Lot Release System (Electronic Tracking System)

- Lot Release System (LRS) is a database that is used to track the status of a lot. All protocols are tracked in the LRS.
- Key Information captured in LRS:
  - Sample and Protocol receipt dates
  - Status of control test data review
  - Status of CBER confirmatory testing (if applicable)
  - Status of alerts for issues that could impact lot release
  - Setting Final Action (Release) Date when CBER's reviews are complete
- Additionally, LRS can associate License supplements to batches to ensure that no product will be released until a license supplement is approved.

Lot Release is Necessary for:

- All lots manufactured and licensed in the US are subject to CBER lot release.
- Lots manufactured in the US, but, not approved in the US may be exported from the US without CBER lot release under Section 802 of the Federal Food, Drug, and Cosmetic Act (FDCA).
- All lots imported into the US for US distribution are subject to CBER lot release.

Final Lot Release

- After review of the protocol and confirmatory testing (if applicable) reviewer informs PRB of completed task.
- PRB compiles all information and generates the Official Release Letter for signature by the delegated CBER authority.
- Vaccine batch release letters are issued (faxed and mailed) for the manufacturing step submitted (product dependent):
  - Drug Substance (Bulk)
  - Drug Product (Final Container)
  - Formulation (if all final container lots are considered to be equivalent)
  - Packaged lots are **not** typically released by CBER

CBER Release Targets and Volumes

- There are no official timelines or legal requirement to take action on lots within a specific time period.
- CBER unofficially targets 30 business days for release after receipt of the lot release protocol (assuming samples are sent in parallel to manufacturer testing)
- Data available indicates:
  - FY 2008 6,313 Lots Submitted; 2,085 vaccine
  - FY 2009 6,511 Lots Submitted; 2,463 vaccine (through 15-Sept-09)
  - Today – Merck alone submits ~2300 vaccine lots/yr
  - Experienced Cycle time < 30 days
  - Lots have been released in as few as 2 days
- In times of critical supply CBER will expedite lot release
- CBER is open to communication with manufacturers regarding the lot release status.

Alternative to Lot Release (Product on Surveillance)

- Alternatives to Lot Release may be allowed when:
  - Acceptable lot release history
  - Continued control of the manufacturing process and facility.
  - Description of major process changes, complaints and corrective actions taken, fate of lots manufactured.
  - These (3) points above are presented to CBER in a license supplement.
  - If approvable, conditions for allowing Alternative to Lot Release are communicated to the manufacturer in the approval letter.
    - For example an alternative to lot release requirement may be for biannually submission of one lot of Drug Product and Drug Substance to CBER under surveillance with samples and protocols.
    - Lots can be released by manufacturer directly to market once conditions are met within approval letter i.e. surveillance lots can be released to market immediately after CBER submitting. CBER will not release a surveillance lot.
  - CBER may reinstate lot release if new conditions warrant i.e. major manufacturing change or testing issue with surveillance lot.
  - Reference Guidance on Alternatives to Lot Release for Licensed Biological Products in US Federal Register.

Summary – CBER's Lot Release

- All licensed vaccine products are subject to CBER lot release unless approved to be on surveillance.
- At a minimum protocols are always reviewed.
- Current regulations do not permit acceptance of release by other regulatory authorities.
- Testing plans are implemented for products.
- CBER values open communications with manufacturers at all stages.

S1-3

A Manufacturer Perspective on Independent Lot Release Regulations

Thierry Pronce
GlaxoSmithKline Vaccines, Belgium.

Vaccines are biological products used in healthy populations. Due to their intrinsic nature, manufacturing processes and target population, the risk induced by a substandard lot of vaccine to Public Health is significantly different than for other pharmaceuticals. For those reasons, many countries have developed a process of systematic independent review of manufacturing and quality control data to ensure the consistent quality of every lot before it is released onto the market. This process is called Independent Lot Release.

Manufacturers recognise the benefits of Independent Lot Release and its added value on a global scale for Public Health, Public Health Authorities and Industry, and share the same common goal to ensure the availability of safe, efficacious and high quality medicines. Based on the accumulated return of experience, Manufacturer's also support that the current systems, which rely not only on the evaluation of manufacturer data, but also on systematic retesting of the vaccine lots by an independent laboratory (NCL – National Control Laboratory), should evolve.

