Increasing International Challenges in Regulatory and Compliance for Diagnostic Products

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Problem Statement

- Since the beginning of the 1980's the regulatory world for IVDs has changed dramatically
- From a few countries regulating IVDs, there are now 60-65 countries that have implemented regulations (~31 in Europe) or will soon implement regulations for IVDs
- IVD regulations are often part of Medical Device regulations or, in some cases,Pharmaceutical regulations
- So far, there is no common worldwide standard for regulating IVD products. The IVD industry very much appreciates GHTF's efforts to support convergence of global IVD regulations.

The Ideal World…

- ✓One common set of worldwide regulatory requirements for products
- ✓One recognized certification to cover worldwide regulatory requirements

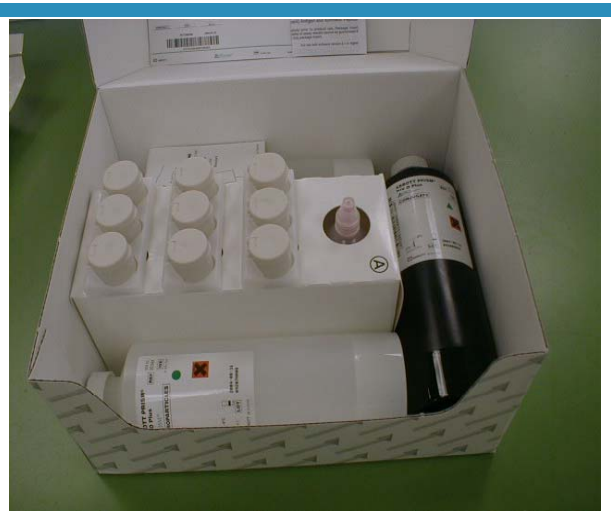
- ✓One recognized QS audit by the country where the manufacturer is located to prove that the company is in compliance with Quality System Requirements

However…..

The Ideal World...

...does not exist!

What is an In-Vitro-Diagnostic Medical Device?



IVDs are reagents which may be used in combination with instruments, software, specimen receptacles, pretreatment reagents, accessories….

GHTF: "a device, whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring, or compatibility purposes. This includes reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles."

The claim of the product (intended use) is declared by the manufacturer and defines whether it is an IVD Medical Device, or general lab reagent or equipment, or an accessory.

Challenges on our Way to Global Harmonization

- Language and cultural differences
- Classification rules, practices
- Multi-varied schemes of regulation
- Local product testing
- Authorities ability/willingness to rely on other authorities‘ work or decisions
- Customers are becoming more regulated
- Increasing use of Other Equipment Manufacturers (OEM)
- Product identification
- Unpredictable regulatory environment for market access

Language: Translations for Professional Users

Currently the following languages are required for **professional users**:

Brazilian Portuguese, Bulgarian, Chinese (Mandarin and Cantonese), Czech, Danish, Estonian, European Portuguese, French, German, Greek, Hungarian, Italian, Japanese, Korean, Latvian, Lithuanian, Norwegian, Polish, Romanian, Russian, Slovakian, Spanish, Swedish, Thai, Turkish;.....

Note: For **lay-users** the country language of the user is required

Quality of translations is paramount

Classification of IVDs

- Medical device **or** IVD **or** drug
- Rules based, risk based **or** risk based **or** none of the above
- 3 classes **or** 4 classes
- Product may be low or medium risk in one country **but** high risk in another country

Varied Regulatory Schemes

- Medical device, or drug, or IVD regulation
- Statutory vs voluntary
- Notification vs approval
- Centralized authority vs local authority vs a combination
- Different agencies or ministries within the same country with competing or overlapping authority
- Use of 3rd parties
- Quality system based vs legacy basis
- Re-registration may or may not be required

