

# Business & Decision

## **Implementing Compliant Medical Device Best Practice Business Processes Using Oracle E-Business Suite**

*A white paper discussing the compliant use of the Oracle Electronic Record, Electronic Signature (E-Records) Framework in the Medical Device Manufacturing Sector*



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## Implementing Compliant Best Practices Using Oracle E-Business Suite

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## Implementing Compliant Best Practice Business Processes Using Oracle E-Business Suite

### Abstract

A number of suppliers to the Life Sciences sector claim to have developed applications or solutions that are 'compliant' to 21CFR Part 11. Many of these are in fact only partial solutions, do not address fundamental issues of data integrity or do not provide the necessary flexibility to allow for a case-by-case interpretation of the predicate rules.

The completeness of the Part 11 solution is of specific concern to the manufactures of medical devices, where enforcement of 21CFR Part 11 has been on the increase in recent years, after a period of inconsistent enforcement across the various divisions of the Food and Drug Administration (FDA).

Whilst all systems can at some fundamental level be reconfigured or customized to meet the requirements of 21CFR Part 11 this is often a costly and time consuming process. Where such solutions rely on hybrid solutions (as allowed under the latest FDA guidance on Part 11<sup>[1]</sup>) the resultant business processes are often inefficient and in some cases non-compliant with the predicate rules.

Oracle Corporation, supported by Business & Decision (formally Mi Services), have developed a flexible and compliant framework that meets the technical requirements of Part 11 but also allows end user organizations to ensure that their business processes can follow industry best practice in a manner that is compliant with the predicate rules, primarily 21 CFR 820 and international equivalents.

This can only be achieved if the implementation process delivers compliant solutions in a manner that allows the system to be cost effectively implemented and validated.

These principles can be applied to the development and implementation of any mission critical system in the pharmaceutical and biotechnology sectors and will be of interest to the developers of such systems as well as those responsible for the validation of compliant applications within the industry.

### Introduction

Over the last four years Oracle Corporation has implemented a technical solution to meet the requirements of US 21CFR Part 11 (Electronic Records, Electronic Signatures - ERES) within the Oracle E-Business Suite.

Leveraging strong security inherent in the underlying Oracle database, this solution meets all of the technical requirements of 21CFR Part 11 and other ERES regulations and guidance. The solution also overcomes many of the problems associated with other systems that claim to be compliant with 21CFR Part 11 (discussed below).

Full details of the E-Records Framework technical solution are available from Oracle Corporation and are referenced throughout. This white paper discusses some of the underlying regulatory issues addressed in the design and implementation of the E-Records Framework as well as issues associated with implementing the E-Business Suite business processes and application within the medical device sector.

## A Partial Relaxation of Part 11

In their latest guidance on 21CFR Part 11, the FDA has undertaken to review the regulation and has outlined areas of relaxed enforcement.

Even since the publication of the draft of this guidance in February 2002, some individuals and organizations have incorrectly interpreted the FDA's change in approach as a total relaxation or withdrawal of the Regulation. A number of Life Science organizations appeared to either abandon their Part 11 programs, chose not to implement programs already committed to, or stated that Part 11 was no longer an issue they would address.

This is of specific concern within the medical devices sector, where Part 11 compliance programs were not as well established as with pharmaceutical manufacturers (for instance). It is partially in response to this reaction that that Agency has re-emphasized that Part 11 has not been withdrawn and that organizations should **"Note that part 11 remains in effect** and that this enforcement discretion applies only as identified in this guidance."<sup>[1]</sup>

Medical device and other Life Sciences organizations should therefore continue to assess their critical systems and undertake corrective actions including the upgrade or replacement of non-compliant systems where necessary.

As discussed elsewhere<sup>[2]</sup> although the new guidance on 21CFR Part 11 allows the use of hybrid solutions and a reliance on logical, procedural and physical security, such solutions do not provide the operational benefits that medical device developers and/or manufacturers should be looking for.

It should be stressed that much of the benefit from implementing best practice business solutions in mission critical systems is achieved through the use of work flow enabled business processes, using electronic signatures to speed up business processes and reduce the cost and time overhead associated with managing paper records and handwritten signatures in a hybrid solution.

Since the FDA's relaxed enforced of 21CFR Part 11 does not extend to the use of electronic signatures, all business solutions will still need to be compliant with these requirements in order to use electronic signatures, and the most efficient solutions will still use compliant electronic records.

## Other "Part 11 Compliant" Solutions?

"Part 11 compliant" solutions have been available for a wide variety of mission critical systems for a number of years. However, some of these solutions are more compliant than others and a number have some key deficiencies.

Some of these deficiencies are technical, and a subset of these can be overcome by following the FDA's latest guidance on Part 11 (leveraging hybrid solutions, physical, logical or procedural security). However, where these deficiencies relate to those areas of Part 11 where enforcement has not been relaxed (such as electronic signatures) the systems or applications may still be non-compliant with Part 11.

Other deficiencies may not relate to technical issues, but to compliance with the predicate rules. A number of systems enforce business processes that are not compliant with the predicate rules, or more usually with the end users business process specific interpretation of the predicate rules.

