Suggestions on how to manage the implementation of new I breakpoints and the ATU in the laboratory system

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How to apply in AST systems?

- New EUCAST “I” breakpoints
- ATU

Focus on automated systems

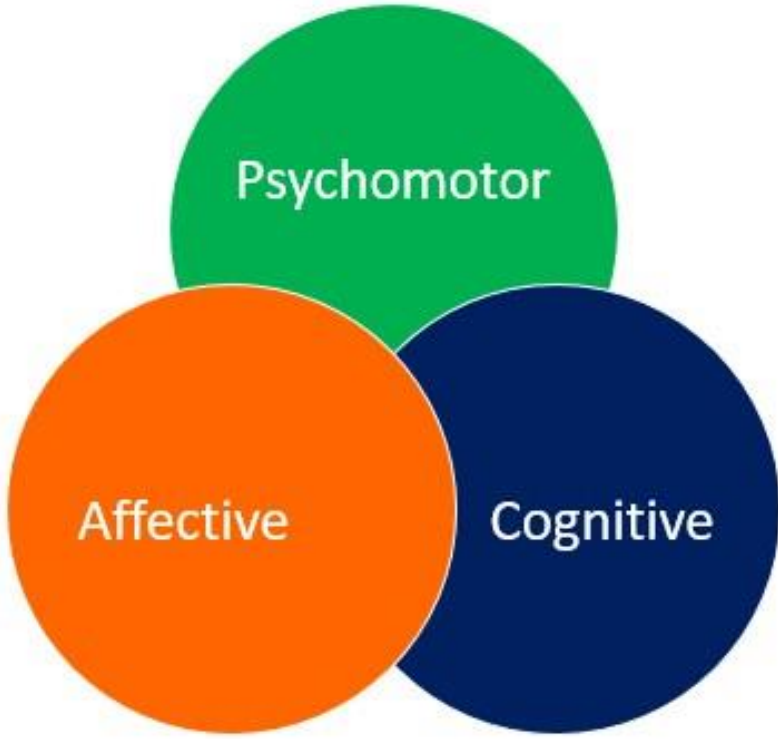
- Phoenix Becton Dickinson
- VITEK bioMérieux

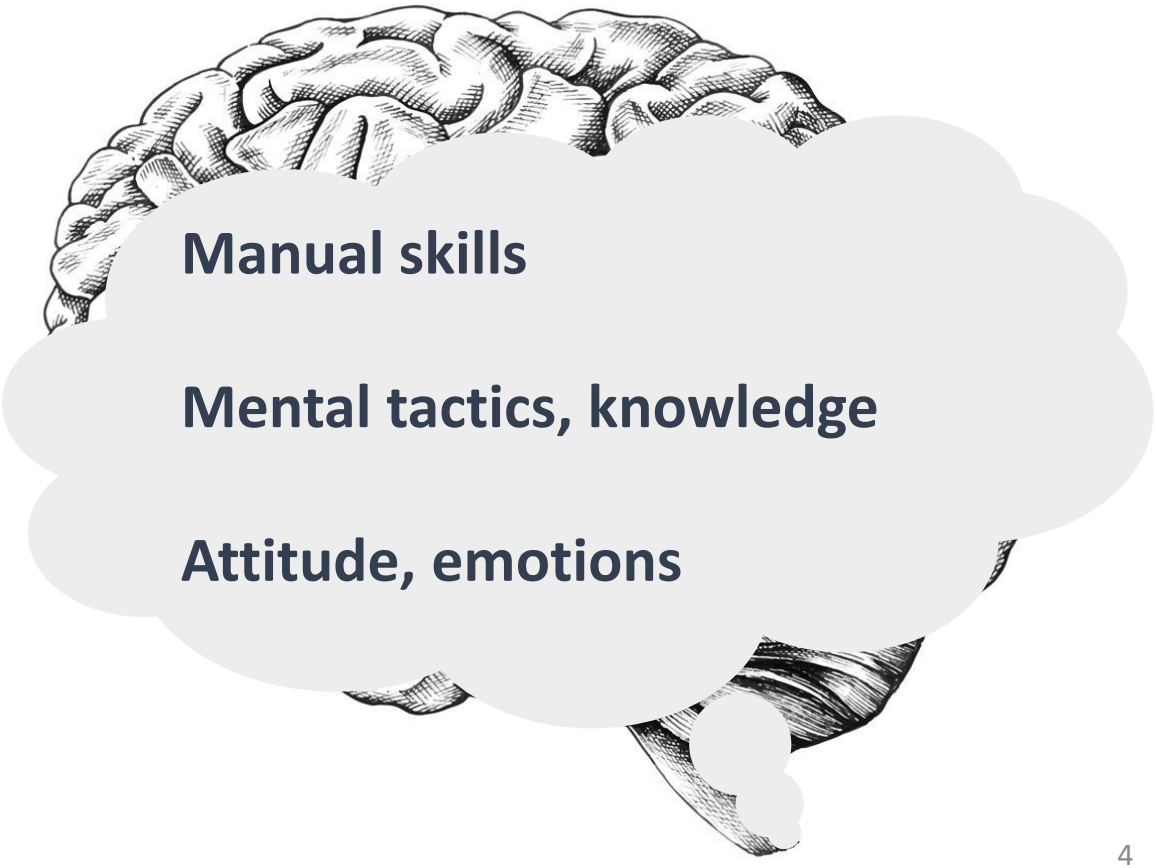
Off-scale breakpoints:

