SYSMEX EDUCATIONAL ENHANCEMENT AND DEVELOPMENT | JUNE 2017

SEED HAEMATOLOGY

The new Sysmex rule set of the *Extended* IPU implements biomedical validation rules according to peer-reviewed recommendations

'The challenges we face today are less about being able to produce information but rather about how to process information.'

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Why Sysmex started developing validation tools

Since the mid-1990s Sysmex has always supplied a rule-based, primarily technical validation tool for haematological analysis results (see Fig. 1), which was later developed further to include body fluid and urinalysis results.

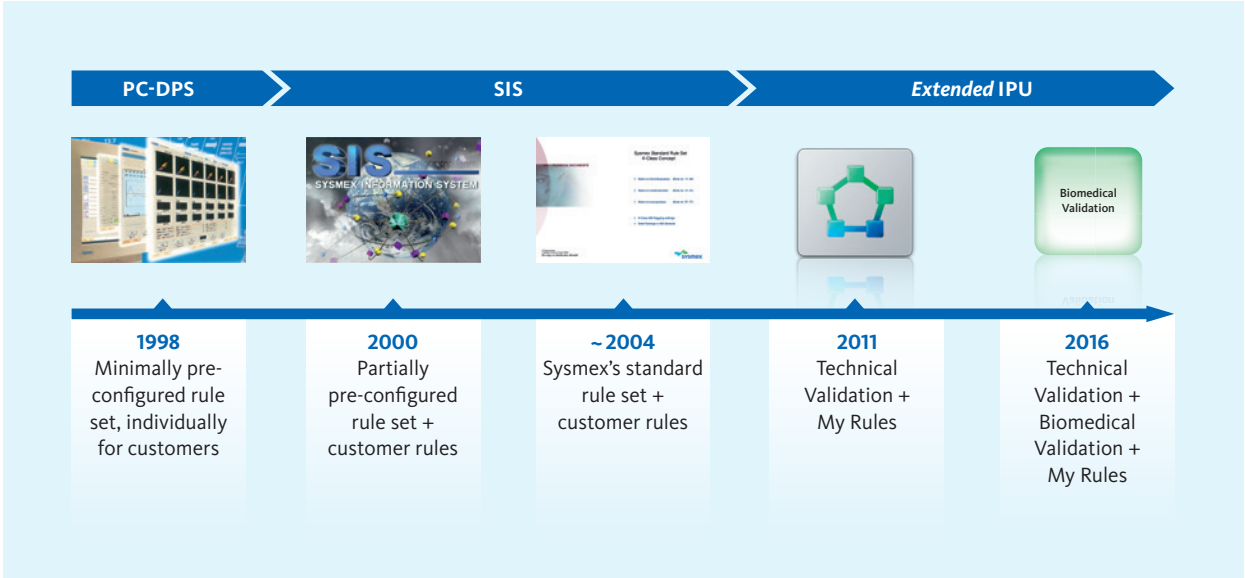

Fig. 1 *The evolution of Sysmex's validation rule sets*

The primary purpose of these systems was to ensure reliable analysis results with the aid of a standardised workflow. Today Sysmex's rule-based validation solution offers, above all, the advantage that the results can be reported at any time with a high degree of reliability, continuity and with unwavering quality – regardless of the level of experience of the staff in a particular laboratory or a specific shift.

One aim of a rule-based solution is to make full use of the technical capabilities of the analytical system(s). On the other hand, economic aspects matter: repeat and reflex measurements as well as the labour-intensive morphological evaluation of smears must be put to best technical and clinical use to optimise the workflow and cost-benefit ratio in the laboratory.

Sysmex's rule sets have always been built on the analytical specifications of the analyser model and class they were designed for. For instance, if interferences have been detected in the initial measurement, there are specific rules to use an alternative method as a reflex test. The interferences as well as the suggested reflex tests are dependent on the actual analyser configuration. To name an example, in the presence of red blood cell fragments an impedance-based platelet result will almost always be falsely elevated. A repeat measurement using the same technology would only confirm the incorrect result, while the use of a fluorescence-based platelet measurement (e.g. PLT-F) will deliver a correct result in the vast majority of cases. By automatically recognising interferences and sensibly controlling repeat measurements, samples can be processed and validated irrespectively of the laboratory staff's know-how.

