

The Proposed Regulatory Framework for IVDs

Shelley Tang
TGA

Outline

- Introduction
- Classification
- Essential Principles
- The GMDN concept
- Proposed requirements for manufacturers

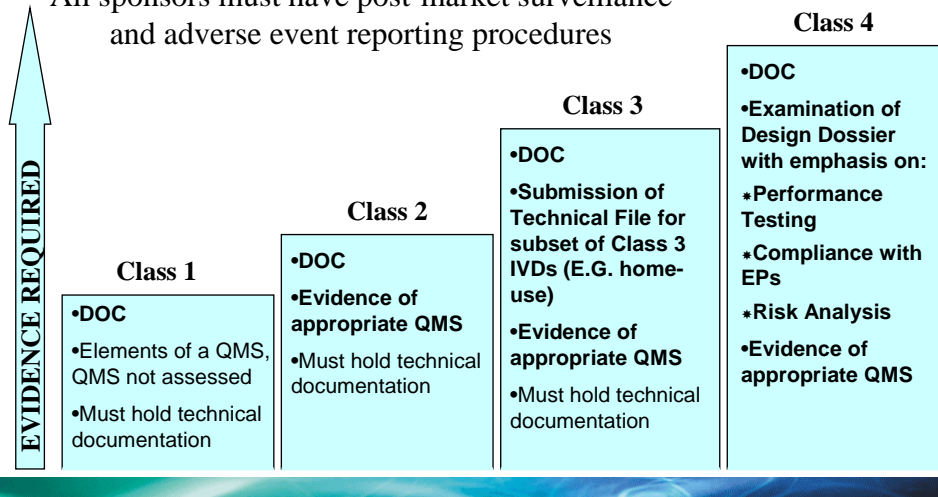
- any medical device which
 - *is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system,*
 - whether used alone or in combination (with other IVDs),
 - *intended by the manufacturer to be used in vitro for the examination of specimens (including blood and tissue donations) derived from the human body,*
 - solely or principally for the purpose of giving information about a physiological or pathological state or a congenital abnormality or to determine safety and compatibility with a potential recipient

- IVDs to be regulated as a subset of medical devices
- all commercial IVDs covered
- “in-house” IVDs to be included in Australia
 - high risk “in-house” IVDs to be regulated as for commercial IVDs
- all IVDs to conform to Essential Principles for quality, safety and performance
- Rule based classification decides level of regulatory involvement
- manufacturers should have internal systems in place to ensure compliance with EPs

- Issue of Product Licence as a basis for approval to supply
- post-market monitoring requirements
- use of standards developed by ISO TC 212 as a basis for demonstrating compliance with the EPs
 - TC 212 Clinical laboratory testing and *in vitro* diagnostic test systems
- provision of Special Access Schemes to allow access to unapproved tests

- Adopts Essential Principles developed by Global Harmonisation Task Force (GHTF)
- Classification rules agreed and aligned with GHTF
- Will use standards developed by ISO TC 212

All sponsors must have post-market surveillance and adverse event reporting procedures



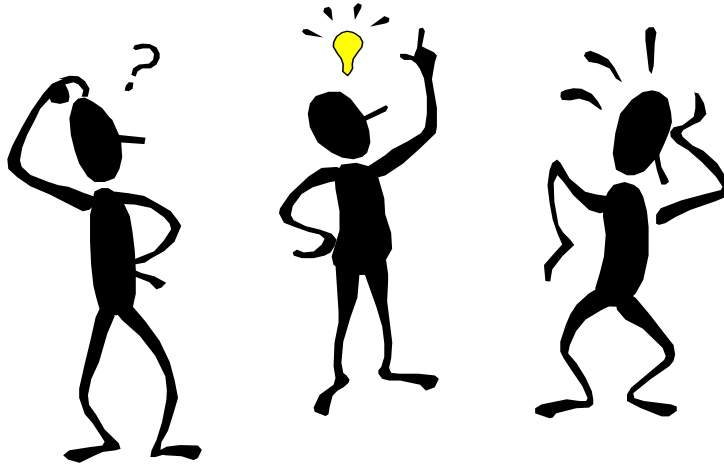
- IVDs for non-therapeutic use
 - blood alcohol testing
 - substance of abuse testing
 - parentage or kinship testing
- Will continue to fall outside the scope of regulation.