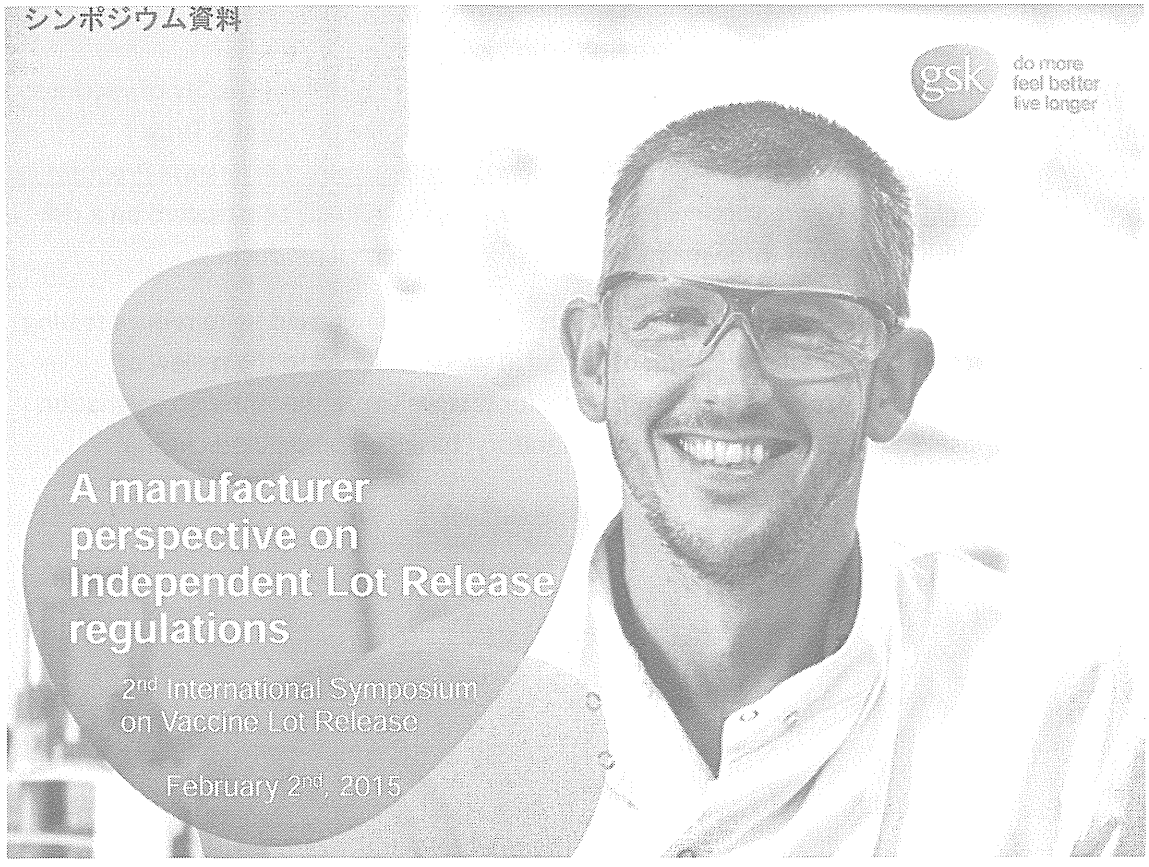
Indeed, in many countries, the NCL is actually re-performing all the Quality Control tests required for the evaluation of the final product (and sometimes on bulks as well), while the added value of this complete testing may be questioned on a risk / benefit ratio to Public Health perspective. In Europe, where the system has already been somewhat optimized, only a selection of tests, most relevant to Safety and Efficacy are selected for the evaluation process. Those requirements are described in technical guidelines which are publicly available on the *EDQM website*. However, this selection process could also be further improved to take into account the Manufacturer's actual process and method capability to calculate the associated risk / benefit of testing from a Public Health perspective. Several examples presented showed that for highly robust processes, retesting do not actually bring added value as the Manufacturer's Quality System will readily catch substandard lots. The usefulness of the system is most apparent for lots / processes that are close to the specification limits. In those instances, retesting will significantly reduce the risk of allowing a substandard lot being marketed. The model also highlighted the paramount importance of the performance of the assay at NCL level, as any added variability or bias will severely lower the capacity of the NCL to actually detect and reject substandard lots. That also in addition the difficulties generated in terms of technical support required from Manufacturers to support the systems on a worldwide perspective.