Many rules do not only assess individual parameters but monitor the constellation of several parameters for medically implausible patterns. Such special characteristics of technical validation may eliminate the need for many cost-intensive repeat measurements while also increasing the sensitivity of pointing out abnormal analysis results, particularly if these would otherwise not have become immediately evident.

The know-how from the last 25 years has been fed into the ever advancing and improving rule set used to date, which is embedded in the *Extended* IPU for all haematology systems, such as the XN-Class, and which works with more than 30 rules. It has been consistently adapted to the latest technological progress, frequently based on knowledge gained from new scientific publications.

However, there is an ever growing need for global standardisation, especially given the rapidly increasing number of accredited laboratories. There is also a great demand for authorised and generally applied decision criteria, based on expert recommendations, but also taking into account the technological developments over recent years. Relying on previously published guidelines proved problematic, as these largely failed to account for patient demographics (e.g. previous results, age, gender, etc.), medical recommendations and the latest technological capabilities.

A 'rule set' for haematology: technology-specific and based on the latest expert recommendations?

Following up on an idea from the International Society for Laboratory Hematology (ISLH), a group of 17 experts in cellular haematology including paediatric haematology formed in recent years and dealt intensively with standardisation in haematological practice. The primary objective of these experts who came together under the banner of the Francophone Group of Cell Haematology (GFHC) was – and still is – to evaluate, harmonise and standardise haematological practice in the context of laboratory accreditation. It has indeed been found that there is still a very heterogeneous assessment of when a blood smear should follow the automated test.

There are hardly any national or local regulations for the direct handling of validation processes to date. On the other hand, the rules applied in a wide range of laboratories have a largely similar general structure.

The first summary of the evaluation by the GFHC was published in March 2014 [1]. The consensus of this expert group was to make recommendations for follow-up actions of automatic blood counts with blood smear microscopy or by extending the analysis profile to include reticulocytes, for example in the case of anaemia.

The proposals and considerations of this group are based on two main criteria: firstly, the discerning analysis of existing published recommendations, and secondly, a study of laboratory practice covering 39 laboratories with a large number of blood smears and that were prepared to answer questions on threshold values and criteria for a smear analysis. The study included private, hospital and university laboratories, using the analysis systems from all leading manufacturers.

All collected data were individually analysed and patient-relevant data, information on cell counts and published reference values from adults and children were taken into account (threshold values, qualitative analyser flags, previous values or a delta check).

The results of this expert group are based on a professional agreement and are published as a minimum recommendation. They largely serve biomedical validation and can be applied in equal measure to all types of laboratories. The conclusions take into account not just the pre-analytical phase, but also the analytical capabilities of the haematology system and its specifications.

The aim is to ensure patients receive the fastest and best possible care

Sysmex strives to follow the latest developments to focus on improved patient care. To this end, from software version 3.1 of the *Extended* IPU, the new rule set features not only the rules for *technical validation* but also for *biomedical validation,* following the consented recommendations of the GFHC.

The rules of technical validation should ensure a result that is technologically flawless and analytically exact, or detect clinically relevant deviations, and offer an automated method of checking doubtful results. These rule algorithms are therefore system-specific to a great extent and have to take the underlying technology with all its functional features and system limits into account. These rules are therefore implemented as a standard, based on more than 25 years of experience in this field.

Together with the progressive XN technology, the validation rule set can help to optimise the workflow in the laboratory and contribute to ensuring efficient patient care.

The biomedical validation rules follow the recommendations of the expert group of the GFHC and are underpinned by the suggested cut-off values, delta check values, and so on. They can be adapted as required and switched on or off.

Overview of the new rule set as of software version 3.1

1. Technical validation

The rules of technical validation should deliver accurate and technically sound analysis results (see Fig. 2). This includes, for instance, detecting false results with a clinical impact and, as a result, delivering a solution in the shape of a reflex measurement that represents the most economical option. All rules for technical validation depend directly on the recommendations of the manufacturer and the analytical capabilities the individual analyser offers. This is why the rules of technical validation are implemented firmly in the *Extended* IPU as standard. Table 1 gives an overview of all technical validation rules.