- Access to home use IVDs

IVDs that will not be approved for home use

- those used to diagnose notifiable infectious diseases
- genetic tests, and
- those used to test for serious disorders such as cancer and myocardial infarction

- Australia –
 - In Australia, legislation proceeding following consultation with all Australian jurisdictions through NCCTG
 - Implementation planned for, at latest July 2006
- New Zealand
 - Proposed for inclusion in the Single Agency scheme
 - Only after consultation on the Agency Rule



Essential Principles



- All IVDs must meet Essential Principles for quality, safety and performance
- These are the basis of the regulatory framework













- EPs are internationally accepted principles of Quality, Safety and Efficacy
- **ALL** IVDs must demonstrate conformity to EPs
- EPs cover design, manufacture, clinical performance, and overall safety to user and person being tested
- EPs define risks to be managed/ results to be achieved, but do not specify how
- Manufacturers determine which EPs are applicable
- Compliance with EPs is the manufacturer's responsibility

- Six general principles
 - Applicable to all medical devices, including IVDs
- 8 specific principles for all medical devices, including IVDs
- 5 specific principles relating to IVDs only


1. The IVD must be designed and manufactured to that when used under the conditions and for the purposes intended, its use will not compromise the health and safety of the patient, user or any other person, as applicable
2. The design and construction of the IVD must conform with safety principles, taking account of the acknowledged state of the art, where this includes identifying and eliminating risks associated with use, and ensuring that adequate protection measures are in place
3. IVD should be suitable for the manufacturer's intended purpose, and be designed, manufactured and packaged in such a way that the intended purpose can be achieved


4. The IVD must be designed and manufactured in a way that ensures it is safe to use over the intended life of the device as prescribed by the manufacturer, and when the IVD has been maintained in accordance with the manufacturer's instructions and if it has not been subjected to abnormal stresses
5. The IVD must be designed, manufactured and packed in such a way that its characteristics and performance will not be adversely effected under the storage and transport conditions prescribed by the manufacturer
6. The benefits of the IVD must outweigh any undesirable side-effects stemming from its intended use.

-  Chemical, Physical and Biological Properties*
-  Medical Devices connected to or equipped with an energy source
-  Infection and Microbial Contamination
-  Construction and environmental properties
-  Labelling
-  Medical Devices with a Measuring Function*
-  Instructions for use*
-  Protection Against Radiation
-  Clinical Evidence
-  IVD Specific Principles

* Amended for IVDs

 Scientific and Technical Properties

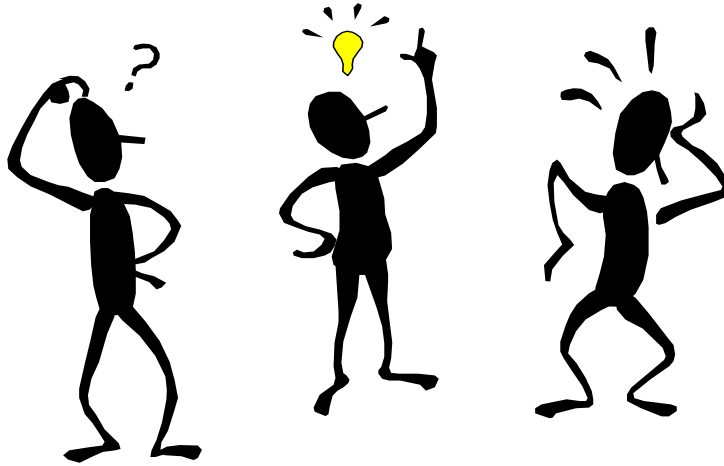
 Traceability of Reagents

 IVDs for lay people - providing appropriate protective measures

- IVDs provide sufficient accuracy precision and stability for intended use, based on appropriate scientific and technical methods
 - design should address sensitivity, specificity, trueness, repeatability, reproducibility, control of known relevant interference, and LOD, as appropriate