From two levels of resistance to two levels of susceptible?

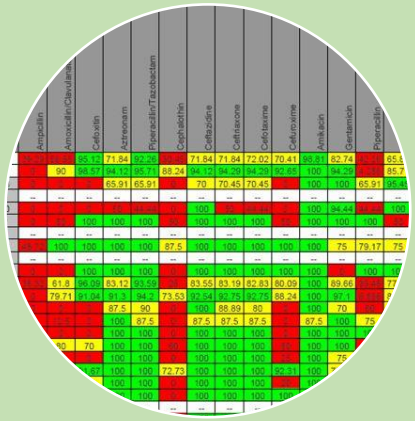
- Implementation in AST system
- Implementation in LIS
- Implementation for clinical use

Learning takes place in three domains…





Acting on different levels



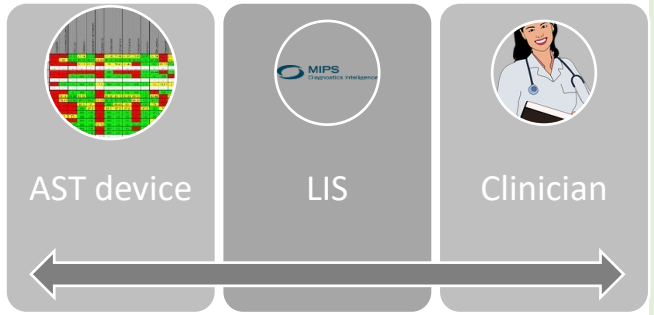
AST device

MIPS Diagnostics Intelligence

LIS

Clinician

Acting on different levels



- Drug
  - Type
  - IV/PO
- Bug
- Infection site
  - urine
  - other

- FQ/penicillins/temocillin/…
  - IV
- *Pseudomonas aeruginosa*
- Urine

EUCAST advice for off-scale breakpoints:

For these situations laboratories should consider adding a note about the need for high exposure, particularly with…

- *Pseudomonas* and piperacillin-tazobactam, ceftazidime, cefepime, imipenem, aztreonam, fluroquinolones, aminoglycosides.
- *Enterobacterales* and aminopenicillins (with or without inhibitor) and cefuroxime.

But how to implement?

INTRODUCTION IN VITEK AES

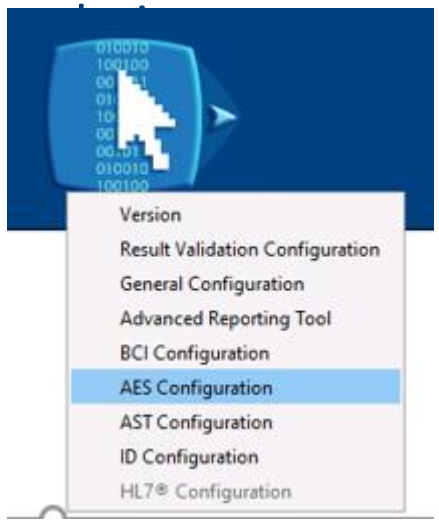
EUCAST breakpoints table V11 (2021) available at http://www.eucast.org