A final area of deficiency is in the cost effective implementation of compliant solutions. While in theory all solutions can be made compliant (by configuration or customization) this is sometimes a time consuming and expensive business. When faced with the costs associated with making existing systems compliant (which often involves an expensive re-implementation) some organizations conclude that replacing a non-compliant system with a compliant system provides a better return on investment and gives a lower total cost of compliant ownership [3]

When considering what makes an effective "Part 11 Compliant" or ERES compliant system Business & Decision have always considered the following key points:

1. The system or application must provide appropriate data integrity at the database level (supported by a qualified IT infrastructure),
2. The application must provide a compliant solution for electronic records and electronic signatures,
3. The application must support (and ideally enforce) best practice business processes, compliant with applicable predicate rules,
4. The system should be able to demonstrate the use of compliant business processes and data integrity during internal audits and external regulatory inspections,
5. It must be possible to implement, validate and maintain such a system in a compliant manner.

Each of these points is discussed in more detail below, with further discussion on the deficiencies in some partial solutions, and reference to the Oracle E-Business Suite solution, leveraging the E-Records Framework.

(It should of course be recognized that no system can be fully compliant with 21CFR Part 11 without the establishment of various procedural controls within the business. These are described in 21CFR Part 11 and supporting guidelines and commentary from the FDA and it should be noted that there is no relaxation of Part 11 in these areas).

### **Strong Security**

Most applications rely on an underlying database to store GxP critical data. In order to optimize performance most modern mission critical systems rely on a commercially developed database. While a solution may be secure at the applications layer the database often provides a weak point in the chain of links required to assure data integrity.

In order to maintain and optimize system performance, database administrators require access to database tables. Most applications rely on the inherent security of the database to ensure that access is restricted and that secure audit trails are generated for any changes that need to be made at the database level (supported by a compliant change control procedure and change control records).

However, relatively few systems differentiate between one table and another, and implement an 'all or nothing' approach to database security. Most applications developers rely on the inherent security of the underlying database, and claims to be 'Part 11 compliant' should only really be made for the applications software, and not the complete system.

Prior to the development of the E-Records Framework, the Oracle E-Business Suite relied on the strong security of the underlying database. Because Oracle effectively owns (develops) both the applications layer and the underlying database layer it is relatively easy to provide a strong, integrated security solution. Oracle *8i* database (and associated utilities) already provided compliance with the usual technical requirements of 21CFR Part 11 including user password and ID management, display of user name on screen and secure, computer generated audit trails.

With the release of Oracle *9i* database this security has been enhanced. This includes the use of a 'virtual private database' to lock database administrators out of critical tables such as the 'Evidence Store', where GxP critical records are held. While a 'superDBA' still needs to control the definition of and access to such virtual private databases, this is much more secure than the majority of most 'Part 11 compliant' applications.

Reference to Oracle's own white papers and technical literature also provides guidance on using a number of tools and utilities to support the qualification of the underlying IT infrastructure, covering issues such as data transport and comparison between development, QA/Test and Production environments and performance monitoring tools.

While no system can be completely compliant to 21CFR Part 11 without some procedural controls in place, these are minimized by the use of the Oracle E-Business Suite, the underlying Oracle database and Applications Server and associated tools and the on-going Total Cost of Compliant Ownership can be minimized.

### **Compliant Electronic Records and Audit Trails**

Providing secure electronic records and secure audit trails has proven to be an on-going challenge, which has been eased in recent years by the introduction of commercially available solutions.

Making individual files secure is relatively easy, but defining and securing an 'electronic record' within a complex relational database is much more complex. The contents of the individual electronic records are defined by the applicable predicate rules (primarily 21CFR Part 820 in the case of medical devices), and these may be comprised of multiple columns from multiple tables within the database.

In a large and complex system such as an Enterprise Resource Planning system (ERP) they may be hundreds of tables (over a thousand in some systems) and data from many of these tables need to be included in any given 'electronic record'.

While this can be solved at the database level, there are three problems with this approach:

1. The individual columns and tables need to be identified and documented
2. Audit trails need to be applied to the appropriate columns and tables
3. Human readable copies of electronic records needs to produced from the electronic records

The first of these problems is an implementation issue, and is covered later in this White Paper.

Some systems provide the ability to enable audit trails at the column and table level, but many systems provide only limited flexibility, requiring audit trails to be enabled on large parts of the database (perhaps only at the table level, or for pre-defined parts of the database schema). Whilst this approach can work, the overhead or maintaining unnecessary audit trails has an adverse impact on processor performance and database space and this often requires expensive and unnecessarily large servers.

The integration between the Oracle E-Business Suite and the underlying database allows complete flexibility to turn on and turn off audit trail at the column, table or database level and this is achieved through configuration. Other solutions either can not provide compliant electronic records and associated audit trails or often require extensive customization, adding to implementation time and cost. In some cases, basic electronic records are enabled for a small subset of the predicate rules, but extensive configuration or customization is required if the end user requires compliance with additional predicate rules (additional biological or radio-pharmaceutical regulations for instance), or has a different interpretation of those rules.