- Where the performance of the devices depends on calibrators the traceability of the values assigned should be assured through a quality management system

- Protection against the risks posed to the patient for devices for self-testing or self-administration
 - Take into account the skill level and environment of the user
 - Variation in user's technique and environment
 - Clear instructions/information
 - Reduce risks involved with handling device/specimen and interpretation
 - Require verification procedure of ongoing efficacy of device



Classification

- Risks of IVD to patients and users can range from
 - little or no risks to patients and users
 - significant potential risk
- Hence the level of regulation should be proportional to the level of potential risk, taking account of the benefits offered by the device
- Risk based classification system based on GHTF guidelines

Why Classify?

- The purpose of classification rules is to determine the level of regulatory oversight required
- The class of device determines the conformity assessment procedure

- Internationally recognised as a more flexible approach to ensure appropriate regulatory oversight
- Flexibility required to accommodate emerging diseases and technologies
- Prescriptive lists become outdated quickly

- the intended use and indications as specified by the manufacturer
 - Specific disorder, condition or risk factor for which the test is intended
 - Manufacturer should classify the IVD
- The technical/ scientific/ medical expertise of the intended user
 - eg lab testing vs home use

- The importance of the information to the diagnosis
 - Sole determinant or one of several
- The impact of the result (true or false) to the individual and/or to public health
- Internationally accepted risk classifications

- These guidelines are encompassed in a set of classification rules
- Rules classify all IVD into 4 different classes
- The rules are capable of accommodating future technological developments
- These mirror GHTF rules

- High public health risk **Class 4**
- High individual risk/ moderate public health risk **Class 3**
- Moderate individual risk/ low public health risk **Class 2**
- Low individual risk/ no public health risk **Class 1**

- Devices in this class represent no public health risk, or low personal risk
 - Lab equipment intended for use in IVD testing
 - Instruments (open system)
 - Eg HPLC, automated differential cell counter
 - Culture media
 - Specimen containers
 - General media

- Devices in this class represent a low public health risk, and moderate personal risk
- Includes those IVDs that
 - detect the presence or exposure to infectious agents not easily propagated in Australia/NZ
 - Cause self-limiting disease
 - Not used exclusively in a diagnostic setting
 - An erroneous result rarely puts the individual in immediate danger

- Devices in this class represent a low public health risk, and moderate personal risk
- Includes
 - sodium, ALT, lactic dehydrogenase, ferritin or folate, computerised cervical cytology, tests for Epstein Barr virus, autoimmune tests such as Anti-DNA Abs, Anti-ENA Abs, Anti-GAD Abs, Anti-IAZ Abs, Abs for diagnosing Coeliac disease, Cardiolipin antibodies, anti-TSH receptor, AMA, genetic tests for diagnosis (*cf* predictive genetic assays).

- Devices in this class represent a moderate public health risk, and high individual risk
- Includes those IVD that
 - detect the presence or exposure to infectious agents that are easily propagated in Australia/NZ
 - An erroneous result may have a major negative impact on outcome
 - Where the IVD provides the critical or sole determinant for a correct diagnosis

moderate public health risk, high individual risk

- Includes
 - IVDs used for tests for diseases on the Australian/NZ Notifiable Diseases list, eg Brucella, Q fever, Leptospirosis,
 - Detecting the presence of, or exposure to, a serious sexually transmitted agent. Such as *Chlamydia trachomatis*, *Neisseria gonorrhoeae* etc.