Based on those analyses, Manufacturers strongly support that the system is now ready to embed some possibilities of waivers for the testing part of the Independent Lot Release process. Indeed, since the implementation of the system, the technical and regulatory environment has seen drastic

changes and improvements which contributed to more robust and consistent Quality of vaccines. This approach has already been implemented by several Agencies, like the Food & Drug Administration (FDA – US) or Health Canada (BGTD *Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs*) where vaccines evaluation program is actually constructed on a risk-based approach revolving around three main categories for commercial products.

Manufacturer's recommendation for the Japanese Lot Release system would be to reduce testing requirements based on a risk-based selection of critical assays associated to the review of production and control protocols, and make provision for test waivers either through a variation process or a proposal submitted by the National Laboratory, based on predefined criteria.

シンポジウム資料



Agenda

1. Introduction
   - ✓ Original concept behind lot release of vaccines in EU
   - ✓ Legal context within EU
   - ✓ Legal context outside of EU
2. Testing as part of Independent Lot Release
   - ✓ Modeling the risk
   - ✓ A fictional example
   - ✓ A real example
   - ✓ In the "grey zone"
   - ✓ Selection of tests
   - ✓ Technical support to NCLs : Manufacturer challenges
3. Risk-based approach to Independent Lot Release
   - ✓ Test waiving

Introduction

Introduction

- Manufacturers in general :
  - *Recognise the benefits of Independent Lot Release and its added value on a global scale for Public Health, Public Health Authorities and Industry*
  - *Share the same common goal to ensure the availability of safe, efficacious and high quality medicines*
- Manufacturers would like to continue to develop the process and explore proposal for improvement in order to maintain the sustainability of the system current benefit to Public Health
- This has to be viewed in light of :
  - *the return of experience from Manufacturers with the Independent Lot Release processes*
  - *the ever increasing market pressure to sustain vaccines availability and the increasing number of manufacturers, products and product batches, and limited resources available to the National Control Laboratories*

Introduction

Original concept behind lot release of vaccines in EU

- **Product**
  - Biological nature versus well characterized products
  - Complex mixture of one or more active ingredient(s) with immonustimulant and/or adjuvant versus one active ingredient and its excipients.
  - One product targeting various diseases and indirectly through the immune system
- **Process**
  - Inherently variable source materials/biological systems
  - Complex production systems
  - Requiring assays by methods subject to variation (*e.g.in vivo*)
  - Reference materials with same inherent variability
- **Population**
  - Prophylactic medicines
  - Target : healthy children / adults
  - Vaccination policies defined by international agencies (WHO, EMEA, CDC,...) and by local governments

Confirmation of the Quality and Safety by retesting by an independent Control Laboratory

Introduction

Legal context within EU (1)

- EU : Official Control Authority Batch Release (OCABR), under EDQM oversight
- As part of the regulation of biological medicinal products, Article 114 of Directive 2001/83/EC relating to medicinal products for human use, as amended by Directive 2004/27/EC, of the European Parliament and of the Council provides that a Member State laboratory may test a batch of an immunological medicinal product before it is placed on the market
- Once OCABR is required by EMA / NRA, samples of **each** batch has to be submitted to one OMCL for examination (mutual recognition system : 1 batch = 1 official release)
- Official Medicines Control Laboratories (OMCLs) support regulatory authorities in controlling the quality of medicinal products for human and veterinary use available on the market

