REGULATORY EXPECTATIONS FOR HUMAN TISSUE RESEARCH

Anthony Chadwick PhD
Global Human Tissue Designate
Covance Regulatory Strategy CDS

Anthony.Chadwick@Covance.com
Human Biological Sample (HBS)

DEFINITION: MATERIAL THAT MAY CONTAIN HUMAN CELLS

► Identifiable material
  • Human bodies, limbs, organs and tissues, excised tumors, skin & bone

► Cell based material
  • Stem cells, bone marrow and primary human cell cultures
  • Cryopreserved hepatocytes

► Clinical Samples / Fluid Samples / Waste
  • Blood, blood derivatives (e.g., Serum, Plasma), Urine, Faeces & Sputum

It does not include
  • Cultured cells which have divided outside the human body
  • Acellular material
Public

Background

Cancer research hampered after Alder Hey

Tuesday May 22, 2001

Guardian Unlimited

New legislation and the Alder Hey scandal is preventing vital cancer research from being carried out in Britain, a specialist claimed last night.

Chris Foster, a pathologist at the Royal Liverpool Hospitals, said studies into breast cancer, which kills 1,000 British women every month, and prostate cancer will now not be conducted at the university laboratories.

He told Channel 4 News: "We have the ability to identify new aspects of these diseases which will be helpful and beneficial to patients... and yet we are being handcuffed and hampered for reasons that I believe are totally spurious."

'Hospital gave me baby's heart in box'

Parents protested outside the GMC in London

A mother who did not know that doctors had kept her child's heart broke down in tears as she told a public inquiry how it was returned four years later.

Helen Rickard, from Bristol, told the inquiry into the city's Royal Infirmary that she held her daughter Samantha's heart in her hand.

"I felt highly privileged to have been able to do that because of who my daughter was."

Samantha died in February 1992 after surgery to repair serious heart defects, but it was not until 1996 that her mother found out the hospital had retained the organ following a post mortem.

Helen Rickard told the inquiry that the discovery had "shocked and distressed" her.

"I buried Samantha believing I buried all of her as she came into this world. I then had the terrible prospect that her heart been removed."

Here In France in 1990’s

• Removal of dead child’s eyes for transplant without parents knowledge or consent

• Scandal over contaminated blood used in transfusions

• Use of tissues for transplant, not screened for HIV

Bristol inquiry to look into child organ removal

At least 29 babies died following heart surgery at Bristol Royal Infirmary

The public inquiry into a child heart operation scandal is likely to look into allegations that a hospital routinely removing organs from the bodies of dead children without their parents' consent.
European Legal Framework

EUROPEAN UNION TISSUE AND CELLS DIRECTIVE (EUTCD) 2004/23/EC

Sets standards for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells intended for human application.

2004/23/EC, issued and ratified by the European Parliament in March 2004,

All member states of the European Community obliged to transpose Directive 2004/23/EC into their national legislature within a period of 2 years.

USE OF HUMAN TISSUE / CELLS / EXTRACTS FOR HUMAN APPLICATION

**FRANCE _ EARLY ADOPTER**

Response to Public Health and Ethics concerns relating to use of human cells and tissues

**Law 94-653** _Respect for the human body_

**Law 94-654** _Donation and Use of Elements and Products of the Human Body_
- Mandatory requirement for Informed Consent
- Data Protection and Confidentiality _Donor confidentiality is protected
- Non commercialisation of donation process

Since 1994, comprehensive legislation regulating human tissue use and banking
- Social Security Laws
- French Public Health Code (CSP; *Code de la Sante Publique*)
- Afssaps authorisation (Clinical Trials, Accreditations and Inspection)
  - Procurement, Traceability, Import and Export, Processing and Storage.
The Human Tissue Authority (HTA) was established on 1 April 2005 to regulate the removal, storage, use and disposal of human bodies, organs and tissue for a number of ‘Scheduled Purposes’ – (research)

Legislation – set out in the **Human Tissue Act 2004 (HT Act)**.

- **Consent** is the fundamental principle for the lawful storage and use of human bodies, body parts, organs and tissue.

- All uses of human tissue must be approved by Local Research Ethics Committee (LREC - NHS).