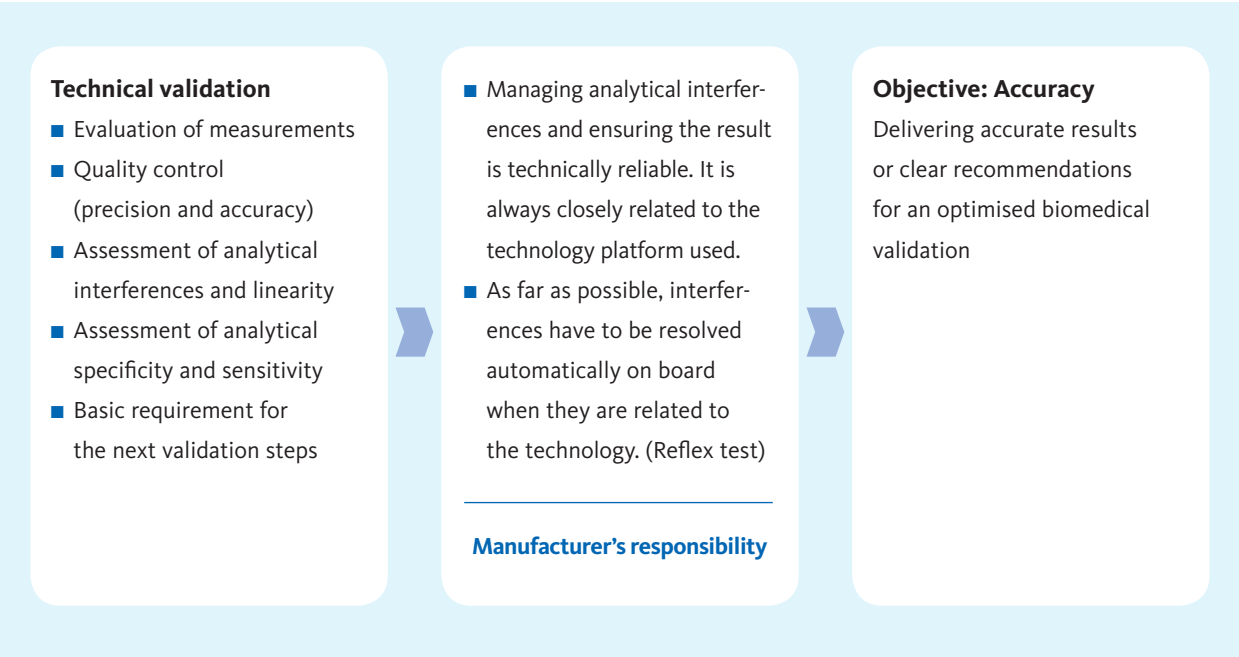

Fig. 2 *The aims of technical validation*

Table 1 *Overview of technical validation rules implemented in the Extended IPU*

Items incorporated into 'Technical Validation'	
Analyser issues	■ Insufficient sample mixing ■ Aspiration error ■ Analyser function error ■ Linearity limit ■ Capillary sample
Workflow issues	■ Initial order microscopy ■ Multiple runs ■ Analysis profile open
Result-related technical validation	
PLT	■ Check for clot ■ PLT Reflex (defined by analyser)
PLT Morphology	■ Platelet clumps? ■ Metrological interference
RBC	■ Cold agglutinins ■ Turbidity/HGB interference ■ RBC interference – high WBC ■ Interference or old sample ■ Deviation RBC and RET channel ■ Delta check MCV or MCHC
RET	■ Interference in the RET channel ■ Abnormal RET scattergram ■ RET-H_e low sensitivity
WBC	■ Abnormal WBC scattergram ■ Interference in the WBC channel ■ Deviation WNR and WDF channel ■ NRBC? (XN-L Series) ■ Low WBC count, diff not possible
WBC Morphology	■ Abnormal DIFF scattergram ■ Left shift? (band cells) ■ Interference Eos. count ■ Blasts/Abn Lympho? ■ Blasts/Abn Lympho? (Reflex to WPC channel) ■ Abnormal Lympho? (WPC channel) ■ Blasts? (WPC channel) ■ ImmGran? (X-Class)