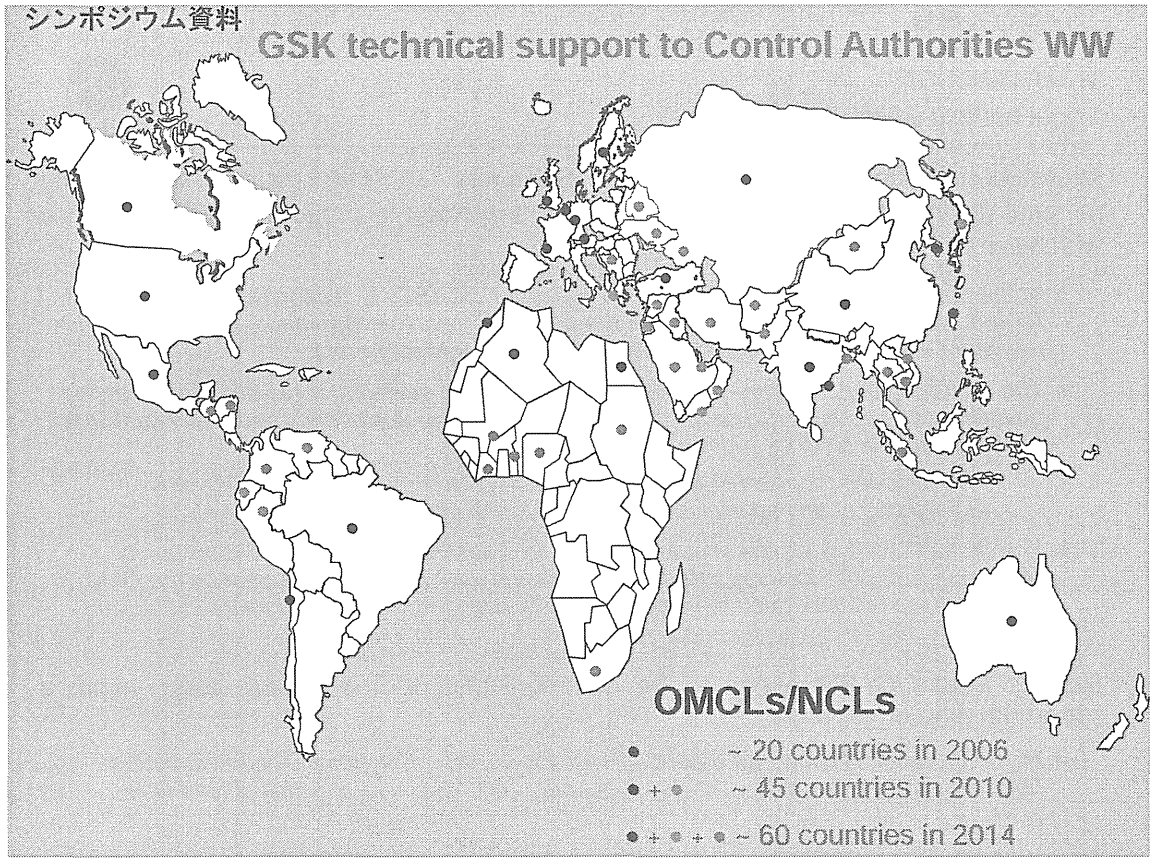
Introduction
Legal context within EU (2)

- Information to be provided to OMCLs (Summary Lot Protocols), as well as the minimal testing requirements performed are described in product specific guidance which are available on the EDQM website.
  - *At the time of submission the OMCL(s) eligible for OCABR, in collaboration with the Rapporteur and Co-rapporteur, signal the need to prepare an appropriate guideline to the relevant OCABR drafting group and/or the OCABR Advisory group*
  - *The drafting group/Advisory group determines if a new guideline is needed, if an existing guideline can be revised to cover the needs or if existing guidelines are already sufficient to cover the new product and reacts appropriately*
    - ✓ *This includes proposal of a list of tests to be performed during OCABR and highlighting of any special issues related to the model protocol*
  - *The draft OCABR guideline should be ready for adoption at the time the Community Marketing Authorization is granted. The guideline will be formally adopted by the OMCL batch release network once the Community Marketing Authorization has been finalized.*
- Results from OCABR needs to be communicated to the Manufacturer within a maximum time of *60 days*
  - *However, process allows for a parallel submission, where samples can be submitted before the lot is released by the Manufacturer ; this helps a lot in terms of lead time*

Introduction
Legal context outside of EU

- Independent batch release procedure is not limited to EU. For several countries, this requirement is already well established, e.g. :
  - *US : 21 CFR 610 GENERAL BIOLOGICAL PRODUCTS STANDARDS : Subpart A – release requirement (610.2 Requests for samples and protocols; official release.)*
  - *Canada : section C.04.015 of the Food and Drug Regulations and associated Lot release program for schedule D (**Biologic**) Drugs*
  - *Japan : article 42(1) and (43) of the Pharmaceutical Affairs Law and associated Minimum Requirements for Biological Products*
  - *South African Regulation 44 pertaining to Act 101 (Medicine Act)*
  - *Etc...*
- International countries have recently introduced specific requirements for the marketing and release of biological products on their local markets following the WHO guidance document on independent batch release (WHO/BS/10.2128)

シンポジウム資料


GSK technical support to Control Authorities WW
OMCLs/NCLs
~ 20 countries in 2006
~ 45 countries in 2010
~ 60 countries in 2014


gsk
Testing as part of Independent Lot Release
2nd International Symposium On Vaccine Lot Release
02 February 2015
10