- Storage of human tissue for research will be subject to licensing and inspection.
UK HTA Codes of Practice

REGULATORS AUDIT BASED ON THESE CODES AND STANDARDS

<table>
<thead>
<tr>
<th>1. Consent</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Donation of solid organs for transplantation</td>
</tr>
<tr>
<td>3. Post-mortem examination</td>
</tr>
<tr>
<td>4. Anatomical examination</td>
</tr>
<tr>
<td>5. Disposal of human tissue</td>
</tr>
<tr>
<td>6. Donation of allogeneic bone marrow and PBSC</td>
</tr>
<tr>
<td>7. Public Display</td>
</tr>
<tr>
<td>8. Import and Export of human tissue and samples</td>
</tr>
<tr>
<td>9. Research</td>
</tr>
</tbody>
</table>
German Tissue Act (July 2007)

RESPONSE TO THE EU TISSUE DIRECTIVE 2004/23/EC

German legal framework

The German Tissue Act (July 2007) set standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

The Tissue Act is not a single law. It is a ‘Legal Framework’ that amends the following:

- Drug Act (AMG since 1976)
- Medicinal Products Act (MPG since 1994)
- Transplantation Act (TPG since 1997)
- Transfusion Act (TFG since 1998)

Human Tissues / Preparations are ‘Medical Products’ under Drug Act.

Informed Consent required for secondary use of surplus tissue samples.

Non-commercialisation of human body and parts.
Swiss Human Research Act (2014)

Federal Act on Research involving Human Beings
(Human Research Act, HRA 810.30) 1 January 2014

• Act applies to research involving identifiable /coded biological material and health-related personal data. (clinical trials)
• Act does not apply to research involving anonymised biological material or anonymised data.
• Informed Consent required.
• Non-commercialisation of human body and parts (non-payment).

Federal Act on Human Genetic Testing
(HGTA 810.12) 1 January 2014

• Act does not apply to genetic testing performed for research purpose
Global Legislative Environment

HBSM / Human Research Protection

► Legislation established in several benchmark government jurisdictions around the world (i.e. US, EU, Japan)

► Standards for the donation, procurement, testing, processing, preservation, storage, disposal, use of, and distribution of human tissues, organs and cells from living or deceased subjects

► Although somewhat different in approach, laws are largely consistent and create a framework for how to manage HBS globally

Privacy and Confidentiality

► Recent significant changes globally

► Sample / Patient identifiers…………Personal Identifiable Information (PII)

There are over 1000 laws, regulations, and guidelines that govern human subject research in 120 countries

Human Research Protection Legislation

<table>
<thead>
<tr>
<th>Informed Consent</th>
<th>Governance and Quality Systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Storage</td>
<td>Contracts</td>
</tr>
<tr>
<td>Sample Management</td>
<td>Training and Resource</td>
</tr>
<tr>
<td>Premises, Facilities, Equipment</td>
<td>Records</td>
</tr>
<tr>
<td>Cleaning, Maintenance,</td>
<td>Sample Disposition</td>
</tr>
<tr>
<td>Transport of Samples</td>
<td>Disposal / Return / Storage</td>
</tr>
</tbody>
</table>

Good Laboratory Practice
Good Clinical Practice
Good Clinical Laboratory Practice

Requirements Overlap
Potential Regulatory Risk

- Sites are subject to inspection by the Management Authorities.

- Risks and Impacts of not complying with legislation range from improvement notices to site closure.

- In many countries of operation (USA, UK & EU) it’s a criminal offence not to comply with the legislation

- Persons responsible for the management of HBS can be imprisoned, including senior leadership.

  - For example, in the USA the CEO and ELT of Biomedical Tissue Services have been imprisoned for 18-54 years for serious breach and bad practices.
Impact HBS Lifecycle

Collection
- Clinical Trials Staff
- Vendors / Suppliers

Source

Disposal
- Return to Donor / Biobank
- Incineration
- Respectful
- MTA / SLA

Use
- Informed Consent
- Sample Identity
- Protection of Privacy / Confidentiality
- Labelling
- Ethics Approval of Research
- Protocol / SOW / MTA

Transport
- Import and Export of HBS
- Return to Donor / Biobank
- MTA / SLA

Further / Future use
- Bioinformatics
- Biorepository
- Amendment
- Informed Consent
- MTA / SLA

Activities Impacted

Storage
- Biorepository
- Informed Consent
- MTA / SLA
- Storage Period
- HBS Security / Integrity

13 Regulatory Expectations for Human Tissue Research | April 2016
Human Biological Samples Policy

Government legislation / Regulatory requirement
• virtually all countries of operation
• strong legal sanctions for non-compliance
• Government inspections of facilities

Voice of Industry
• Transparent HBS policies
• Refuse work in non-compliant labs
• Approve source / supply of HBS
• Representation & Warranty

Company has created individual global policies around the management of human biological samples [HBS].

