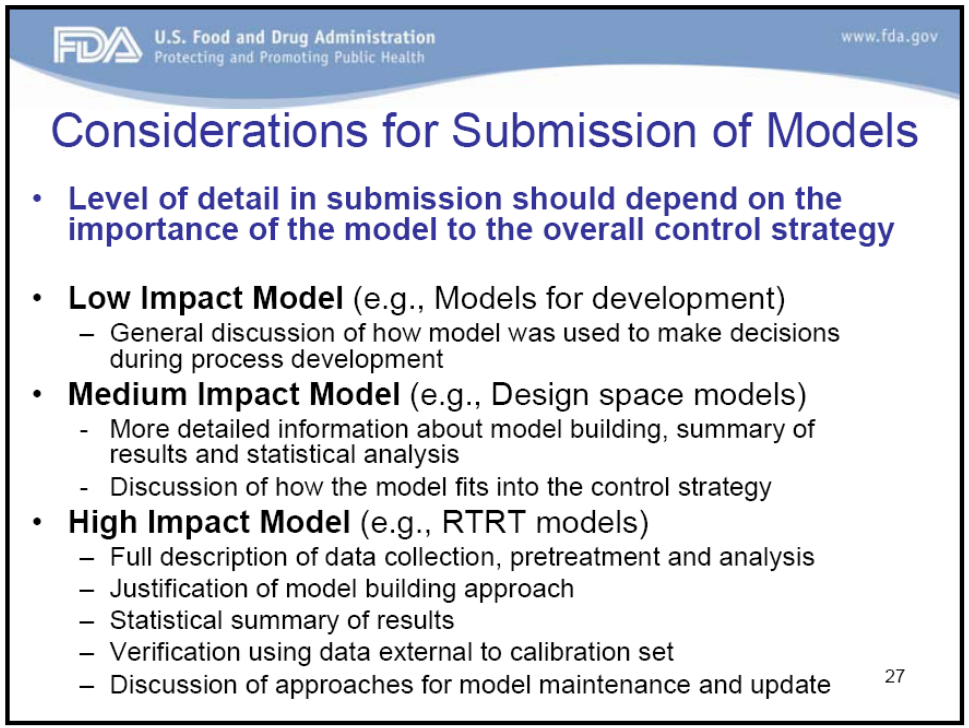
Discussion points on Regulation of NIR Methods



- 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



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