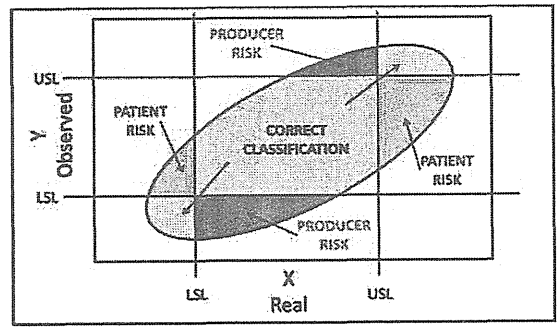
Testing as part of Independent Lot Release
Introduction

- With the exception of EU, most of the Independent Lot release regulation rely on a full testing of the final container (sometimes also on bulk material) for the assessment of individual lots
- However, WHO acknowledged that laboratory testing by an NCL should only be considered under defined circumstances, where it provides added value to the evaluation being performed.
  - *It also advise that when NCLs receive only a handful of lots, testing can represent a challenge in regards to maintaining experienced, competent and skilled laboratory staff required to generate meaningful data needed to verify the test results of the Manufacturer*
- Question is :

  ➔ *Can we model the risk / benefit ratio of retesting by NCLs ?*
- GSK has developed a statistical model that can estimates the impact of NCL retesting both on manufacturing activities (i.e. "Manufacturer risk"), as well as on a Public Health perspective (i.e. "Patient risk")

Testing as part of Independent Lot Release
Modeling the risk....

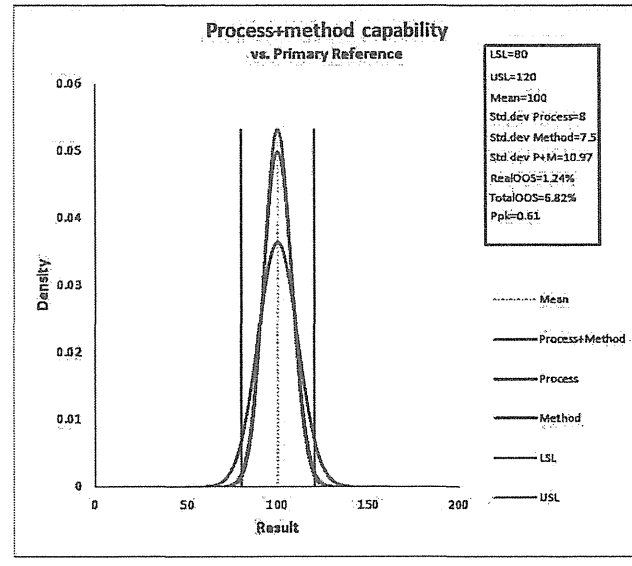
- The following diagram summarizes the combination of both process variability (« real value » of a batch Quality attribute) and analytical one (« observed or measured value ») :



- Both OMCL and Manufacturer's testing objective is to reduce batch misclassification
  - *Patient risk is bound to the misclassification of a non-compliant batch as within specification*
  - *Manufacturer risk is bound to the misclassification of a compliant batch as being out-of-specification*

Testing as part of Independent Lot Release
A fictional example

- Let's us pick up a theoretical example of a potency assay with a specification set to 80 – 120 % of nominal content
- For this example, a centered process at the target concentration is selected, with a variability of 8 %. The product would be assayed by ELISA (7.5% variability)
- If we assume a normal distribution, we obtain the following profiles :



- Which we can model into probabilities…..

Testing as part of Independent Lot Release
A fictional example

- Manufacturer perspective…..

Lower Spec. Limit	80
Upper Spec. Limit	120
Average Process	100
Std.dev Process	8.0
Var Process	64
Std.dev method GSK	7.5
Variance Method GSK	56
Std.dev Process + Method GSK	11.0

Theoretical OOS rate based on process variability ("real" OOS rate)	1.2%
Theoretical Good batch rate based on process variability ("real" Good batch rate)	98.8%

Producer risk (Good Batches Falsely declared FAIL)	6.04%
Patient risk (Bad Batches Falsely declared PASS)	0.46%

- NCL perspective…

OMCL Bias vs GSK	0.0
Std.dev method OMCL	7.5
Variance Method OMCL	56
Std.dev Process + Method OMCL	10.97

Assuming equal performance and no bias….

Good Batches declared PASS at Manufacturer and FAIL at NCL	5.67%
Bad Batches declared PASS at Manufacturer and PASS at OMCL	0.17%

➔ An additional 1 out of 20 lots will be potentially rejected by NCL

➔ Patient risk reduced by a three-fold

Testing as part of Independent Lot Release
A real example – HiB PRRP by HPLC

- Manufacturer perspective.....