moderate public health risk, high individual risk

- Includes
 - Detecting the presence in cerebrospinal fluid or blood of an infectious agent that constitutes a significant public health risk. Examples: *Neisseria meningitidis* or *Cryptococcus neoformans*.
 - Determining infective disease status or immune status, and where there is a risk that an erroneous result will lead to a patient management decision resulting in an imminent life-threatening situation for the patient. Example: Influenza, *Haemophilus influenzae B*

moderate public health risk, high individual risk

- Includes
 - Detecting the presence of an infectious agent where there is a significant risk that an erroneous result would cause death or severe disability to the individual or foetus being tested. Examples: *Toxoplasma*, *Varicella Zoster Virus*.
 - Screening pre-natal women in order to determine their immune status towards transmissible agents. Examples: Rubella IgG.

moderate public health risk, high individual risk

- Includes
 - Screening for, or in the diagnosis of, cancer, including cancer staging, where initial therapeutic decisions will be made based on the outcome of the test results.
 - Predictive genetic screening, when the outcome of the test would ordinarily result in a substantial impact on the life of the individual. Example: Huntington's Disease

moderate public health risk, high individual risk

- Includes
 - Monitoring levels of medicines, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in an immediate life-threatening situation for the patient.
Examples: Cardiac markers, cyclosporine, prothrombin time testing, digoxin, paracetamol, Gentamycin, Tobramycin, potassium, calcium, troponin, glucose, taerolimus, sirolimus

Devices in this class represent a high public health risk, and high individual risk

- Includes all IVDs used for screening of the blood supply and organ and tissue donations for pathogens
 - Screening markers for HIV, HCV, HBV, Syphilis, HTLV
 - IVDs used for screening of select populations eg CMV IgG, Parvovirus NAT, and malaria Abs

high public health risk, high individual risk

- Includes IVDs to transmissible agents that causes a serious disease with a risk of propagation in the Australian population
 - Eg Diagnostic markers for HIV, HCV
 - Potentially diagnostic markers to avian influenza
 - Excludes viral load and genotyping markers

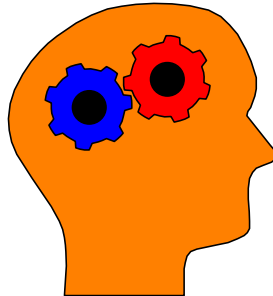
high public health risk, high individual risk

- Includes IVDs with an intended function of detecting agents used in biowarfare
 - eg anthrax
- Includes high risk blood grouping tests
 - ABO, rhesus, anti-Kell

- The manufacturer is responsible for applying the classification rules
- The classification rules are based on the manufacturer's intended purposes and in some cases, more than 1 rule may apply
 - If this happens the higher classification applies

- The classification must be consistent with the information accompanying the IVD
 - including the label, directions for use, brochures and operating manuals

- Software intended to drive or influence the use of the IVD falls under the same classification as the IVD
- Instruments that are part of a closed system eg Bayer Centaur, Abbott Axsym are regulated with each IVD, and not separately
- Open systems eg Tecan are Class 1



Proposed Regulatory Framework for IVDs - Assessment Procedures

- Conformity Assessment Certificate (CAC) issued by the Agency required for:
 - All Class 4 IVDs
 - IVDs manufactured in Australia/New Zealand
 - Any others for which appropriate overseas certification does not exist
- CAC is per manufacturer, for scope of IVDs manufactured. It is not product specific.

- Obligations on manufacturers
- Purpose:
 - to demonstrate compliance with the Essential Principles
 - quality, safety and performance



- Amount of information to be submitted increases with risk
- Agency audit of all Australian/NZ and some overseas manufacturers
- Use of standards
 - the Agency will designate (gazette) specific standards which manufacturers and sponsors can choose to use in complying with one or more specific EPs



Elements

- Quality Management System requirements
- Design Dossier for Class 4
- Performance Testing
- Technical Documentation
- Declaration of Conformity
- Post market monitoring
- Reporting requirements



Quality Management Systems

- cover manufacture of the IVDs
- compliance with ISO 13485:2003 required
- assessment (through on-site audit) required
 - may be by the Agency
 - for overseas manufacturers an assessment by a recognised European Notified Body may be accepted
- ongoing surveillance required