• Sets standards for HBS lifecycle from all sources, including biobanks and commercial.
• Industry should only be using approved suppliers already known to enforce the legislative requirements
Mandatory requirement to confirm informed consent and ethics approval allows the ‘use’ intended by our Global facilities
Access to Human Biological Samples
Human Biological Sample Sources

INDUSTRY HAS 4 POTENTIAL ROUTES TO OBTAIN HBS:

- **Direct access from patient, through relationship with hospital**
  - Fresh Human Livers, Skin, Lymph Nodes

- **Obtained from staff/employees**
  - Fresh Blood, Urine, Feces, Saliva, Buccal Cells

- **Commercial Approved Suppliers**
  - National Biobanks
  - Cell based models, microsomes, blood, plasma, CSF
  - Large list on global basis

- **Clinical Studies**
  - Blood, Urine and other samples from clinical trials
  - Client / Central Lab /Clinical Site

---

**Global Legislation (General)**

Human biological samples shall be obtained **only** with the approval of an independent ethics committee and with **full** informed consent of the donor.
Procurement / Commercial Vendors

MAINTAIN ‘APPROVED’ SUPPLIERS DATABASE

► Evidence of Informed Consent Form (ICF) template
  • ICF meets criteria (HBS policy / Legislation) for use in service offering.
  • Evidence that suitable patient information is used / provided.

► Evidence of Ethics approval (IRB, IEC, REC) for tissue sourced.
  • Ethics approval / ICF must cover potential use of HBS.

► Contractual Agreement_ SLA / MTA with each supplier
  • Representations and warranties
  • Sample Disposition (Storage / Return / Disposal)
  • Anonymous samples obtained from supplier

► Licence / Permit / Accreditations etc.

► Supplier Audits to confirm consent process and evidence of good practice.
BBMRI-ERIC

Biobanking and BioMolecular resources Research Infrastructure – European Research Infrastructure Consortium

Largest Health Research Infrastructure in Europe
16 Member States (inc France, Germany, Sweden, UK)

► Increase the quality, visibility and accessibility of EU world class Human Biological Samples for academic and commercial researchers.

► Provide Guidance and Biobank Audit Scheme to highlight best practice

► Harmonisation of Standards for the collection and storage of Human Biological Samples and Data.

► Work with all stakeholders (SUPPLY AND DEMAND)
HBS from Staff Volunteers

Employees considered dependant relationship / vulnerable, by EC

Applies to Blood, Urine, Saliva, Sputum, Sperm, Buccal Cells etc……..

► Ethics Approval obtained (REC / IEC / IRB)

► Informed consent obtained from subjects
  • Donor Information Leaflet for each matrix
  • Include Use of the Human Biological Samples

► Confidentiality and Privacy protected throughout
  • Material collected, labelled, data recorded ensuring anonymity
  • Donor ID and information not shared with Ops areas / QA etc…

► Must not ‘pay’ for tissue and exploit commercially.
Clinical Trials_GCP

Interaction with Subject (SOURCE)
- Clinical Trial Protocol
- Informed Consent Form (ICF) and Information.
- Ethics approval (IRB, IEC, REC)

Sample Analysis (USE)
- Working Document (Protocol / Sample Analysis Outline / Work Order etc)
- SLA (source or sponsor) / MTA (Country of Origin)

Data Privacy + Confidentiality
- Sample Labelling / Identity

Sample Disposition / Use of Data (FUTURE / DISPOSAL)
- Destroy / Return to Origin / Stored securely for further research.
- Further / Future use of samples (outside of protocol and outside IRB / IEC)
- ICF and MTA (Country of Origin)
## Informed Consent Form (ICF)

<table>
<thead>
<tr>
<th>HBS LIFECYCLE</th>
<th>ICF CORE ELEMENTS</th>
</tr>
</thead>
</table>
| **SOURCE**   | ICF Approval from IEC / IRB  
Subject Informed Consent Obtained |
| **PRIVACY / ID** | HBS and accompanying information anonymised or coded  
ICF includes Data Privacy to protect donor identity |
| **USE**      | HBS / Data may be used for commercial research  
Consent obtained for activity to be performed by Analytical Lab  
HBS / Data may be used for Genetics (DNA) research |
| **STORAGE**  | Storage Period specified or indefinite ?  
Impact on Archive and Further Use activities  
Contradict with Regulatory or Contract Requirements ! |
| **FUTURE USE** | ICF covers anticipated future activity at a future time. (Generic / Enduring Consent) |
| **TRANSPORT** | HBS may be transferred (exported) to 3rd party |
| **DISPOSAL (DISPOSITION)** | Destroy / Return to Origin / Store for further research !  
End of Use / Notification ? |
Withdrawal of Informed Consent

COMMUNICATE TO ALL HBS END-USERS

Lab Must be informed promptly (Sponsor Responsibility)
- Lab must demonstrate Due Diligence / Contractual Agreement
- Stop Analysis of samples
- No further information / data will be generated

Action will be in line with ICF / Client instruction
- No data for results collected following withdrawal will be reported
- Samples may disappear from study / report expect it.