This is important as the capability of systems such as the Oracle E-Business Suite extends beyond Good Manufacturing Practice (GMP) and also addresses multiple areas such as plant, equipment and process maintenance, product distribution and recall, product development, and corrective action planning and reporting.

As medical device manufacturers generally do a good job with respect to GMP, regulatory focus is starting to shift to other areas within the enterprise and systems should be capable of supporting a risk based approach to 21CFR Part 11 in all areas of their business.

This flexibility built in to the Oracle ERES Framework provides users with the complete freedom to implement compliant audit trails in accordance with their own interpretation of the applicable predicate rules, thereby ensuring that the application is compliant with 21 CFR Part 11 and predicate rule requirements for data retention. This is achieved without imposing unnecessary overhead on server performance.

Finally, Oracles use of dedicated database tables for GxP critical electronic records (in the form of the Evidence Store) allows electronic records to be defined using data from any table in the master data or transactional databases, and for a separate copy of that dataset to be retained as the secure electronic record.

This becomes the 'master data of record' ensuring that there is no confusion over which records are considered to contain the master data. Where appropriate, these electronic records can be signed.

These electronic records can be stored in human readable form, as plain text (which is guaranteed to be legible for the retention period of the data, whatever the changes in technology). Electronic records may also be formatted by the use of XML style sheets, allowing users to format standard reports (see below) or create new reports for electronic records. In order to ensure that XML formatted electronic records remain legible the XML style sheet can be secured, version controlled and an optional approval signature can be required before any formatting changes are implemented.

Full audit trails are provided for any changes to electronic records, electronic records may be archived or exported in a number of different formats (using validated tools) and the master data in the Evidence Store can be secured using standard features of the Oracle 9i database.

When compared to other "Part 11 compliant" solutions, the Oracle E-Business Suite has several major advantages when supporting demonstrable regulatory compliance with respect to Electronic Records:

- The content of the electronic record can be taken from any table in the system,
- The use of a separate Evidence Store provides clear evidence of which data is defined as the master record,
- The Evidence Store can be secured by the use of the underlying Oracle 9i virtual private database facility,
- Electronic records can be formatted by the end user to provide evidence in a format that is easily understood by auditors and regulatory inspectors (i.e. the equivalent of existing paper records).

### **Compliant Electronic Signatures and Workflow**

Implementing compliant electronic signatures is relatively easy in many systems. The challenges usually arise in securely associating such signatures with the associated electronic record, especially when the 'record' is comprised of multiple entries in multiple tables in a relational database. Another challenge is ensuring that such signatures support the use of flexible workflow, which greatly improves the operational efficiency in most medical device organizations.

Because separate master electronic records are created in the Evidence Store, securely attaching compliant electronic signatures to electronic records is easily achieved in the Oracle E-Business Suite. Components of the signature are included as part of the secure record and all signature components are treated as electronic records (in accordance with 21CFR Part 11).

What is more, because the user sees the formatted electronic record (report) at the time of signing, and because a clear notification is clearly displayed to the user, the act of applying the electronic signature is clearly placed in context.

In addition, when electronic records are reviewed, they are displayed in a fully formatted manner complete with any electronic signatures that have been applied. This 'sign-what-you-see, see-what-you-sign' approach means that signatures can be reviewed along with the records to which they apply and ensures that users signatures can be properly placed in context at the time of signing and at the time of any subsequent regulatory review.

The Oracle E-Business Suite E-Records Framework also provides a great deal of flexibility in where and when electronic signatures need to be applied. Leveraging the tools provided as part of the E-Records Framework, and in combination with Oracles use of standard transactional forms and workflow-enabled transactions, electronic signatures can be applied to any standard transaction or to any standard or user defined workflow. This means that electronic signatures can again be enabled in accordance with the end users interpretation of the applicable regulations.

Where defined in applicable predicate rules such as 21CFR Part 820, standard transactions can use electronic signatures. Compliant electronic signatures can also be applied where the end user wishes to modify these transactions, or create customized workflows to optimize business efficiencies.

Because the initial enforcement occurred in the pharmaceutical sector, a number of "Part 11 compliant" solutions have actually embedded compliance with the pharmaceutical sector predicate rules into their applications, but have totally ignored the medical devices sector, where enforcement was less consistent until four years ago.

Unlike other systems that provide limited flexibility as to where and when electronic signatures can be signed, the Oracle E-Business Suite provides complete flexibility with respect to:

- How many signatures are required for a given transaction, or step in a workflow,
- Whether or not the individual signature of a named individual is required, or any signature from a defined group of users (user profile),
- Whether signatures are required immediately, before the transaction can proceed to the next step in the transaction or workflow (such as a second person confirming data entered in the manufacturing area or laboratory), or whether they can be deferred for later signature (such as QA specification approval),
- Whether signatures may be collected in parallel, from multiple users, or whether they must be captured in series (one after the other, in a defined sequence).

The use of compliant electronic signatures means that a trade-off can be achieved between streamlining efficient business processes and enforcing a pre-defined sequence of events (in accordance with the applicable predicate rules and 21CFR Part 11).