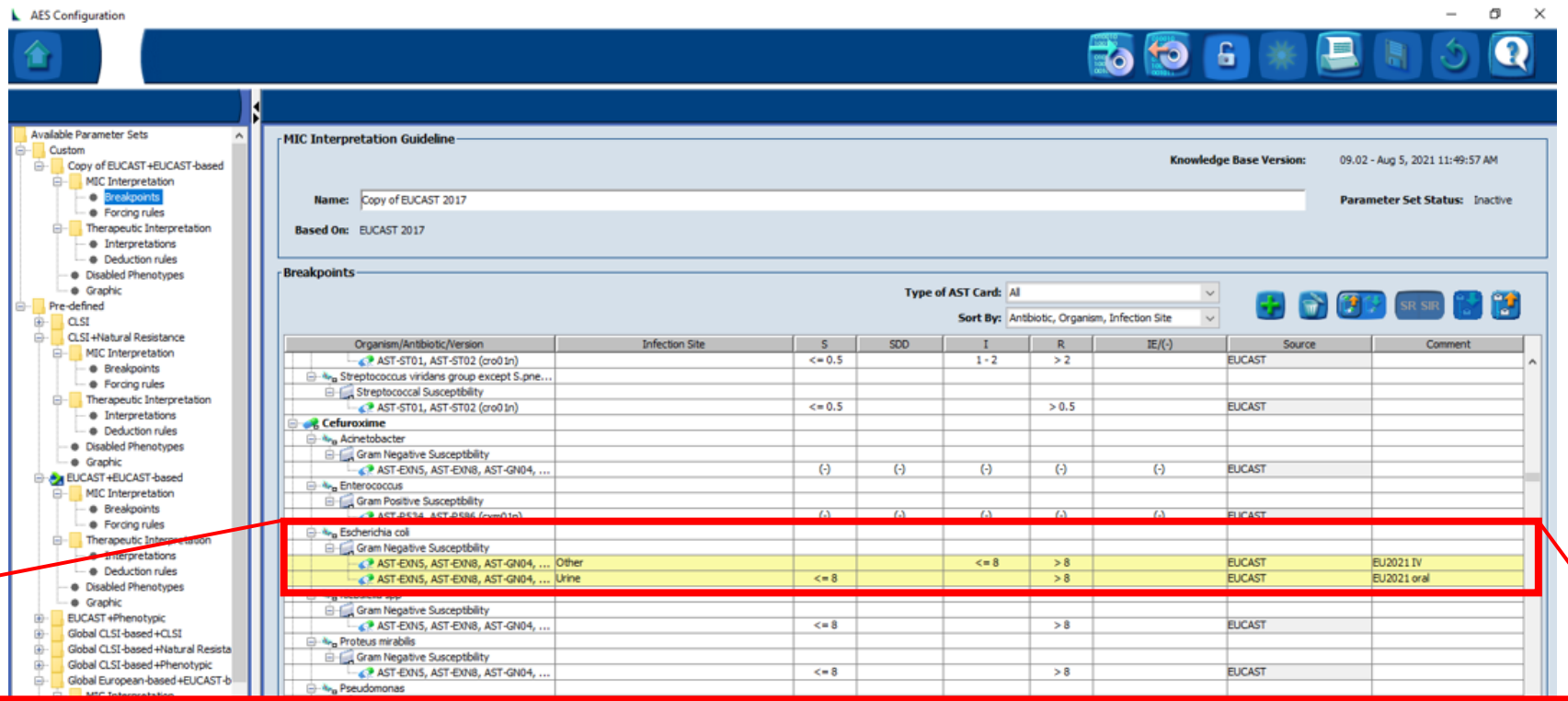
EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Cephalosporins[1]	MIC breakpoints (mg/L)		
	S ≤	R >	ATU
Cefuroxime iv, *E. coli, Klebsiella* spp. (except *K. aerogenes*), *Raoultella* spp. and *P. mirabilis*	0.001	8	
Cefuroxime oral (uncomplicated UTI only), *E. coli, Klebsiella* spp. (except *K. aerogenes*), *Raoultella* spp. and *P. mirabilis*	8	8	

Cephalosporins	Standard dosage	High dosage	Uncomplicated UTI
Cefuroxime iv	0.75 g x 3 iv	1.5 g x 3 iv	
Cefuroxime oral	0.25 g x 2 oral	0.5 g x 2 oral	0.25 g x 2 oral