Lower Spec. Limit	80
Upper Spec. Limit	120
Average Process	98
Std.dev Process	3.2
Var Process	10
Std.dev method GSK	2.6
Variance Method GSK	7
Std.dev Process + Method GSK	4.1

Theoretical OOS rate based on process variability ("real" OOS rate)	0.0%
Theoretical Good batch rate based on process variability ("real" Good batch	100.0%

Producer risk (Good Batches Falsely declared FAIL)	0.00%
Patient risk (Bad Batches Falsely declared PASS)	0.00%

- NCL perspective...

OMCL Bias vs GSK	0.0
Std.dev method OMCL	2.6
Variance Method OMCL	7
Std.dev Process + Method OMCL	4.12

Assuming equal performance and no bias....

Good Batches declared PASS at Manufacturer and FAIL at NCL	0.00%

➔ No increased risk of lot rejection by NCL

Bad Batches declared PASS at Manufacturer and PASS at OMCL	0.00%

➔ No additional benefit for Patient risk.

Added value of NCL testing ?

Testing as part of Independent Lot Release
In the "grey zone" – HiB PRRP alternative scenario (1)

- Manufacturer perspective.....

Lower Spec. Limit	80
Upper Spec. Limit	120
Average Process	98
Std.dev Process	3.2
Var Process	10
Std.dev method GSK	2.6
Variance Method GSK	7
Std.dev Process + Method GSK	4.1

Theoretical OOS rate based on process variability ("real" OOS rate)	0.0%
Theoretical Good batch rate based on process variability ("real" Good batch	100.0%

Producer risk (Good Batches Falsely declared FAIL)	0.00%
Patient risk (Bad Batches Falsely declared PASS)	0.00%

- NCL perspective...

OMCL Bias vs GSK	1.0
Std.dev method OMCL	10.0
Variance Method OMCL	100
Std.dev Process + Method OMCL	10.50

NCL is using a colorimetric assay (orcinol) with a pre-treatment of the samples (dialysis)

Good Batches declared PASS at Manufacturer and FAIL at NCL	5.79%

➔ 1 out of 20 lots will be potentially rejected by NCL

Bad Batches declared PASS at Manufacturer and PASS at OMCL	0.00%

➔ No additional benefit for Patient risk.

Added value of NCL testing ?

シンポジウム資料

Testing as part of Independent Lot Release

In the "grey zone" – HiB PRRP alternative scenario (2)

- Based on the same process and method performance, let's see what would happen if the process would drift from its nominal value (100%) towards 70 %
- What would now be the impact of NCL retesting on both Manufacturer risk and Patient risk ?

Both laboratories are using the HPLC assay

		"Manufactuer risk" (%)		"Patient risk" (%)	
		@ Manuf	@ Manuf + NCL	@ Manuf	@ Manuf + NCL
Process average (%)	90	0.7	1.4	0.0	0.0
	85	7.2	13.9	1.9	0.6
	80	10.9	19.4	10.9	2.4
	75	1.9	3.2	7.2	0.6
	70	0.0	0.1	0.7	0.0

NCL is using the colorimetric assay

		"Manufactuer risk" (%)		"Patient risk" (%)	
		@ Manuf	@ Manuf + NCL	@ Manuf	@ Manuf + NCL
Process average (%)	90	0.7	15.6	0.0	0.0
	85	7.2	30.7	1.9	0.9
	80	10.9	25.1	10.9	4.8
	75	1.9	3.5	7.2	2.4
	70	0.0	0.1	0.7	0.1

- In both instances, the maximal patient risk is reached when the process mean is at the specification limit. The maximal patient risk zone is contained within a ± 2 σ (method) from the limits.
- When the process drift outside of this zone, both laboratories are able to correctly classify the evaluated lots
- *Note that the use of the colorimetric assay significantly degrades the manufacturer risk*

Testing as part of Independent Lot Release

In the "grey zone" – HiB PRRP incident scenario

- Now based on the previous HiB data, let's imagine an hypothetical case where the actual batch under evaluation is really out-of-specification, but was not captured as such by the Manufacturer Quality System
- What would be the probability of NCL testing to reject the lot ?