Technical Documentation

- description of the product
- manufacturing process and controls
- design inputs
- testing
- risk analysis
- clinical data (performance evaluation data)
- stability studies
- labelling, instructions for use



Technical Documentation

- held in Technical File for product
- collated in form of Design Dossier for Class 4 products
- must be submitted for assessment as required



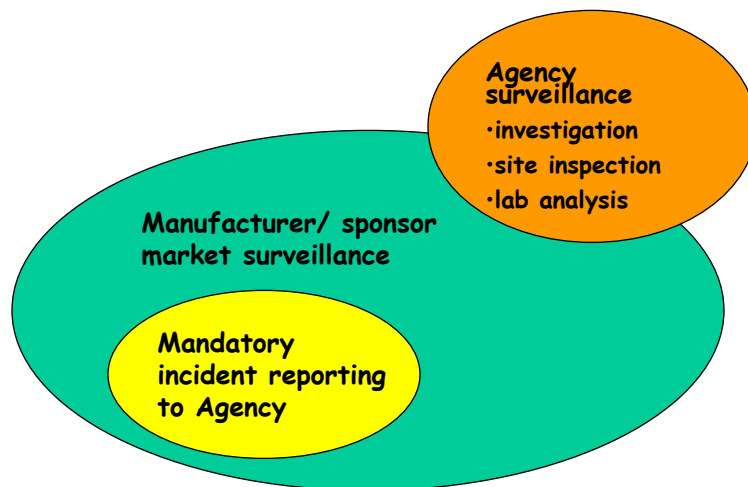
Declaration of Conformity

- Manufacturer's declaration that
 - conformity assessment procedures have been applied to the manufacture
 - IVD(s) comply with the relevant Essential Principles
 - must specify the IVDs to which it applies



Post-market monitoring

- manufacturer must have procedures in place to gather information on performance in the post-market phase
- must actively seek information
- must feed that information back to consider impacts on design
- must take corrective action on poor performance





Class 1

- manufacturer “self certifies” compliance to EPs
“declaration of conformity”
- elements of a QMS
- QMS not assessed
- must hold technical documentation
- subject to post-market audit



Class 2

- require a QMS, and assessment of the QMS
- technical documentation to be held, and
checked in the context of on-site audit
- signs DOC after issue of certification
- must have post-market surveillance in place
- must have procedures to notify the Agency of
adverse events



Class 3

- require a QMS, and assessment of the QMS
- Technical File to be submitted for assessment if required (will be assessed for a subset of Class IIIs)
- signs DOC after issue of certification
- must have post-market surveillance in place
- must have procedures to notify the Agency of adverse events



Class 4

- require a QMS, and assessment of the QMS
- Design Dossier to be submitted for assessment
- performance testing by Agency
- signs DOC after issue of certification
- must have post-market surveillance in place
- must have procedures to notify the Agency of adverse events

- Currently conducted for Australia by National Serology Reference Laboratory (NRL)
- Stage 1 - performance data
 - NRL evaluates clinical trial data
- Stage 2 - preliminary trials at NRL
 - product tested using selected panels of characterised samples
- Stage 3 - evaluation of performance
 - product tested either at the NRL or at a designated laboratory
- Looking at how it will work with the Single Agency Scheme

- Required for all Class 4 IVDs
- Scope for abridgement
 - IVDs for which performance testing is not required
 - IVDs registered on the ARTG at the time of commencement
 - Adequate testing data exists under European certification
 - IVD has been used in Australia for some time and adequate data exists on performance
 - Case by case basis

- If product is manufactured overseas and has appropriate certification,
 - o/s certificates accepted for Class 3 and below
- Except for a subset (mainly Class 3), which require Technical File Review

- European IVDD certification under Annex IV or VII
- ISO 13485 certification issued by a Notified Body designated under the MRAs existing between Europe and Australia/New Zealand

Technical File Review (TFR) will be conducted on a specified subset of IVDs, yet to be determined.