AES CONFIGURATION - BREAKPOINTS



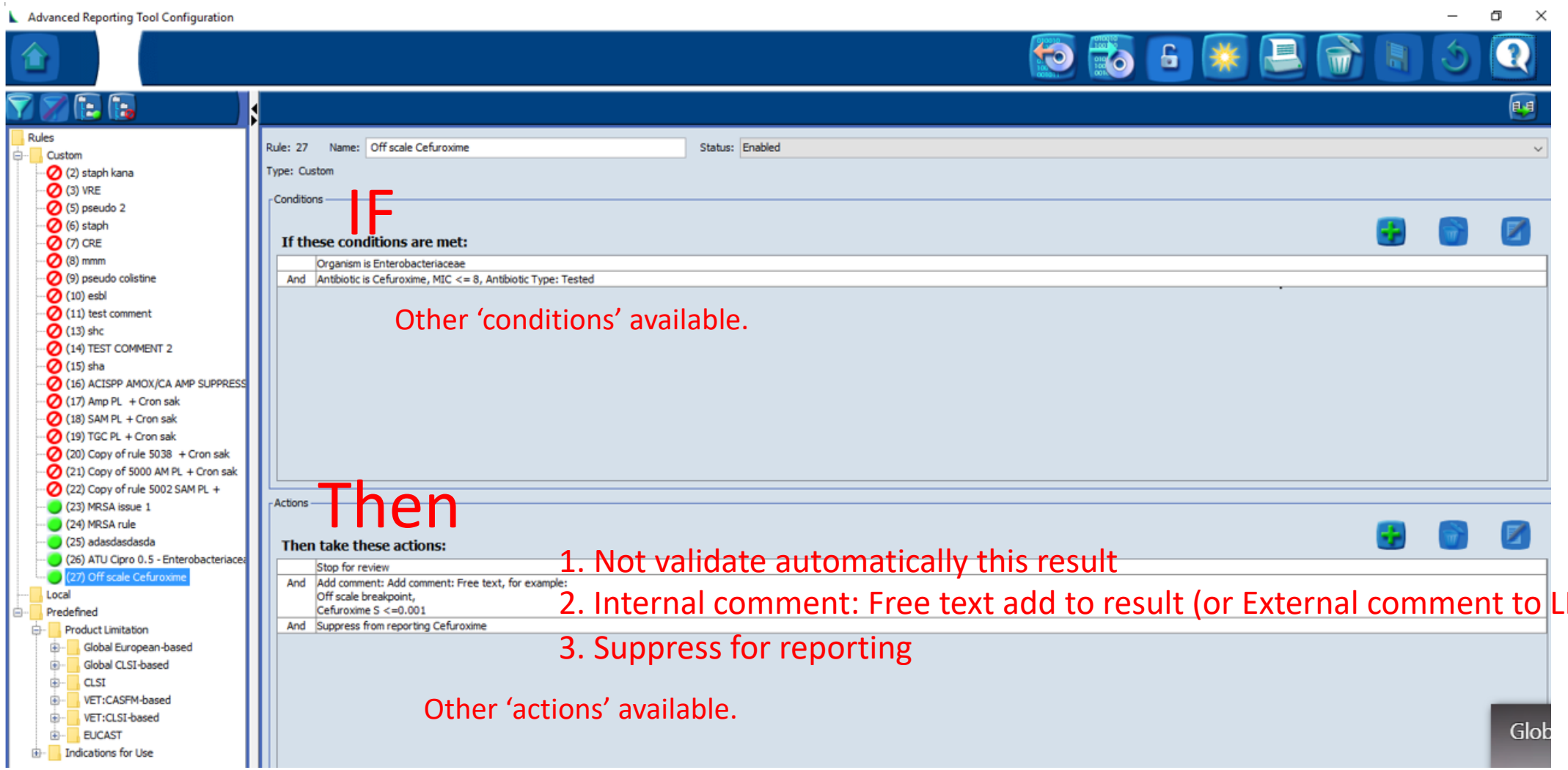


Organism/Antibiotic/Version	Infection Site	S	SDD	I	R	IE/(-)	Source	Comment
Escherichia coli								
Gram Negative Susceptibility								
AST-EXN5, AST-EXN8, AST-GN04, AST-N020, AST-N315, AST-NT...	Other			<= 8	> 8		EUCAST	EU2021 IV
AST-EXN5, AST-EXN8, AST-GN04, AST-N020, AST-N315, AST-NT...	Urine	<= 8			> 8		EUCAST	EU2021 oral

