21 CFR Part 11 Compliant Recipe and Batch Management – What’s Missing?

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KEY WORDS

ABSTRACT

In this paper (and associated presentation), the requirements to manage various levels of batch recipe within the pharmaceutical and other sectors within the Life Sciences sectors industry will be discussed, as well as the requirements to maintain secure batch records, including compliance with various electronic records and electronic signatures guidance.

Examples of how this can be achieved within an ERP solution (without the need for a separate MES level batch or recipe management solution) will also be discussed.

Key points in the paper include:

- The definition and management of key attributes in the master and control recipes, critical to product quality and patient safety,
- The requirement to review electronic batch records as if they were paper,
- The use of ‘what you see is what you get’ batch record review, including the use of compliant electronic signatures,
- A discussion of the advantages and disadvantages of an ‘ERP only’ solution.

Like any other industry involved in complex batch manufacturing, the pharmaceutical and associated industries has a need to manage recipes and associated attributes in an efficient manner. There is also a regulatory requirement to ensure the security and integrity of recipe attributes that are critical to
product quality and patient safety. The pharmaceutical industry also has regulatory requirements to review and approve each batch of product and to maintain batch records for many years (decades in some cases).

This paper highlights such regulatory needs and compares these to the business needs of other industries involved in batch manufacturing.

These requirements can be met through the use of S88 compliant software packages, but integrating such solutions from the Enterprise level through to the shop floor often presents problems. Typical issues include assuring the integrity of data through multiple interfaces, maintaining compliant audit trails of any changes made and in the context aware implementation of electronic signatures.

An additional problem with an ERP only solution is the traditional difficulty of applying and securely linking compliant electronic signatures to a batch record that is effectively just a collection of rows in multiple tables in a relational database. How does the user understand what he is signing? How can a context specific signature be demonstrated to appropriate regulatory agencies?

Working with Mi Services Group, Oracle Corporation has implemented a recipe and batch management model, incorporating electronic record and electronic signature capability and specifically designed to meet the needs of the pharmaceutical industry. This includes the ability to provide integration to the shop floor and well as context specific electronic signatures that can be demonstrated to regulatory inspectors.

The associated presentation will include a demonstration of this solution and this paper discusses the definition and documentation of key recipe and batch attributes, the use of master and control recipes within the Oracle E-Business Suite and the XML formatting and electronic signature of ‘what you see is what you get’ batch records.

However, while modern Enterprise Resource Planning systems can manage a number of these issues the industry often prefers to go for a ‘best of breed’ approach, integrating leading edge batch and recipe management solutions to the shop floor level.

In conclusion the presentation will discuss the advantages and disadvantages of an ‘ERP only’ solution, including pre-requisites for successfully linking ERP systems directly to the shop floor and reasons why the use of best of breed batch and recipe management solutions should still be considered.

1. Introduction

Based in part on solutions initially developed by Mi Services Group, Oracle Corporation has implemented a technical solution to meet the requirements of FDA enforced 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. The solution also overcomes many of the problems associated with other systems that claim to be compliant with 21CFR Part 11.

Full details of the ERES 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 ERES Framework to support the use of regulatory compliant electronic batch records.

2. 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.

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.” [1,2]

Life Sciences organizations should therefore continue to assess their critical systems and undertake corrective actions including the upgrade or replacement of noncompliant systems where necessary. Whilst reviewing the regulatory compliance of existing systems and potential replacements, organizations should review the efficiency with which the requirements of 21CFR Part 11 can be implemented, including the critical area of electronic batch records.

As discussed elsewhere [1] 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 life sciences organizations 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 currently [1,2] 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.

3. 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, including recipe management and batch reporting solutions. However, some of these solutions are more compliant than others and a number of them 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.

While implementation of the S88 and S95 standards does not in any way conflict with the requirement to implement business processes that comply with the predicate rules, lack of attention to the detailed requirements of such regulations can mean that recipe and batch management solutions may not be compliant.

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 (often involving 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” system Mi Services 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 including recipes and batch records,
3. The application must support (and ideally enforce) best practice business processes such as those defined by S88, 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 inspection,
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 ERES Framework.

(It should of course be recognized that no system is 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).

4. Regulatory Requirements for Recipe and Batch Management

The requirements for recipe and batch management are defined in various regulations. In the pharmaceutical sector 21CFR Part 211 defines the requirements for associated record keeping.