The Agency will also retain the capacity to undertake a random TFR on any Class 1, 2 or 3 IVD.

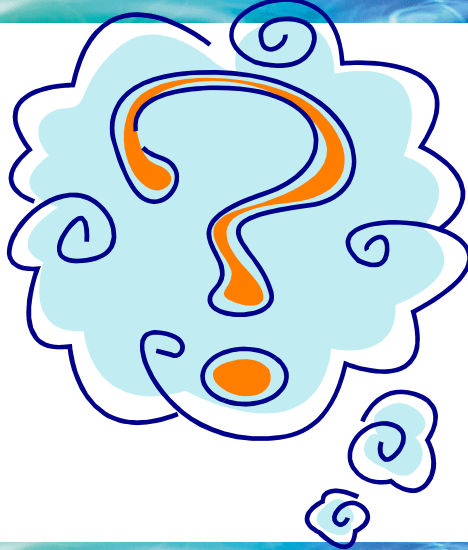
Proposal for mandatory review:

- IVDs for home use
- IVDs for PoC use
- IVDs for sexually transmitted infections
- Assays for genotyping and viral load testing for HIV and HCV (HBV?)
- Non-kit-related controls used with Class 4 IVDs

Desk Top Review:

- Intention is to ensure that an appropriate CAP has been applied
- calls in the documentation generated by the manufacturer, but
- needs to support the Declaration of Conformity to Agency requirements
- ensures that the links between the manufacturer and sponsor are in place

- When a TFR is required, the Agency will request a sub-set of documents
 - Original QMS certificate
 - EP checklist
 - Risk analysis
 - Summary of performance testing data
 - Declaration of Conformity
- Documents must be supplied in English
- Sponsor will have 20 days to supply



Global Medical Device Nomenclature (GMDN) Codes

- Collection of internationally recognised terms
- describes and catalogues medical devices including IVDs
- endorsed by the Joint Agency
- official classification system for medical devices for the European Economic area
- 12 categories to encompass all medical devices
 - 1 is for IVDs

- Information/detail held by the Agency increases with classification
- Each time a new GMDN is used, it results in a new product licence
- No hierarchical structure in current GMDN terms for IVDs
- Therefore a requirement for Agency purposes that GMDN terms are available that allow grouping of like products
 - Grouping is appropriate to Class
- Currently, few such terms available
- TGA member of the GMDN Maintenance Agency
 - investigating possible solutions for this requirement, in conjunction with industry

- Classes 1 to 3
 - GMDN appropriate to Class
- Class 4
 - GMDN and Unique Product Identifier
 - eg 30768 Human Immunodeficiency Virus nucleic acid kit Nuclisens EasyQ HIV-1 v1

- Large groupings, reflecting low risk of these IVDs
 - Reagents
 - Instruments
 - Lab ware
 - Supporting software
 - Sample containers
 - Culture media
- GMDN 01000 Reagents <s>



Class 2 IVDs

- Clinical Chemistry
 - Substrates
 - Electrolytes
 - Enzymes
 - Metabolic assays
 - QC/Cals/Std
 - Other
- GMDN 11300
 - Reagents, Clinical Chemistry, Enzymes <s>
- Immunochemistry
 - Specific proteins
 - Allergy
 - Tumour markers
 - Thyroid function tests
 - Vitamin tests
 - TDM
 - Autoimmune/rheumatoid
 - DoA/toxicology
 - fertility/pregnancy
 - Anaemia
 - Cardiac
- GMDN 12200
 - Reagents, Immunochemistry, Allergy <s>



Class 2 IVDs

- Haematology
 - FBE
 - haemostasis/coagulation
 - Immunohaematology
 - Tissue typing
 - Cell markers (flow cyto)
 - Cytokines/immuno-modulators
 - Controls/cals/stds
- GMDN 13100
 - Reagents, Haematology, FBE<s>
- Microbiology*
 - Parasitology
 - Virology
 - Bacteriology
 - Chlamydiaeae
 - Mycology
 - Multiplexing
 - Controls/cals/stds
- GMDN 14200
 - Reagents, Microbiology, Virology <s>