Sample fate to be confirmed
- Return
- Storage
- Destroy

MTA / Country Specific
Further Use of HBS / Amendment

IF USE / ANALYSIS IS NOT PART OF THE STUDY OR CLINICAL TRIAL PROTOCOL

Sponsor / Researcher request Change

- Samples will be stored for X years
- Study amendment
- Additional analysis
- Stored samples re-analysed for NEW BIOMARKER

Action must be in line with ICF or MTA

- Storage period must be in agreement with ICF
- Additional work must be in agreement with ICF etc……..

Amendment to ICF / Ethics Approval

- Labs will require ‘information’ on ICF from HBS Source / Investigators
- Amendments to ICF and other documents
- Anonymous Samples / Data and EC approval
Privacy & Confidentiality

A CHANGE IN PRACTICE?

Subject initials and DOB count as personally identifiable information (PII)
EC Data Protection (95/46/EC) restrict collection of subject initials and DOB.
Ethics Committees in certain countries (e.g. Germany, Belgium) request that DOB and initials are not collected.

► USA “Safe harbor” now invalid
► 2016_ New Clinical Trial Regulations
► 2018_ New EU General Data Protection Regulation

Appropriate mechanism to transfer EU personal data to the US?
In Germany, some local DP regulators will not support export of HBS or personal data from the EU to the US (model clauses included)
Sweden, Restrict time EU personal data can be outside Sweden (MTA)

Many companies have developed GCP / Privacy policies and prohibit the use of DOB and initials (PII) as identifiers, even by service providers (CRO).
Sample ID _ Privacy and Confidentiality

Subject Initials and Names will not be acceptable

- Anthony Chadwick
- AC

Subject Date of birth will not be acceptable

- DD-MMM-YYYY
- 11 SEP-1971

Identifier code should not be based on the HBS Donor’s initials, names or date of birth unless it is considered medically relevant to do so.

“ Pharma Quote “

Samples with personal identifiers, such as: Name, Date of Birth, and/or initials would contravene Good Clinical Practice (GCP) and Subject confidentiality
SURROGATE DOB
DETERMINATION OF AGE FOR REFERENCE RANGE

Days
0 - 2mn

Months
2mn - 2yrs

Years
2yrs - Adult

DD MM YYYY
Req Form

DD MM YYYY
IT System
Sample Labelling and Identification
GCP AND DATA PROTECTION

Clinical trial samples should be labelled in such a way as to allow their unequivocal identification.

HBS will be de-identified (anonymised) to protect the confidentiality of the HBS donor in compliance with Personal Data Protection legislation.

In all cases the most appropriate means is to use a coded label. Identifier code should not be based on subject initials / names or date of birth.

If Identifiable Biological Samples, Data or Documents are received
• Enable identification / are not anonymous
• Redaction policy to protect identity
• Report to Sponsor
Archive or Biorepository

**GCP Guidance**
Samples and specimens should be retained as required by GCP but only as long as the quality of the preparation permits evaluation.

Samples may be retained for further analysis outside of the original aims of the trial, provided this is defined in the clinical protocol and approved by the Ethics Committee.

CAP / CLIA requirements 10-20yrs for specimens

**However ICF and MTA are legal documents**

**ICF:** Samples will be destroyed following analysis (or within 30 days)

**MTA:** Samples will be destroyed / returned to country of origin following analysis (30 day return).
Transport of HBS

Sample Security / Integrity

- Minimise risk of theft or damage during transport
- Defined process to release material to other organisations

Traceability of sample

- Audit trail from source, transfer, use and disposal of tissue must be maintained during transport. Records of delivery and receipt.