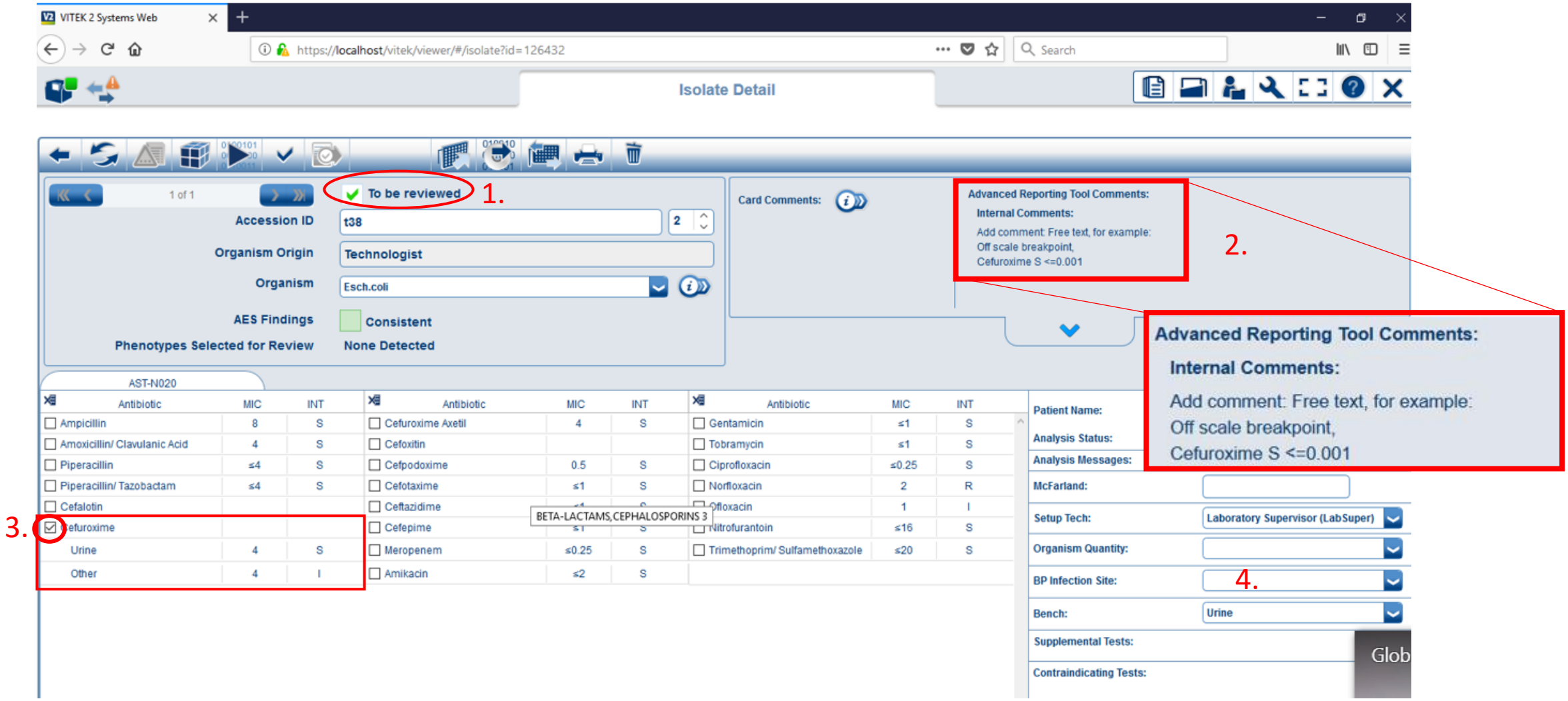
BIOART RULES

Not active

Active



RESULT SCREEN



HOW TO SEND TO LIS?

- Possibility 1:

Define a 'Breakpoint Infection Site', when loading the VITEK card,

Only 1 breakpoint will be taken in account.

So only one MIC and Interpretation will be sent to LIS

- Possibility 2

No infection site is introduced,

Both MIC's and Interpretations will be sent to LIS

LIS has to be programmed to receipt the right MIC/Interpretation, depending on the infection site.