The Oracle E-Business Suite therefore has several major advantages when supporting demonstrable regulatory compliance with respect to Electronic Signatures:

- Users sign electronic records in full knowledge of what they are signing,
- Signatures are securely attached to the electronic records to which they apply, and are secured in the Evidence Store,
- Subsequent review of signed records shows all applicable signatures clearly appended to the records to which they relate,
- Business efficiency is optimized through the flexible use of electronic signatures on standard transactions and workflow enabled processes.

## Why is Flexibility So Important?

The latest guidance from the FDA <sup>[1]</sup> states, “We recommend that you determine, based on the predicate rules, whether specific records are part 11 records. We recommend that you document such decisions.”

Unfortunately most of the predicate rules were never written with computer systems in mind and the language is often ambiguous as to what is defined as an electronic record and signature. Words like ‘approve’, ‘reviewed’, ‘verified’ and ‘established specification’ may infer the creation of records or the application of a signature, but this is open to interpretation by the end user.

Because Part 11 was initially enforced in the pharmaceutical sector, a number of suppliers have interpreted 21 CFR Parts 210 and 211 and used this as the basis for designing their “Part 11 compliant” solutions. This often provides a narrow interpretation, ignoring those parts of the regulations where the use of electronic records and signatures is inferred, and where end-users are currently capturing paper records and hand-written signatures. This is clearly a major issue in the medical devices sector, where different processes are used and where different predicate rules apply.

Such pharmaceutical focused Part 11 implementations often ‘hard-code’ such records and signatures into the application and require extensive configuration and customization to make any changes. There are four main problems with this lack of flexibility:

1. They may not support users in other sectors in the Life Sciences industry, such as medical devices, biomedical, applied nutrition, over-the-counter or active pharmaceutical ingredients (APIs).
2. They may not support those organizations that require a system to support multiple business units across all of these sectors.
3. They may not support the use of electronic records and electronic signatures against requirements defined in non-US regulations (EU Directives for instance).
4. They are expensive to re-configure or customize to provide such compliant support (if it is at all possible with hard-coded solutions).

In addition, some user organizations may have different data retention requirements in different locations. These may be because different parts of the organization are subject to different regulations where different data retention requirements are mandated. Organizations must therefore make and document a decision as to whether different data retention periods will be supported by the system, or whether the most stringent requirements for data retention will apply to the entire organization.

Business & Decision have consistently applied a narrow interpretation of the scope of 21CFR Part 11, and realized some time ago that the ambiguity of many sections of the predicate rules required an organization to document their interpretation of the predicate rules.

Business & Decision have produced a series of so called ‘Predicate Rule Maps’, identifying which sub-sections of the predicate rules may infer the retention of

records or the use of signatures. Although these do not provide a definitive system or application specific interpretation, our experience is that they allow end users to quickly determine what they consider to be those records and signatures that are defined by the predicate rules, and therefore within the scope of 21CFR Part 11.

There are however three caveats here:

1. It is always the responsibility of the end user organization to provide the definitive interpretation of the predicate rule, within the context of the specific process and product under consideration.
2. The precise scope of Part 11 can differ from system to system, depending upon the exact functionality of the system and the context within which it is used.
3. As confirmed in the new guidance, reliance upon electronic records even when duplicate paper records exist may still bring a system within the scope of Part 11.

The flexibility of the Oracle E-Business Suite ERES Framework means that the use of electronic records and electronic signatures can quickly and easily be tailored to an individual organization.

Because the Oracle workflow engine supports different workflow routings based upon the values of master or transactional data, the same instance of the system can enforce different workflows for different product classes, or different national or international regulations.

As an example, additional design controls and signatures may be required for the design and development of a Class I medical device (as opposed to a Class III medical device), or additional controls may be required to ensure that only a Qualified Person can release a batch of finished pharmaceutical to be used with pharmacotherapeutic medical devices.

### **The Changing Regulatory Landscape**

Whilst flexibility is important at the time of implementing a system, flexibility is equally as important during the operational life of the system. In the medical devices sector, new standards such as ISO 13485 mean that the regulatory landscape is changing. At a time when the FDA has committed to review their pharmaceutical GMP regulations <sup>[4]</sup> and new regulations are likely in the food sector, it should be recognized that changes will need to be made to systems in order to remain compliant with changes in regulations.

The limited flexibility inherent in other solutions means that existing users of other systems face significant costs associated with a virtual re-implementation of their systems when such changes in the regulations take place.

The flexible nature of the Oracle ERES Framework, combined with the detailed documentation provided as part of the original implementation (see below) mean that it is relatively easy and extremely cost effective to implement such changes as part of the standard change control process.

## The Breadth of Regulations

Initial enforcement actions around 21CFR Part 11 were very much taken in the pharmaceutical sector followed by the medical device sector, with relatively little or no enforcement in other sectors such as food, applied nutrition, veterinary, or cosmetics.

2002 saw a more concerted and coordinated attempt by the Agency to enforce Part 11 more consistently (albeit with a continuing technical bias towards compliance), including the Center for Devices and Radiological Health (CDRH).