Product Testing

- Authorities may have little or no experience or expertise for testing IVDs and for establishing appropriate product specifications or standards
- Inappropriate use of diluted samples, purified antibodies, foreign matrix material for testing product performance rather than authentic specimens
- Products may fail when tested against the specifications developed by authorities resulting in significant time delays to critical users such as blood banks
- Training by experienced testing houses is often required (e.g.Paul-Ehrlich-Institute for Hepatitis B, C or HIV test kits)
- Batch verification may be duplicated by various authorities, often to different specifications
- Testing product to determine overall quality is an inefficient and unreliable indicator of true product performance

Reliance on Other Authorities' Assessments, i.e. Quality System Audits

- IVD Companies have moved over the last decade to be certified for ISO 9000 and/or ISO 13485
- Several countries have implemented or are in the process of incorporating Quality System Requirements into their Regulatory framework (e.g. US, EU, Canada, Australia, Japan, Brazil)
- Regulatory authorities usually do their own inspections to prove that companies are in compliance with ISO 9000 and/or 13485. May use accredited certifying bodies.
- As a result, there is incredible duplication of effort. Trust for the certificates from ISO certification bodies???? Or from those issued by other authorities???
- A number of authorities have little or no experience in auditing quality systems in conjunction with the QS standards above

Customers are more regulated

- Accreditated laboratories may perform supplier audits of IVD companies
- Laboratories often require copies of product release testing results (quality control testing), certificates of origin and free sale, and proof of good manufacturing practice
- Requirements for bids and tenders often include regulatory/quality standards to be met

Increasing Use of OEMs

- An IVD company may decide to subcontract Research & Development and/or manufacturing to an outside company
- Product is still under control by the IVD company via contract and supplier audits (i.e., per the contracting company's QS requirements)
- Regulatory Bodies may not consider the concept of "Legal Manufacturer" and may request legal documents (e.g. Certificate for Free Sale) from the OEM manufacturer as well as other documents that are more appropriately supplied by the "Legal" entity of the product.
- Regulatory Bodies may have conflicting requirements for labeling when there is more than one party involved, i.e. who's name and address is on the kit or on vials? What happens when the product label says "product of Japan" but the name and place of business of the manufacturer (legal manufacturer) on the label has a USA address?

Unpredictable Regulatory Environment

- For new products, long and uncertain approval times may discourage companies from the investment in the expensive and often lengthy develoment process
- Unlike drugs, IVDs have a relatively short life span as second and third generation assays are very common. If the regulatory turn-around-time is too long, innovation and next generation product improvement is derailed.
- For on market products, changes to submissions are judged differently: may require a notification in one country and a new full blown submission in another country – this means the manufacturer has to keep both manufacturing lines for a period of time (1 year or longer) at higher costs (smaller batch sizes per product during conversion)

- Manufacturer may decide not to modify a product because of the regulatory work involved, which may lead to missing opportunities for product improvements

Product Identification: coding and barcoding

- Product codes: EDMN, GMDN, ECRI, GTIN? (LA, EU, Asia)
- Barcode systems and identification of products (Spain, Saudi Arabia, Turkey)- EAN vs. HIBIC
- Import requirements vs. Customer inventory control

And More….

- IP: Submission files may contain confidential information: Is the information protected within the authorities?

- Use of electronic media for instructions-for-use (Internet, CD-ROMs, etc); acceptance is mixed in different jurisdictions

Where are we going in the Future?

Today

- The EU/EFTA has harmonized the regulations of 31countries.
- GHTF (Global Harmonization Task Force) works on harmonization of the regulatory systems of Australia, Canada, EU, Japan and US and encourages the participation of other nations with the hope of promoting the convergence of international regulatory requirements and practices
- Asia has been active in this area through AHWP and ASEAN meetings/workshops, APEC (Asian Pacific Economic Corporation) conferences which support regulatory bodies to encourage harmonization of regulations (last held 3/2008: Kuala Lumpur)
- Latin America has participated in APEC meetings (Santiago de Chile, 5/2006); also continues its work via Mercosul

We may yet go in the Right Direction....

"Our future is created by what we do today, not tomorrow"

Robert Kiyosaki

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Thank You!!

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