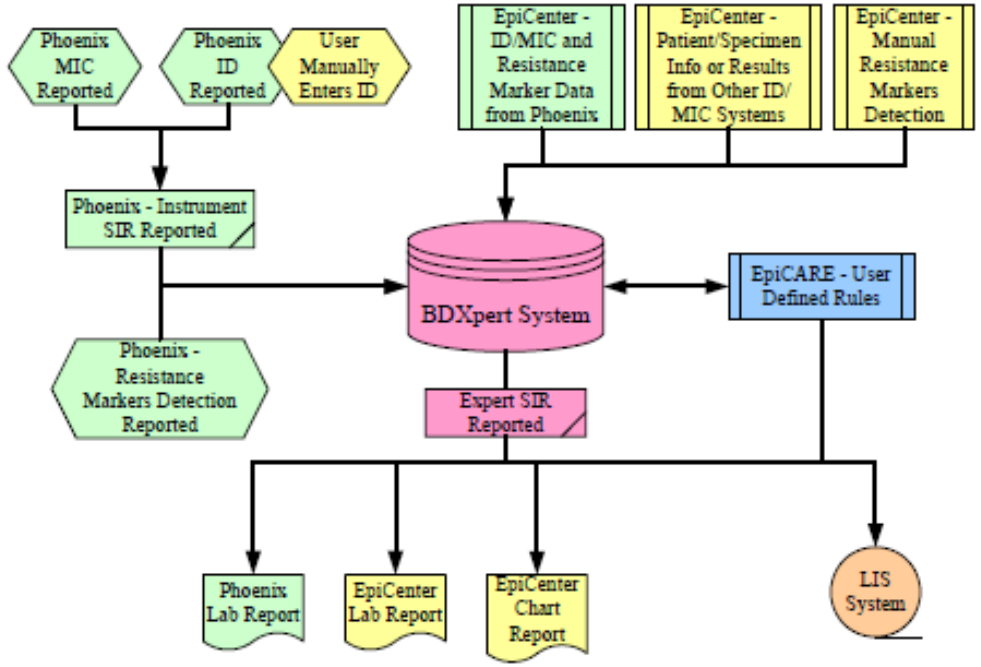
Introduction in BDXpert System

BDXpert™ System User's Manual

For BD Phoenix™ and BD EpiCenter™

PUD 6.81

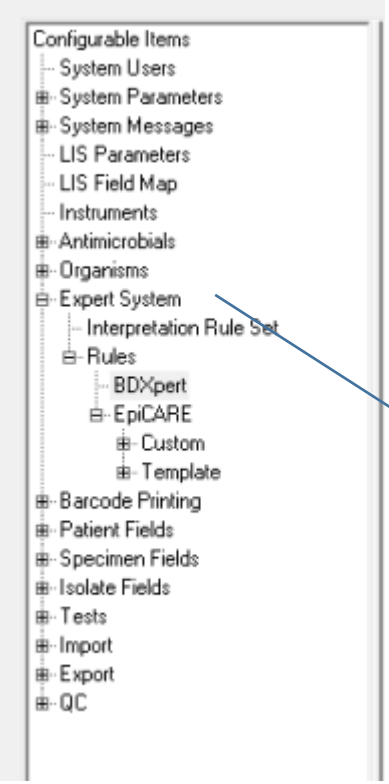
EUCAST Standard



*Exposure is a function of how the mode of administration, dose, dosing time, as well as distribution and excretion of the antimicrobial agent will influence the infecting organism at the site of infection.

For wild-type organisms (organisms without phenotypically detectable resistance mechanisms to the agent), EUCAST has assigned an arbitrary, "off scale" MIC breakpoint of S <=0.001. These organism-agent combinations should never be reported as "Susceptible, standard dosing regimen" (S). To address these organism-agent combinations, a series of BDXpert rules (982 – 992) were created to change the interpreted SIR for any MIC below the resistant breakpoint to "Susceptible, increased exposure" (I).

Expert rules epicenter Phoenix



- Expert system
  - * Interpretation Rule Set
  - * Rules:
    - °BDXpert
    - °EpiCARE
      - - Custom
      - - Template

Enabled
Disabled

Enabled
Disabled

IF/AND/THEN
Write it yourself

Breakpoints configuration Phoenix

RULE	IF	ORGANISM	AND	DRUG	AND		THEN	ACTION	AND	MESSAGE		

Logic Table by Organism — Enterobacterales — L009741(13) 2020-09

Rule	IF: Organism/Group	AND: Drug(s)	AND: Logic Criteria	THEN: Action	AND: Message Chartable Text	Application	Reference
984	Escherichia coli or Klebsiella species (except K. aerogenes) or Raoultella species or Proteus mirabilis	cefuroxime	S MIC <=8	1 Change any listed drug with SIR of S to SIR of I. 2 Print message.	For Escherichia coli, Klebsiella species (except K. aerogenes), Raoultella species and Proteus mirabilis, a cefuroxime MIC of <=8 mcg/mL should be considered "susceptible, increased exposure (I)."	Phoenix and EpiCenter	EUCAST 2020 (v10.0) Enterobacterales

BDXpert rules are categorized according to the following:

Rule Number	Standard
1-399, 2100+	CLSI
401-699	SFM
737-999	EUCAST

Rules applying to all standards:

Rule Series	Description
1000 series	Mostly intrinsic rules (note: does not apply to EUCAST)
1400 series	Resistance marker rules that can be disabled by the user
1500 series	Resistance marker rules that cannot be disabled by the user
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Breakpoints configuration Phoenix

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Customize to LIS

DTG	Specimen Lab Report	Chart Report
A	YES	YES
B	YES	YES
C	YES	NO
U	YES, for urine specimen or unspecified	YES, for urine specimen
O	YES	NO
I	YES	NO
N	YES	NO

Drug Test Group

specimen source

Because some rules are applicable only for a specific specimen source, a standardized list of these has been established in EpiCenter ONLY. The only applicable specimen source descriptions referenced by BDXpert rules are: BLOOD (blood), CNS (central nervous system), EYE (eye), GI (gastrointestinal), RESP (respiratory), SBS (sterile body site), URINE (urine), and UNS (unspecified).

But sometines it still stays a bit confusing…

Ceftazidime	0.001	8
Ceftazidime-avibactam, *P. aeruginosa*	8[2]	8[2]

I or S label for:

- Same molecule
- No inherent inhibitor activity for Pseudomonas
- BUT difference in dosage regimens

Dosages (v 11.0) - file for printing and screen (1 Jan, 2021)

	Standard dosage	High dosage	Uncomplicated UTI
Ceftazidime	1 g x 3 iv	2 g x 3 iv or 1 g x 6 iv	
Ceftazidime-avibactam	(2 g ceftazidime + 0.5 g avibactam) x 3 iv over 2 hours		

ATU: area of technical uncertainty

- Warning
- No mandatory action
- If lab decides to act on the warning, then:

  - Implementation in AST system
  - Implementation in LIS

How can the ATU be implemented in laboratory practices?