There has been some concern that the levels of enforcement previously seen in the pharmaceutical sector will be applied across all other sectors, leading to cosmetics and food organizations joining lobbying groups such as the Industry Coalition. This is a sensible concern, since pharmaceuticals and Class III medical devices generally represent a more direct risk to patient health and safety than do veterinary products or general foodstuffs.

It would be inappropriate for the Agency to reduce the cost of compliance in one or two sectors (pharmaceuticals and medical devices), while massively increasing the cost of compliance to cosmetics manufacturers and food producers if this does not address significant risk.

The key issue here is to understand that compliance activities and enforcement actions will be based upon risk to product quality, patient (consumer) safety and data integrity. Of these, the second issue is the cornerstone of the Agency's remit. While product quality and data integrity play a role in patient safety, this very much depends upon the modality of the product (what it does and how it interacts with the human body) and the criticality of the data.

Most foodstuffs and cosmetics have a relatively well-understood interaction with consumers, but medical devices and pharmaceutical products are far more critical. When a sensible risk based approach is taken towards compliance with and enforcement of 21CFR Part 11, the most stringent controls and enforcement actions should continue to be taken around higher risk products and industry sectors.

This means that although the veterinary health, food, applied nutrition and cosmetics sectors can not afford to ignore 21CFR Part 11, a sensible risk based approach will allow the cost of compliance to be in-line with the assessed risk to patient (consumer) health and safety.

There are however two caveats to this point:

1. Some products within relatively 'low risk' sectors never the less represent a significant risk to patient (consumer) safety. Seafood products are a good example of such risks. Where business processes support the development, manufacture, distribution or marketing of products governed by existing predicate rules, Part 11 clearly applies and compliance must be seen as a key requirement.

2. New regulations around nutritional supplements and food (the latter derived from the Prevention of Bioterrorism Act 2002 <sup>[5]</sup>) will bring in new predicate rules, and draft changes to regulations such as 21CFR part 111 and 112 <sup>[6]</sup> specifically state that 21CFR 11 part applies (as it does to any predicate rule).

In summary, 21CFR Part 11 continues to apply to all sectors, depending upon the scope of the predicate rules, and new regulations will extend the current scope of Part 11. The impact of this can however be managed through the use of appropriate risk assessment and mitigation activities, focused on patient (consumer) safety.

These principles certainly apply to medical device manufacturers where the principles of hazard analysis are well understood. While Part 11 will continue to be an issue that the medical device sector will need to address, this can be achieved in a pragmatic and cost-effective manner.

## Finished Pharmaceuticals First

Because of initial enforcement activity, the initial implementation of the Oracle ERES Framework within the E-Business Suite was within the pharmaceutical sector, specifically within the Oracle Process Manufacturing Modules, looking at 21CFR Parts 210 and 211 (finished pharmaceuticals).

Working with Business & Decision and their Pharmaceuticals Customer Advisory Board, Oracle interpreted Parts 210 and 211 in order to determine:

- Where a pragmatic interpretation of 21CFR Parts 210 and 211 indicated that electronic records should be captured in the Evidence Store
- Where a pragmatic interpretation of 21CFR Parts 210 and 211 indicated that electronic signatures should be captured
- How the electronic records and signatures should be formatted and displayed to demonstrably support compliance during any regulatory inspection.

This functionality was released in January 2003 and is more fully described in the accompanying product announcement [7]. This solution has been adopted by a number of pharmaceutical clients in both the US and other parts of the world.

## Medical Devices

Although enforcement of 21CFR Part 11 was slower with medical device manufacturers, the FDA has been taking significant steps to enforce Part 11 in the medical devices sector for the last three years. As a result of this enforcement clients in this sector also require a standard solution for ERES compliance within the discrete manufacturing solution (Oracle Discrete Manufacturing).

It should however be noted that prior to Oracle developing a standard solution based upon the ERES Framework the strong security available in Oracle always allowed a compliant solution to be developed. Business & Decision developed a number of Part 11 compliant solutions for medical device manufacturers, relying upon the strong underlying security of the Oracle database and customization at the applications layer.

Again working with Business & Decision and users in the medical devices sector (the Medical Device Customer Advisory Board), Oracle has again provided a pragmatic analysis of 21 CFR Part 820 to again determine where a reasonable interpretation of the regulation would require electronic records and electronic signatures to be applied.

Taking this opportunity, Oracle has identified more than 50 key transactions and business events in modules such as Item Master, Bill of Material and Routing, Engineering, Work in Process, Quality, Inventory, Purchasing, Receiving and Shipping, to be enabled for e-records and e-signatures.



These business process and transactions have been mapped against 21CFR Part 820 and reviewed by Business & Decision (who have also reviewed these against the applicable EU Directives and ISO 13485). One specific area of focus was data required to support the Device Master Record (DMR) and the Design History File (DHF).

The complexity of the transactions in the Oracle E-Business Suite means that a number of business processes create or update data which forms part of the DMR or DHF. These have all been identified and appropriate entries are made in the Evidence Store, supported by the use of compliant electronic signatures where required by the regulations.