In the medical device sector 21CFR Part 820 defines such requirements. The majority of medical devices are manufactured in discrete ‘lots’ and while the principles of S88 and S95 may be applied it is more usual to leverage different process manufacturing models in a discrete manufacturing environment. However, certain medical devices are manufactured using more traditional process manufacturing batch oriented processes and the S88 standards and much more applicable and 21CFR Part 820 may need to be interpreted in this respect (liquid bandages and surgical adhesives are two such examples).

New regulations are also starting to define recipe and batch record requirements, such as the draft 21CFR Part 111 which applies to dietary supplements and medical nutrition.

Such requirements not only apply in the US. The European Union has similar Directives governing Good Manufacturing Practice for pharmaceuticals (2004/93/EC) and the manufacture of medical devices is also governed by ISO standards (ISO 13485). Similar international guidance [4] also exists for the use of compliant electronic records, audit trails and electronic signatures.

All of these regulations have similar requirements for the creation, management, storage and retrieval of key attributes associated with product recipes and batch records. These include attributes such as:

- Product name, strength and dosage form,
- Formulation with intent to achieve 100% of the active ingredients,
- Traceability between raw materials and individual batches,
- Correct weights and measures,
- Equipment identification,
- Verification of formulation by a second person,
• Significant manufacturing steps and dates,
• In process and laboratory results and sampling details,
• Actual yields and percentages,
• Description of containers, closures packaging and labelling,
• Examination, investigation or inspection results.

Note that this list is not comprehensive with respect to all of the potential regulations that may apply to an organisation manufacturing products for multiple markets. Specific requirements also exist in some of these regulations that require that ‘appropriate controls’ are exercised over batch recipes (21CFR Part 211.68(b) for example), which infers the use of secure access and full audit trails.

It should also be noted that these regulatory requirements are subject to interpretation by the manufacturer. As an example, what constitutes a ‘significant manufacturing step’ and what should be interpreted as a formal investigation?

While standards such as S88 and S95 provide a consistent model for the definition of recipes and batch records it can be seen that life sciences organizations face a number of problems:

1. Although the recipe management requirements required by regulations such as 21CFR Part 211 (which uses the terms ‘master production and control records) can be met within the S88/S95 models, the requirements for batch records goes well beyond the traditional ‘batch record’
2. Recipe and batch management requirements must be clearly interpreted with respect to specific product profiles and individual products.
5. The Need to Review Batch Records

Regulations such as 21CFR Part 211 also define a requirement for a second person (often the Quality Assurance group or a ‘Qualified Person’) should review all batch records.

There is also a regulatory requirement to ensure that all batch records are available for review during a regulatory inspection, throughout the life of such records (which may be decades for certain product profiles with an extended shelf life).

While later revisions to regulations such as 21CFR Part 211 recognizes that such records may be made available by computerized means (211.180[c]) there is a still a requirement for immediate access.

Because of the long history of using paper batch records, there is also a pre-conceived expectation with respect to the content and format of a batch record – an expectation that many computer based systems fail to meet.

6. The Problem with Tradition ERP Batch Records

While ERP systems have long been able to provide basic records of batch production, there have traditionally been three major failings with respect to meeting regulatory expectations for batch records (in addition to the technical requirements of 21CFR Part 11).

These challenges are:

1. Assuring the data integrity of batch records.
2. Formatting the batch records to meet regulatory expectations.
3. Including all of the necessary content in the batch records, including attachments.

Each of these is interlinked to some extent and can not be considered in isolation. Achieving regulatory compliance and meeting the expectations of regulatory inspectors is not always the same thing and can only be achieved by considering each element during the design of an electronic batch record solution. Issues associated with each of these challenges are discussed in further detail below.
7. 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, very 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 ERES Framework, Oracle E-Business Suite relied on the strong security of the underlying database. Because Oracle effectively owns 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 (including batch 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 that 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 and associated tools and the ongoing Total Cost of Compliant Ownership can be minimized.
8. Compliant Electronic Recipes, Batch Records and Audit Trails

Providing secure electronic recipes, batch records and secure audit trails has proven to be an ongoing 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 master and control recipes and batch records are defined by the applicable predicate rules (see above), and these may be comprised of multiple columns from multiple tables within the relational database.

In a large and complex system such as an Enterprise Resource System (ERP) there 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 need to be produced from the electronic records.

The first of these problems is an implementation issue, and is outside the scope of 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 Oracle ERES Framework allows flexibility with respect to turning on (and turning off) audit trails 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 (including batch 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, 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 life sciences organizations 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 21CFR Part 11 and predicate rule requirements for data retention. This is achieved without imposing unnecessary overhead on server performance.