The technical validation includes rules that

a. relate to and resolve problems concerning the blood sample, the sample volume or the analyser (e. g. insufficient blood volume or mixing, capillary blood measurement, etc.).
b. relate to the workflow (e. g. open analysis profile, initial orders, etc.).
c. detect interferences, morphological abnormalities, inaccuracies or other sample abnormalities (e. g. red blood cell fragments, linearity limits, clots, etc.) and, as far as possible, resolve these by activating alternative methods.

2. Biomedical validation

Once the analysis results have been technically validated and considered reliable, they can be looked at from a clinical angle to search for suspect results. The task of biomedical validation is to recognise abnormal or conspicuous quantitative results (see Fig. 3).

There is a reason behind every abnormal count. The main question to consider is: Does the patient face a hereditary or an acquired disease? In case of an acquired disease, the next question would be: Is it a reactive/inflammatory or a malignant condition? Based on the findings compiled by the GFHC, there are approximately 20 rules looking at things such as cut-off values, assessment of previous values or additional patient information. They also take into account whether the results are initial (a patient is measured for the first time) or already part of the follow-up of a patient.

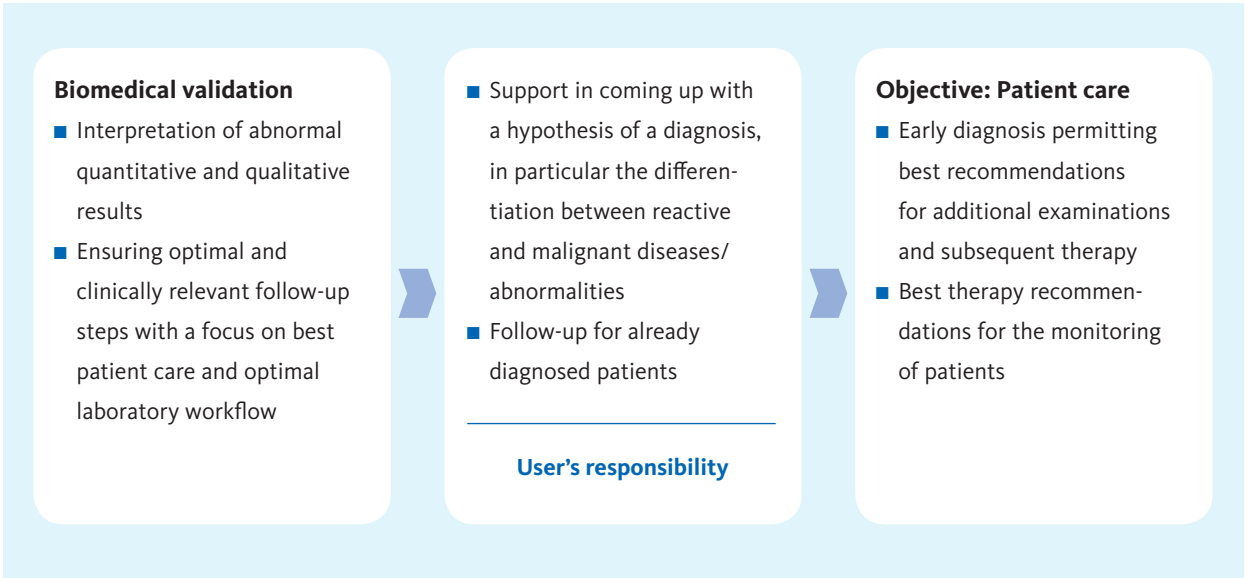

Fig. 3 *The aims of biomedical validation*

The latest findings from the GFHC evaluation reports that investigated the rules especially for the Sysmex analysers have already been included in the *Extended* IPU's rule set [2]. An overview of these biomedical validation rules is shown in Table 2.