Depending upon the user specific implementation of the applicable predicate rules other functional areas such as Sales and Customer Returns and Complaints may also need to be included within the scope of the ERES Framework. The flexibility of the Oracle ERES solution allows individual organizations to define where they make the distinction between a customer complaint and the monitoring and reporting of adverse events under 21CFR Part 803, and apply the ERES Framework accordingly.

Other functionality supported by the Oracle E-Business Suite allows the electronic equivalent of paper forms to be managed and signed as approved electronic templates. These can be used as the master templates for reports stored in the Oracle Evidence Store, with full version control and approval supported by workflow.

This allows individual users to change the layout of default e-record templates or to create their own, thereby allowing the E-Business Suite to closely match the layout and content of existing paper records.

Based upon the experience of developing a compliant solution for other medical device clients using customization (prior to the availability of the ERES Framework), Business & Decision estimate that using the Oracle E-Business Suite ERES Framework means that a compliant solution can be implemented in less than a tenth of the time when compared to traditional customization.

Based upon experience with the Oracle ERES Framework in Oracle Process Manufacturing, Business & Decision estimates that the use of the Oracle ERES Framework is between two and five times faster than using other ERP systems with their limited Part 11 solutions (depending upon the scope of the predicate rules and the completeness of the "Part 11 compliant" solution available in other ERP systems).

### **Best Practice Business Processes**

Based upon the development work undertaken by the Oracle Discrete Manufacturing development teams, pre-configured solutions now exist for medical device sectors. These solutions leverage the ERES Framework and a pragmatic interpretation of 21CFR 820. (This mirrors the approach taken by the Oracle

Process Manufacturing team for finished pharmaceuticals against 21CFR parts 210 and 211).

Using their extensive knowledge of best practice business processes in these sectors, Business & Decision have developed standard pre-configured solutions based upon industry best practice business processes. These are accompanied by the use of a complimentary implementation approach that delivers a compliant, validated solution (see 'Compliant, Validated Implementations' below).

Unlike some other solutions, these best practice business processes are not generic discrete manufacturing processes, but are specifically developed for use by medical device manufacturers. The key differentiator is that these provide best practice business processes that are compliant with the requirements of 21 CFR part 820 (and other international medical device quality regulations and standards).

### **Other Sectors**

As described above, 21CFR Part 11 also applies to other sectors within Life Sciences, and there are other regulations that also need to be considered. The fact that the Oracle ERES Framework is so flexible means that regulatory compliance can be assured for any sector within Life Sciences and against any set of regulations.

This is an issue for some companies who are developing and manufacturing products that are covered by multiple regulations (such as pharmacotherapeutic devices, which combine the drug delivery device and the active drug).

Although the basic Process Manufacturing and Discrete Manufacturing implementations are based around a pragmatic interpretation of 21CFR Parts 210 and 211 and 21CFR Part 820 respectively, the flexibility of the ERES Framework allows these solutions to be quickly modified to support:

- End user specific interpretation of 21CFR Parts 210, 211 and 820
- Other sectors, such as over-the-counter and biomedical
- Areas of changing regulations such as applied nutrition (and the pending GMP regulations in this sector – 21CFR Parts 111 and 112)
- Active pharmaceutical ingredients (ICH Q7a <sup>[8]</sup>)
- Other national and international regulations

## It's Not Just 21CFR Part 11

It should be noted that although most focus on electronic records and electronic signatures has been driven by the FDA and 21CFR Part 11, other guidance on the use of electronic records, audit trails and electronic signatures does exist and applies to many organizations that do not export to the US.

Specifically, the latest guidance from the Pharmaceutical Inspection Cooperation Scheme <sup>[9]</sup> provides guidance on the use of compliant electronic records, audit trails and electronic signatures. This is very similar in nature to the FDA's latest guidance and those organizations that do not export to the US should take specific note of this if they have failed to address ERES compliance issues to date.

While Oracle continue to leverage the ERES Framework in the development of the latest versions of existing and new modules in the E-Business Suite (such as Enterprise Asset Management), experienced partners such as Business & Decision are able to leverage the ERES Framework to ensure that individual client implementations are compliant with 21CFR Part 11, US predicate rules and other international regulations and guidelines.

## Compliant, Validated Implementations

As referenced above, the Oracle ERES Framework significant reduces the cost of implementing a compliant solution, but only when the implementation approach is designed to leverage the flexibility and technical compliance of the solution.

Based upon many years experience as an Oracle Certified Advantage Partner, and having worked alongside the Oracle development teams to develop and leverage the Oracle ERES Framework, Business & Decision has developed a complimentary implementation approach based upon the Business & Decision standard approach to the validation of ERP systems ("Regulated ERP").

In order to deliver on time and on budget, modern ERP system implementations typically use a Rapid Applications Development (RAD) approach to deliver solutions. Business & Decision have developed a generic ERP implementation model as shown below.