*this area requires further development

Reagents, immunochemistry, tumour markers <s>
Reagents, immunochemistry, tumour markers, cancer antigens
Reagents, immunochemistry, tumour markers, receptor assays
Reagents, immunochemistry, tumour markers, oncoproteins
Reagents, immunochemistry, tumour markers, other tumour markers

Reagents, immunochemistry, fertility / pregnancy hormones / proteins <s>
Reagents, immunochemistry, fertility / pregnancy hormones / proteins, fertility function hormones / proteins
Reagents, immunochemistry, fertility / pregnancy hormones / proteins, pregnancy testing hormones / proteins

Reagents, immunochemistry, therapeutic drug monitoring <s>
Reagents, immunochemistry, therapeutic drug monitoring, central nervous systems
Reagents, immunochemistry, therapeutic drug monitoring, antibiotic
Reagents, immunochemistry, therapeutic drug monitoring, anti-asthma
Reagents, immunochemistry, therapeutic drug monitoring, anti-neoplastic

- GMDN 12620
Reagents, Immunochemistry, TDM, antibiotic <s>

Reagents, haematology / immunochemistry <s>
Reagents, haematology / immunochemistry / reagent red blood cells
Reagents, haematology / immunochemistry / typing and grouping sera
Reagents, haematology / immunochemistry / associated IH Reagents

Reagents, immunochemistry, specific proteins <s>
Reagents, immunochemistry, specific proteins, immunoglobulins (without IgE)
Reagents, immunochemistry, specific proteins, complement components
Reagents, immunochemistry, specific proteins, transport proteins
Reagents, immunochemistry, specific proteins, lipoproteins
Reagents, immunochemistry, specific proteins, other specific proteins

Reagents, Microbiology, Bacteriology <s>
Reagents, Microbiology, Bacteriology, Gonococcus
Reagents, Microbiology, Bacteriology, Helicobacter pylori
Reagents, Microbiology, Bacteriology, Syphilis
Reagents, Microbiology, Bacteriology, Legionella
Reagents, Microbiology, Bacteriology, Borellia burgdorferi
Reagents, Microbiology, Bacteriology, Mycobacteria
Reagents, Microbiology, Bacteriology, Pertussis
Reagents, Microbiology, Bacteriology, Salmonella
Reagents, Microbiology, Bacteriology, Streptococcus
Reagents, Microbiology, Bacteriology, Staphylococcus
Reagents, Microbiology, Bacteriology, Listeria
Reagents, Microbiology, Bacteriology, Campiobacter
Reagents, Microbiology, Bacteriology, Shigella
Reagents, Microbiology, Bacteriology, Yersinia

Reagents, Microbiology, Virology <s>
Reagents, Microbiology, Virology, Hepatitis Virus, Hepatitis A
Reagents, Microbiology, Virology, Hepatitis Virus, Hepatitis B
Reagents, Microbiology, Virology, Hepatitis Virus, Hepatitis C
Reagents, Microbiology, Virology, Hepatitis Virus, Hepatitis D
Reagents, Microbiology, Virology, Hepatitis Virus, Hepatitis E
Reagents, Microbiology, Virology, Influenza, Influenza A
Reagents, Microbiology, Virology, Influenza, Influenza B
Reagents, Microbiology, Virology, Influenza, Influenza C
Reagents, Microbiology, Virology, Other Viruses, Rubella

- GMDN 12210
Reagents, Microbiology, Virology, Hepatitis Virus, Hepatitis A <s>

- GMDN and Unique Product Identifier (UPI)
- 12345
 - Reagents, Microbiology, Virology, Hepatitis Virus, Hepatitis C Virus, Ag/Ab
- UPI
 - AXSYM HIV Ag/Ab Combination Assay