The biomedical rule algorithms help to identify those findings for which follow-up tests, such as further microscopic assessment of the blood smear or an additional reticulocyte analysis, are recommended by experts because these tests are expected to deliver valuable additional diagnostic information.

Table 2 *Overview of biomedical validation rules recommended by the GFHC that have been implemented in the Extended IPU*

Items incorporated into 'Biomedical Validation'	
PLT recommendation	■ PLT low ■ Delta check PLT
RBC recommendation	■ HGB low (RET & SMEAR) ■ MCV low (RET) ■ MCV high (RET & SMEAR) ■ RDW high ■ Dimorphic population ■ Red cell fragments ■ NRBC present
RET recommendation	■ Reticulocytosis
WBC recommendation	■ Neutropenia ■ IG high ■ Lymphocytosis ■ Monocytosis ■ Monocytopenia ■ Basophilia ■ Eosinophilia ■ Leucocytopenia (DIFF) ■ Leucocytosis (DIFF) ■ Aplasia ■ Aplasia recovery

The biomedical validation rules recommend follow-up tests, such as microscopy of the blood smear or an additional reticulocyte analysis. *All biomedical rules are designed so as to assist in the diagnostic process as early as possible and to ensure a high quality level of patient monitoring.* This means each patient result is checked for an initial or a follow-up situation. The criteria for both are based on the GFHC recommendations and set for adults as well as for children.

These criteria as well as the biomedical validation rules as such can be customised to the specific laboratory's requirements, if needed.

The general recommendations of the GFHC were published in 2014. The original article can be downloaded free of charge (see link in reference [1]). Cornet *et al.* investigated the laboratory routine with Sysmex analysers and the rules recommended by the GFHC in place [2]. More than 30,000 samples were analysed in two university laboratories in this evaluation. The aim of those conducting the tests (members of the GFHC) was to evaluate and improve the biomedical validation rules in laboratory routine with regards to smear workflow. By means of various adjustments it was possible to reduce the smear rate by some 6 % without a loss of clinical benefit. The proposed modifications include an increase in the cut-off value for a smear for isolated cases of immature granulocytes (IG%) from 5 % to 10 %, and the rule that both an isolated thrombocytosis and a low MCV no longer result in a morphological assessment. Another adjustment is that no smear is produced if isolated 'Blasts/Abnormal Lympho?' and/or 'Atypical Lympho?' flags are detected within 72 hours and no abnormal cells were found previously in the smear and no other rule has been activated.

The co-operation with the GFHC during the implementation of the biomedical validation rules and their evaluation using Sysmex technology was very rewarding and showed several interesting areas to further investigate the biomedical validation rules using Sysmex technology. Based on the findings by Cornet *et al.*, Sysmex has adapted its 'Biomedical Validation' rule set and integrated the suggested changes for the 'IG high' rule (cut-off changed from 5 % to 10 %), 'thrombocytosis' rule (suppression of slides) and 'MCV low' rule (reflex for RET channel).

Following the philosophy of continuously advancing the rules to the latest findings, Sysmex will maintain to update the rule set accordingly.

What this means for you

The new Biomedical Validation rule set is pre-installed in the *Extended* IPU as of version 3.1. This means that from now on all installations of the *Extended* IPU will contain both the technical and biomedical validation rule set as described above. All rules will be discussed in detail with you personally within the rule set meeting.

If you are using an existing rule set in your *Extended* IPU you may, of course, continue to use this even after a software update.

Of course, there is also the option of upgrading your existing rule set to include the new 'Biomedical Validation'. Your Sysmex representative will be happy to make you a personal offer.

References

[1] ***Genevieve F et al.*** *(2014): Smear microscopy revision: propositions by the GFHC, Feuillets de Biologie (Vol LVI N° 317). Free download of the French and English version: http://www.gfhc.fr/fr/documents/page-2/*

[2] ***Cornet E et al.*** *(2016): Evaluation and optimization of the extended information process unit (E-IPU) validation module integrating the sysmex flag systems and the recommendations of the French-speaking cellular hematology group (GFHC). Scand J Clin Lab Invest. 76(6):465 – 71.*

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EN.N.06/17