- Laboratories **without IT support** (manual **S** ,**I** and **R** categorisation on MIC or disk diffusion results)
  - List manually species/agents with ATUs and proposals on how to handle each.
- Laboratories **with IT support** (where **S** ,**I** and **R** categorisation is performed automatically on entering MIC or disk diffusion results)
  - Develop the software to include IF/THEN algorithms such as:
    IF *S. aureus* and ceftaroline and MIC 1 mg/L (or zone 19-20 mm), THEN take ACTION*…"
    IF *E. coli* and piperacillintazobactam MIC 16 mg/L (or zone 18 – 19), THEN take ACTION*…"

The basic principle is the same irrespective of which methods are used, but there may be an ATU in only one system.

- Disk diffusion
- MIC determination
- Semi-automated AST devices

MIC determination

- Automatic reading with computerized interpretation of full scale MIC determination.
  - Introduce ATU (species, agent, interval) to generate:
    - ”Warning signal” (sound, light, asterisk in report protocol, ….)
    - Block automatic interpretation and force manual decisions.
- Manual reading of full scale MIC determination
  - print a manual list of ATUs or use EUCAST breakpoint table printout

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Fluoroquinolones	MIC breakpoints (mg/L)		
	S ≤	R >	ATU
Ciprofloxacin	0.25	0.5	0.5

ADVANCED REPORTING TOOL - CONFIGURATION

Advanced Reporting Tool Configuration

Rules
- Custom
  - (2) staph kana
  - (3) VRE
  - (5) pseudo 2
  - (6) staph
  - (7) CRE
  - (8) mmm
  - (9) pseudo colistine
  - (10) esbl
  - (11) test comment
  - (13) shc
  - (14) TEST COMMENT 2
  - (15) sha
  - (16) ACISPP AMOX/CA AMP SUPPRESS
  - (17) Amp PL + Cron sak
  - (18) SAM PL + Cron sak
  - (19) TGC PL + Cron sak
  - (20) Copy of rule 5038 + Cron sak
  - (21) Copy of 5000 AM PL + Cron sak
  - (22) Copy of rule 5002 SAM PL +
  - (23) MRSA issue 1
  - (24) MRSA rule
  - (25) adasdasdasda
  - (26) ATU Cipro 0.5 - Enterobacteriacea
  - (27) Off scale Cefuroxime
- Local
- Predefined
  - Product Limitation
    - Global European-based
    - Global CLSI-based
    - CLSI
    - VET:CASFM-based
    - VET:CLSI-based
    - EUCAST
  - Indications for Use

Rule: 26 Name: ATU Cipro 0.5 - Enterobacteriaceae Status: Enabled

Type: Custom

IF

Conditions

If these conditions are met:

	Organism is Enterobacteriaceae
And	Antibiotic is Ciprofloxacin, MIC = 0.5, Antibiotic Type: Tested

Other ‘conditions’ available.