		NCL test method	
		HPLC	Colorimetric
Lot true value (%)	80	50.0	46.2
	78	77.9	53.8
	76	93.8	61.2
	74	98.9	68.3
	72	99.9	74.8
	70	100.0	80.4
	65	100.0	90.9
	60	100.0	96.5
	55	100.0	98.9
	50	100.0	99.7

- With the HPLC assay, sub-potent lot (< 75% in content) would be readily captured by the testing at NCL
- However, with the colorimetric assay, this is not the case. Only largely sub-potent lot (< 65%) would be rejected with a strong confidence

Testing as part of Independent Lot Release
Selection of tests

- In addition to the risk modeling, one can also ask about the scope / relevance of some tests which are frequently required by National Control Laboratories
- Examples ....
  - *Sterility testing* *(Table extracted from TGA guidelines for sterility testing of therapeutic goods)*

    Probabilities of detecting a contaminated lot in a single test

Percentage of items contaminated	0.1 %	1.0 %	2.0 %	5.0 %
Sample size 10	1 %	9 %	18 %	40 %
Sample size 20	**2 %**	**18 %**	**33 %**	**65 %**
Sample size 50	5 %	39 %	64 %	92 %
Sample size 100	9 %	100 %	87 %	99 %

Low probability to detect a non-sterile lot, unless heavily contaminated

If the test is repeated the probability of including a contaminated item remains the same. However, the probability of both tests being positive is the product of both individual probabilities which is lower than the probability of a single test.

Useful to include into testing program from NCL ?

Testing as part of Independent Lot Release
Selection of tests

- *Abnormal Toxicity test (ATT)*

  Test originally designed in the early 1900's to detect phenol (used as preservative) in biological preparation (1) and later on shifted to its current use

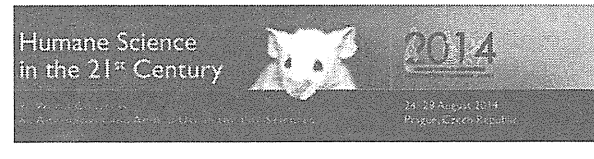
  The Ph.Eur. deleted the ATT as a final product test in 1995 after a retrospective analysis had shown that the test served no useful purpose anymore (all batches passed the test)

  However, after 20 years the test is still stipulated in other parts of the world (regulations from WHO, Japan, Russia, China, India ...)

  - *Although FDA recently published a proposal to modify as well general safety test (GST) requirements for erroneous toxic contaminants in inactivated influenza vaccines, allergenic products and other biologics intended for human use*

Should this test continue to be included into testing program from NCL ?

(1) Klaus Cussler (PEI – Germany) at the



Testing as part of Independent Lot Release

Technical support to NCLs : Manufacturer challenges

- Different methods of analysis used by the Manufacturer and by the NCL
  - *Acceptance criteria registered in the MA used by the NCL*
  - *Assay difference may increase the risk of discrepant data*
- Some acceptance criteria for specification can be close to the overall manufacturing variability
  - *Testing performed in different laboratories with different equipment, operators, environment = different lab performance*
  - *Increase the risk of OOS and of rejecting a « good » batch*
- For the sake of independency, or due to local political context, some NCLs are reluctant to communicate with Manufacturers
  - *Some root cause for failure not identified and recurrent OOS situation faced*
  - *Drift in the method of analysis at NCL not identified on time*
  - *Late communication to the Manufacturer can impact lot release and patient availability of the vaccine.*

Testing as part of Independent Lot Release

Technical support to NCLs : Manufacturer challenges

- Technical support activities requires the supply of proprietary QC reagents
  - *Strain on manufacturer stock – need of more frequent bridging*
  - *Requirements for customs clearance / regulations makes it difficult to sustain NCLs in some countries*
- Moreover, in some countries, high turn-over in NCLs scientist makes it difficult to establish good relationship to efficiently support their activities or to efficiently maintain technical know-how

シンポジウム資料

Testing as part of Independent Lot Release
Conclusion

- Under nominal / controlled condition, the added value of testing in the evaluation of vaccine lots performed by National Control Laboratories is depended on :
  - *The nature / scope of the test being considered*
  - *The overall variability of the manufacturing process (method and production) as compared to the specification*
- In order to ensure the full benefit of the testing, the method used by National Control Laboratories should be the same as the one from the Manufacturer (or possess at least equivalent precision), and shows no bias
  - *Formal test transfer should be considered to properly assess test performance at both end*
  - *Regular comparison / monitoring of test data from Manufacturer and NCL should be considered to ensure satisfactory performance over time*
- The full potential of testing by National Control Laboratories is achieved only for lots close to the specification limits or in incidental situations
  - *highly sur / sub-potent lots should be captured by the testing in place at Manufacturer*