Finally, Oracle’s use of dedicated database tables for GxP critical electronic records such as control recipes and batch 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 – see figure below). 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.
Although most ERP solutions are able to provide standard batch reports these seldom include all of the information required by the regulations. Lack of technical compliance with 21CFR Part 11 often means that custom reports need to be printed and signed in any systems, thereby negating the efficiencies of using an integrated ERP solution.

Many other ERP based solutions are only able to rely upon querying the underlying relational database tables to provide ‘evidence’ that recipes and batch reports have not been subject to unauthorized change. This is difficult to explain to a regulatory inspector with 20 years experience inspecting paper records and who has no little or no concept of the relational databases underlying a transaction based system.

In the Oracle E-Business Suite, the ability to format compliant batch records is a big advantage during regulatory inspections, where batch reports can be retrieved from the evidence store and displayed in a format with which the inspector is familiar.
In developing the Oracle ERES Framework, standard reports (including batch reports) have been defined based upon ‘inspection cases’, by asking what information regulatory inspectors typically expect to review during a regulatory inspection. These have been used to define standard reports to which a pre-defined set of data is written for storage in the Evidence Store. This reduces the amount of work required to implement electronic batch records but the standard reports are fully configurable to meet the needs of specific users.

In addition, 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.

Because the critical control recipes and batch records are stored as XML data, they can be ‘mined’ to support inspections and investigations, allowing questions such as “show me all the batch reports approved by a particular person, between these dates” or “show me all batches that use this lot of raw material” to easy be performed – and demonstrated during a regulatory inspection.

![Figure 2 – Querying Electronic Records in Oracle E-Business Suite](image)

Finally, unlike other ERP solutions, the Oracle ERES Framework also allows other files to be attached to any electronic record. This includes the ability to version control attachments and sign them electronically. This provides the capability to provide a complete batch record (exceeded the dataset defined in S88 and S95).

It is therefore possible to include laboratory results in the form of a spreadsheet attachment, to include an investigation report in the form of a word processor file or to scan copies of packaging and labelling ‘starting materials’ as a .PDF file. All of these can be reviewed in context as part of the
overall batch record and remain securely attached to the batch record to support future regulatory inspections.

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,
- The ability to ‘data mine’ critical electronic records,
- The ability to include ‘attachments’ within the batch record.

9. 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.

As discussed above, requirements to review and approve master recipes, control recipes and batch records mean that the compliant use of electronic signatures is necessary of any life sciences organization of to operate efficiently and in a compliant manner in a paperless environment.

Because separate master electronic records are created in the Evidence Store, securely attaching compliant electronic signatures to electronic records is easily achieved. 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 batch 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 allows signatures to 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.
Figure 3(a) – Applying Electronic Signatures in Oracle E-Business Suite

Figure 3(b) – Applying Electronic Signatures in Oracle E-Business Suite

“What You See Is What You Sign”
The Oracle E-Business Suite ERES 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 ERES Framework (in combination with Oracle’s 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 user’s interpretation of the applicable regulations.

Where defined in applicable predicate rules such as 21CFR Part 211 and 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 three 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 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 recipes and batch reports 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.

**10. Why is Flexibility So Important?**

The new guidance from the FDA [2] 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 21CFR 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.

Mi Services 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.

Mi Services 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, different electronic signatures may be required for the approval of control recipes for different manufacturing sites, or additional controls may be required to ensure that only a Qualified Person can review an electronic batch record and release a batch of finished pharmaceutical to be used with pharmacotherapeutic medical devices.

### 11. 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 the same time the FDA has committed to review their pharmaceutical GMP regulations \(^5\) and new regulations are likely in the food sector. It should therefore 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.

This allows different life sciences organizations to quickly review and revise the content, format, review and approval of their recipes and batch records as new regulatory requirements are introduced, or as the interpretation of current Good Manufacturing Practice (cGMP) changes over time.
13. Other Industries - 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.

While some responses to the FDA’s request for comment on the status of Part 11 have elicited some calls for the rule to be totally withdrawn, to do so would not be consistent with the Agency’s role in protecting public health.

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 are and should 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 [6]) will bring in new predicate rules, and draft changes to regulations such as 21CFR part 111 and 112 [7] 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 most likely confirm 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.

The use of a flexible recipe management and batch record solution within the Oracle E-Business Suite means that the scope of critical electronic records and electronic signatures can be applied on a case by case basis, leveraging risk assessment where appropriate.