This generic model is designed to:

- Allow system specific RAD implementation approaches to be modified to support system validation and regulatory compliance
- Allow project specific implementation approaches to be developed to meet the implementation and validation requirements of individual clients. These approaches are based upon the project scope and the specific roles and responsibilities of the implementers and clients.
- Allow the project specific implementation approaches to be mapped against recognized validation lifecycle models. This is necessary in order to allow inspectors from regulatory agencies such as the US Food and Drug Administration (FDA) or U.K. Medicinal and Health products Regulatory Agency (MHRA) to understand how a RAD implementation approach has been used to support validation of the system. The generic model is mapped against the GAMP 4 'V' model, which Business & Decision have helped develop through more than ten years work at the heart of the

GAMP Forum (and which now forms the basis of FDA and MHRA training in computer systems validation).

Recognizing the differences in the approach to validating systems in the pharmaceutical and medical device sectors, Business & Decision have a specific version of this methodology for use in implementation in the medical devices sector.

Although most of the implementation and validation activities are identical, the validation plan and certain key validation deliverables recognize the different regulatory stance and differences in validation terminology within the medical devices sector.

While the Oracle E-Business Suite is not classified as a medical device, this approach ensures that the project deliverables are consistent with regulatory expectations of CDER, including the use of appropriate language (an example would be hazard analysis versus risk assessment).

### **Streamlined, not Rapid**

Oracle has a standard RAD implementation model for Oracle 11i, called FastForward. This is designed for the rapid implementation of standard solutions in non-regulated industries. While in some cases this can deliver a working system in periods less than four months the level of documentation produced is generally not suitable for the delivery of a compliant, validated system within the medical devices sector.

For the Life Science industries, Business & Decision has developed a generic implementation model for the industry. Rather than being based upon FastForward, this model is based around a streamlined version of the traditional Oracle AIM methodology.

The AIM methodology leverages implementation accelerators, standard business processes, and standard documentation to streamline implementation and reduce the cost. The Oracle 11i E-Business Suite Life Sciences implementation model developed by Business & Decision includes additional activities integrated with AIM that support the validation and regulatory compliance of the solution. This includes specific activities and deliverables supporting key tasks such as unit and integration testing of customized reports and interfaces.

This approach is complementary to other third party implementation models, which are also based upon the Oracle AIM approach, and can be mapped to any standard 5-stage implementation approach.

This model is not a standard 'out-of-the-box' implementation methodology because:

- In order to support the validation of the system it is necessary to demonstrate that the implementation meets the specific User

Requirements of the individual client. While standard business processes and documentation templates can be used to accelerate this process, it is important to provide documentary proof that all business processes correspond to the specific User Requirements of the individual client.

- End clients are responsible to the regulatory authorities for the appropriate validation of the system. While Business & Decision can support or execute some or most of the validation activities, this must be under the clearly delegated authority of the User and it is important to define the exact roles and responsibilities within each project specific implementation model.
- Each medical device organization manufactures different products, with a different potential risk to patient safety. Project implementations activities must be scoped in accordance with project specific Hazard Analysis. These will ensure that the implementation (hazard mitigation) and verification activities are appropriate to the hazard. This approach will minimize the cost of implementing and validating the system while still achieving regulatory compliance because this cost reduction is justified on the basis of a documented hazard analysis.
- Clients often operate under different predicate rules, and different predicate rules often apply to different parts of the client organization. For example 21 CFR Part 820 in the USA, and EU Directive 93/42/EEC and ISO 13485 in Europe. The project specific implementation model must recognize these differences in regulatory requirements and the implementation must assure compliance with all applicable regulations.
- Different clients are able to supply different levels of resource and expertise. The final project implementation model will depend upon the availability and expertise of client resources and the clear definition of project roles and responsibilities.
- It is usually necessary to ensure that project activities and deliverables comply with any existing client Policies, Guidelines and Standard Operation Procedures with respect to computer system validation and the implementation model must reflect this requirement.

### **ERES Compliance**

ERES compliance is an integral feature of the Oracle/Business & Decision Oracle 11i implementation methodology.

During the first conference room pilot an industry specific best practice business processes are used to accelerate the design process, in this case based upon standard Oracle business scenarios and workflows. These are supplemented by any existing business models that the client may possess. This is used to prepare a business Blueprint, leading to the definition of the 'To-Be' Business Model (the 'Corporate Business Model' in the Generic Regulated ERP Implementation Model).

During the first conference room pilot Business & Decision and Core Team members from the clients Quality Assurance or Regulatory Compliance Function will identify all predicate rules that apply to the Corporate Business Model. This may include regulations from the US Code of Federal Regulations (for instance 21CFR Parts 58, 803 and 820). For multinational rollouts other regulations will also need to be considered.

This process will identify the predicate rules with which compliance must be demonstrated, and which predicate rule maps Business & Decision will use during

the second conference room pilot. (A predicate rule map is an annotated version of a predicate rule that identifies all potential records and signatures that may either be explicitly or implicitly required by the rule).

During the second round of conference room pilots, detailed design and documentation of the individual business scenarios will take place. These are typically documented as workflows, (swim lane diagrams) to:

- Identify all transactions within each business scenario
- Identify user profiles authorized to conduct all transactions
- Identify key operations performed outside the system (either manually or in external systems), thereby identifying interfaces to other systems of paper based processes

In the Oracle 11i implementation model, standard 'best practice' transactions and workflows are used to accelerate the production of these diagrams, which form a critical part of the Functional Requirement Specifications.