Then

Actions

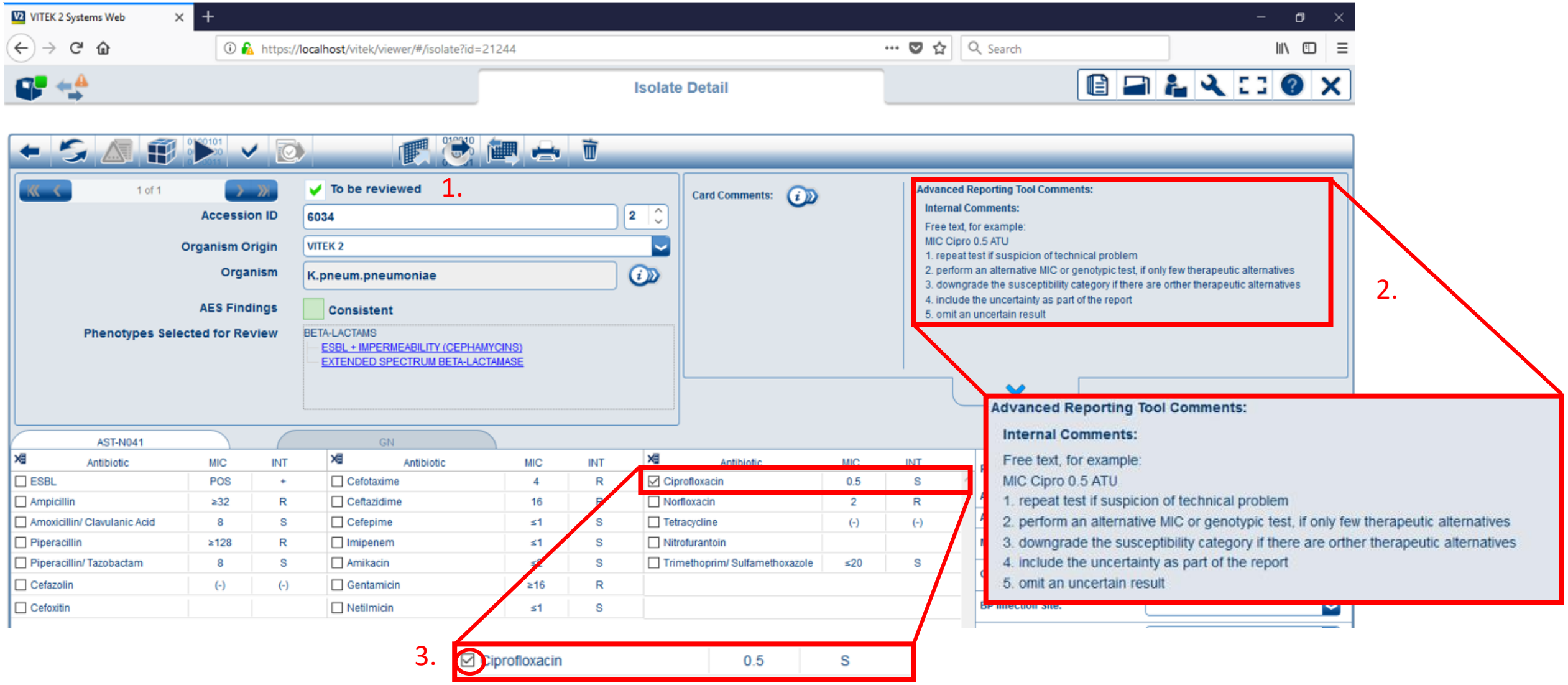
Then take these actions:

	Stop for review
And	Add comment: Free text, for example: MIC Cipro 0.5 ATU 1. repeat test if suspicion of technical problem 2. perform an alternative MIC or genotypic test, if only few therapeutic alternatives 3. downgrade the susceptibility category if there are orther therapeutic alternatives 4. include the uncertainty as part of the report 5. omit an uncertain result
And	Suppress from reporting Ciprofloxacin

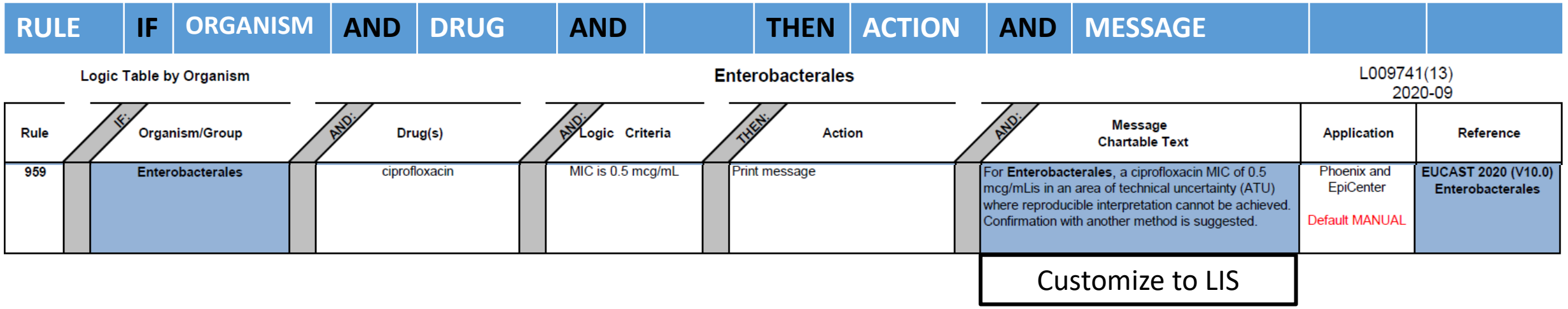
1. Not validate automatically this result
2. Internal comment: Free text add to result
   (or External comment to LIS)
3. Suppress for reporting

Other ‘actions’ available.

RESULT SCREEN



Introduction BDXpert system



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FOLLOW-UP

- bioMérieux will organise a webinar for VITEK users end October 2021
- BD Life Science provides support with planned software updates to individual clients

Special thanks to:

- Cécile Malentjer, bioMérieux
- Jurgen Vandamme, bioMérieux

- Lut Van den Broecke, BD Life Science
- Eric Nulens, AZ Sint-Jan Brugge

- EUCAST: slides used for this presentation can be found in their original form at www.eucast.org