Whilst other industries have no such regulatory requirements around the use of electronic recipe and batch records (and associated signatures), there is often competitive advantage to be gained from the use of electronic signature enabled workflow based transactions and the assurance of batch quality through the use of appropriate controls.

This is especially the case where other critical products (such as hazardous materials) are manufactured and other industries can therefore derive benefit from appropriately leveraging the developments made in support of the life sciences industry.

14. Best Practice Business Processes

Based upon the development work undertaken by the Oracle development teams, pre-configured solutions now exist for the pharmaceutical and medical device sectors. These solutions leverage the ERES Framework and a pragmatic interpretation of 21CFR Parts 210, 211 and 820.
Using their extensive knowledge of best practice business processes in these sectors, Mi Services 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 manufacturing processes, but are specifically developed for use by life sciences sector. The key differentiator is that these provide best practice business processes that are compliant with the requirements of the predicate rules and incorporate compliant recipe management and batch records.

15. 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 [4] 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 continues 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 Mi Services are able to leverage the ERES Framework to ensure that individual client implementations are compliant with 21CFR Part 11, US predicate rules (enforced by the FDA) and other international regulations and guidelines.

19. What’s Missing – The MES Layer?

Based above it could be concluded that at least one ERP solution is capable of providing a comprehensive recipe and batch management solution for the life sciences sector, doing away with the need for dedicated MES layer recipe and batch management solutions.

There are however a number of areas in which dedicated best of breed MES solutions still have advantages.

ERP systems still do not fully comply with S88 and S95. This is partly because the relational database structure makes it difficult to fully map against the S88 and S95 models and because the business process terminology used in the implementation of these systems differs (to a greater or lesser extent) from S88 and S95 terminology.
In addition, ERP systems still do not provide an acceptable presentation layer to the process operators, who are used to SCADA type graphics and MES type recipe and batch presentations. This makes it difficult to replace MES and SCADA type solutions where a significant degree of operator involvement is required.

All of these problems can be overcome, but customisation may be required and this usually requires a significant increase in validation costs.

Technically it is possible that ERP systems can be directly integrated to the control/automation layer and this has been done on a number of occasions. This is time consuming and complex, but does provide significant return on investment in the right circumstances.

In terms of where this can best be achieved without an intervening MES recipe and/or batch management solution, the disadvantages of the ERP solution would suggest that this is best achieved where there is little or no change required in plant configuration and where little or no operator involvement is required (i.e. highly automated operations).

In Life Sciences this points towards use principally in:

- Primary (bulk / API) production,
- ‘lights out’ secondary manufacturing
- Large volume discrete manufacturing.

In these circumstances it may be possible to use the compliant recipe and batch management solution incorporated as part of the Oracle E-Business Suite ERES Framework with the need for an intervening MES solution.

However, for the majority of batch operations (pilot plants, multi-purpose primary plants, flexible secondary manufacturing, short-run discrete production or highly configurable medical devices) there will be a requirement for mid-layer recipe/batch management solutions for the foreseeable future.

The one exception to this is the requirement for an additional, dedicated electronic batch record system (EBRS). While such solutions provide all of the benefits described above, such solutions require additional investment. Since this functionality is now capable of being incorporated into the ERP solution the need for a separate dedicated EBRS is less clear.

In many cases ERP systems such as the Oracle E-Business Suite can replace a separate EBRS and the decision as to whether to use a separate EBRS or leverage the flexibility of the ERP system can only be decided based upon a detailed study of specific requirements and cost/benefits analysis.
20. 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 Mi Services and by developing a standard, flexible ERES Framework, Oracle has developed a solution that sets the benchmark in the industry.

By considering regulatory requirements from the outset, the result is a recipe and batch record management solution that is capable of meeting the technical requirements of 21CFR Part 11 and the expectations of various regulatory authorities during inspections.

Whilst this does not do away with the need for a separate recipe and batch management solutions in all circumstances, there is now a much reduced need for separate EBRS solutions and in some circumstances it is possible that MES will become ‘the missing layer’.

References
2. FDA “Guidance for Industry. Part 11, Electronic Records; Electronic Signatures — Scope and Application”. Note that many responses to the current FDA docket in 21CFR Part 11 suggest an overall relaxation on the technical controls that apply to 21CFR Part 11, with all organizations using a risk based combination of technical and procedural controls, physical and logical security to demonstrate appropriate compliance with the intent of the Rule. The Agency’s response is yet to be published.
7. 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”