Risk-based approach to Independent Lot Release

Risk-based approach to Independent Lot Release
Introduction

- As regards the origin of the lot release regulations, Vaccines technical and regulatory environment has seen drastic changes and evolutions such as :
  - *Improvements in sterility insurance principles – update to Annex 1*
  - *Implementation of Risk management (ICH Q9) and Pharmaceutical Development (QbD initiative)*
  - *Increase in number of cGMP inspection, both domestic and from abroad*
- In addition, since the implementation of the Independent Lot Release process, tremendous experience has been accumulated by the National Control Laboratories about Manufacturers and established product lines
- Manufacturers consider that the system could still be further refined to ensure continuous application of the current system to new products / new manufacturers, while for established products, testing waivers should be considered (*risk-based approach*)

Risk-based approach to Independent Lot Release
Test waiving

- Test waiving is already implemented by :
  - *US FDA (Federal Register, Vol 58 (1993), 137, pages 3871)*
  - *Based on acceptable lot release history, continued control of the manufacturing process and facility (inspection history), description of major process changes, complaints and CAPAs.*
  - *Above information is submitted as a Pre-Approval Supplement (PAS)*
- Is also part of the regulation of some EU Member States
  - *see article 32 of the German Drug Law*
- And is in line with WHO recommendation on Independent Lot Release :
  - *"...Independent lot release involves the confirmation that each lot meets the specifications in the approved marketing authorization for the product. Under defined circumstances, laboratory testing by an NCL can provide added value to this confirmation. The need for testing should however be justified according to criteria as specified in this document and the laboratory should operate under an appropriate quality assurance system..."*

Risk-based approach to Independent Lot Release

Test waiving

- In a risk-based concept, probably the most evolved regulation for Independent Lot Release is Health Canada Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs
- BGTD takes a risk-based approach to Independent Lot Release of biological products. The degree of oversight to which a Schedule D (biologic) drug is subjected is based on :
  - *Product indication*
  - *Nature of the Product*
  - *Production History*
  - *Inspection History*
- The different level of oversights for registered products are :
  - *Group 1: pre-approval stage (IND's)*
  - *Group 2: Sample Testing and Protocol Review*
  - *Group 3: Protocol Review and Periodic Testing*
  - *Group 4: Notification and Periodic Testing*

Risk-based approach to Independent Lot Release

Test waiving

- The initial assignment of a product to an Evaluation Group upon receiving approval is at the discretion of BGTD, taking into account considerations outlined above
- Products that are manufactured from well controlled raw materials through reliable and consistent processes, and that can be readily assessed with respect to identity, purity and potency through reliable test protocols may be assigned to Evaluation Group 4 at the time of approval
- Based on the accumulated knowledge on the product and Manufacturer, the degree of oversight to which a Schedule D (biologic) drug is subjected can change

Risk-based approach to Independent Lot Release
Conclusion

- Based on the above examples and previous discussion about testing efficiency, there is an opportunity to evolve the concept of Independent Lot Release
  - *Full testing should be replaced by a selection of the most relevant assay ; statistical models can help in selecting the most appropriate ones so as to insure Public Safety*
  - *Systematic testing could be discontinued and replaced by evaluation of the manufacturer data through SLP review and a monitoring of product consistency*
  - *In that context, testing could be considered by NCL when a trend is identified or when the batch under evaluation is deemed out-of-consistency (OOC)*

- Networking and / or recognition of the decision of another regulatory authority should also be considered / encouraged
  - *Already recommended by WHO*
  - *Memorandum of Understanding signed between BGTD and EDQM – information on batches and testing is now shared between both entities*
  - *Israel has signed an ACAA with the EU. All rules for OCABR in the EU/EEA apply also to Israel for vaccines.*

Risk-based approach to Independent Lot Release
Conclusion

- Similar systems of test waiver or reduced testing based on the following assumptions could be considered :
  - *An administrative release by NCLs based on the review of manufacturer's production and control protocol*
  - *No systematic re-testing by the NCL of every batch before release onto the market for well known vaccines*
  - *But with periodic testing of the OMCL under defined conditions for monitoring purposes and for retaining technical expertise*

- Conditions to be granted reduced testing scheme could be based upon (e.g. BGTD guidelines) :
  - *Product indication*
  - *Nature of the Product*
  - *Production History*
  - *Inspection History*
  - *Post marketing surveillance*