Using the predicate rule maps identified as part of the first conference room pilot, Business & Decision and members of the clients Quality Assurance or Regulatory Compliance function would then map the business scenarios to the requirements of the applicable predicate rules.

This process is accelerated by the Oracle 11i ERES Framework, which defines a standard set of Electronic Records and Electronic Signatures for use by medical device organizations. Although this is an important accelerator, as described above it is up to each individual client to determine their own interpretation of each predicate rule as it applies to their own business and products.

In some instances this process will be used to challenge the need for existing records and signatures that may currently be implemented in a paper based system, but which have no basis in the regulations. Defining a minimum set of records and signatures for implementation in the system will improve the operational efficiency of the final system whilst still assuring regulatory compliance.

Based upon the client specific interpretation of the applicable predicate rules, the individual transactions within the business scenarios (swim lanes) will then be marked up with ERES requirements.

ERES Summaries are then produced which map the individual transactions against the sub-sections of the predicate rules which define those transactions as GxP critical and document where the controls of the Oracle 11i ERES Framework should be applied

The output of the second conference room pilot is therefore a complete set of documents (User Requirement Specifications, Functional Requirement Specifications [swim lanes], Application Configuration Set-Ups and ERES Summaries] that clearly demonstrate complete traceability between:

- Business Models to Predicate Rules,
- Predicate Rules to ERES Scope,
- ERES Scope to Transactions and Workflow,
- Transactions and Workflow to Package Configuration,

- Package Configuration to Oracle 11i ERES Framework set-up.

This approach compliments the approach taken by Oracle and Business & Decision during the development of the ERES Framework, leverages the inherent flexibility of the ERES Framework and delivers a validated and compliant solution in a streamlined and cost effective manner.

## Conclusions

As described above, Oracle Corporation committed to develop an ERES solution that was fully compliant with the technical controls identified in 21CFR Part 11. By leveraging the underlying security of the Oracle 9i database, the regulatory expertise of Business & Decision and by developing a standard, flexible ERES Framework, Oracle has developed a solution that sets the benchmark in the industry.

Unlike most other organizations, Oracle has recognized the needs of the medical device community and has developed a set of standard business processes with compliance to 21 CFR Parts 11 and 820 'pre-configured'.

Business & Decision's development of a complimentary implementation approach ensures that this solution can be used as the basis of a cost effective, validated and compliant solution. Furthermore, the combination of the ERES Framework and the implementation approach ensures that such systems can remain in compliance, despite pending changes in the regulatory landscape.

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## References

- <sup>1</sup> "Guidance for Industry: Part 11, Electronic Records; Electronic Signatures — Scope and Application", August 2003, Pharmaceutical GMPs. Available from the Dockets section of the FDA website <http://www.fda.gov/>
- <sup>2</sup> See Mi-Services White Paper "Leveraging 21 CFR Part 11 Compliance for Business Benefit in a Changed Enforcement Regime", September 2003.
- <sup>3</sup> See Business & Decision White Paper "Enabling Effective Corporate Governance", October 2003, for details on Total Cost of Compliant Ownership.
- <sup>4</sup> See "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach; A Science and Risk-Based Approach to Product Quality Regulation Incorporating an Integrated Quality Systems Approach" at <http://www.fda.gov/oc/guidance/gmp.html>.
- <sup>5</sup> Public Health Security and Bioterrorism Preparedness and Response Act of 2002, June 12<sup>th</sup> 2002
- <sup>6</sup> For details see Federal Register: March 13, 2003 (Volume 68, Number 49) "Current Good Manufacturing Practice in Manufacturing, Packing, or Holding Dietary Ingredients and Dietary Supplements"
- <sup>7</sup> See Oracle Product Announcement "Oracle Electronic Records and Signatures Framework", January 2003
- <sup>8</sup> "Guidance for Industry Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients", August 2001

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<sup>9</sup> PIC/S Guidance “Good Practices For Computerized Systems in Regulated GxP Environments”, August 2003 (in force from 1<sup>st</sup> September 2003)

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## Business & Decision and Oracle in Life Sciences

Business & Decision (formally Mi Services) has been involved in computer systems validation for over two decades and with the complex issue of Electronic Records and Electronic Signatures since consultation on 21CFR Part 11 started in the early part of the 1990s.

Our Life Sciences consultancy teams provide expert guidance on compliance and computer systems validation issues as well as business consultancy and IT and computer systems implementation services.

Business & Decision are an Oracle Certified Advantage Partner, with specific emphasis in Life Sciences. Working closely with the Oracle E-Business Suite development teams, Business & Decision supported the development of the Oracle E-Records Framework, leveraging customized solutions previously developed by Business & Decision.

The current E-Business Suite best practice business solutions for Life Sciences are the result of close collaboration between Business & Decision and Oracle. These leverage Oracles technical expertise, Business & Decision in-depth knowledge of global regulations and computer systems validation and our joint understanding of industry best practices in Life Sciences.

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