Material Transfer Agreement with Transport Company

- Define roles and responsibilities of both parties, specify storage requirements to maintain integrity, security, traceability, risk assessments, responsibility for disposal of material
# Agreements, HBS Lifecycle

<table>
<thead>
<tr>
<th>Agreement Type</th>
<th>HBS Lifecycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Informed Consent Form</td>
<td>SOURCE</td>
</tr>
<tr>
<td>2. Material Transfer Agreement (MTA) Tissue Transfer Agreements</td>
<td>SOURCE / USE / DISPOSAL</td>
</tr>
<tr>
<td>3. Ethical Statements / Ethical Certificates</td>
<td>USE</td>
</tr>
<tr>
<td>4. Study Working Documents</td>
<td>USE / DISPOSITION</td>
</tr>
<tr>
<td>Protocol</td>
<td></td>
</tr>
<tr>
<td>Statement of Work (SOW)</td>
<td></td>
</tr>
<tr>
<td>Sample Analysis Outline (SAO)</td>
<td></td>
</tr>
<tr>
<td>5. Master Laboratory Service Agreements (MLSA)</td>
<td>Service</td>
</tr>
<tr>
<td>6. Task Orders / Purchase Orders / Work Order</td>
<td>USE</td>
</tr>
<tr>
<td>7. End of Use Certificates / Disposal Certificates</td>
<td>DISPOSAL</td>
</tr>
<tr>
<td>8. Disposition of HBS Return / Destruction</td>
<td>DISPOSAL</td>
</tr>
</tbody>
</table>
AGREEMENT on the transfer of biological material

The purpose of this agreement is to regulate the parties’ responsibilities when biological material and associated coded personal data is to be transferred from a sample principal to a recipient, who will use this for a research project that has been approved by an ethics committee in Sweden.

The agreement is both an agreement on the transfer of biological material and a personal data assistance contract. Moreover, it regulates how the biological material and associated coded personal data should be handled on expiry of the agreement so that the material and the coded personal data no longer can be used for research or any other purpose.

1. PARTIES
This agreement applies between the principal investigator, the sample principal in Sweden, and the referred investigator.

State the estimated end date for using the biological materials according to this agreement

State when the analysis is planned to be finished (year, month):

Samples will be:
- [ ] Completely consumed during analysis.
- [ ] Destroyed after analysis. Estimate date for destruction of samples (year, month):
- [ ] Returned after analysis. Estimate date for return of samples (year, month):
- [ ] Other:

The responsible researcher and the recipient are responsible for the destruction or return of biological materials and coded personal data.
MTA or End of Use Certificate

END USE CERTIFICATE

COVANCE CENTRAL LABORATORY SERVICES S.A., with offices located at 7 rue Moïse-Marches, 1217 Meyrin, Geneva, Switzerland (“Covance”) hereby certifies that it is receiving Human Biological Samples from investigator sites in Turkey in connection with the following protocol on behalf of [Sponsor] (“Sponsor”).

Protocol Title: YYY, YYY

1. Covance receives Human Biological Samples against its appointment by the Sponsor as the laboratory for the purposes of performing services pursuant to the referenced protocol (“Protocol”) to carry out the protocol specific tests on patient Human Biological Samples.

2. Covance certifies that the Human Biological Samples will not be used for any purpose other than the purposes of the Study as set out in the Protocol, and that such use shall not be changed nor the items modified or replicated without the prior consent of the Government of Turkey, which consent shall be obtained and provided to Covance by Sponsor.

3. Covance will use the Human Biological Samples in compliance with European Union Universal Declaration on the Human Genome and Human Rights.

4. Human Biological Samples will be transferred to Covance by Sponsor without the identity or any personally identifiable information of the individuals.

5. Before transferring Human Biological Samples to Covance, a Ministry of Health and Ethics Committee approved informed consent form must be obtained from each subject who is providing Human Biological Samples.

6. If anticipated further use of Human Biological Samples will fall outside the scope specified in the Protocol and subject consent form, as required by the laws; Covance will stop any further use and inform Sponsor.

7. Covance shall not provide the Human Biological Samples to any third party without the written approval of sending institution (“Institution”) or Sponsor. Covance will notify Institution of any request by a third party.

8. Covance acknowledges and agrees that the Human Biological Samples to be dispatched under this Certificate shall be utilized for research purposes and have some risks associated with their usage. Appropriate preventive actions should be taken for those risks.

9. Covance agrees to return or dispose of all materials and to evidence such acts accordingly in the event of termination of the agreement or withdrawal of written consent of the volunteer referred to in item 2.

10. Covance agrees that the Human Biological Samples shall not be used for any purpose that relate to the development of Weapons of Mass Destruction.

Full name of the clinical trial: [blank]

Protocol code: [blank]

Summary of the clinical trial:

By this agreement, the investigator and the institution who send the biological material requires the CONSINEE and CONSIGNOR to agree on the below terms before sending (Specify biological material type and amount) which shall be used for [blank] to be dispatched to the address [blank] of [blank].

1. Delivered biological materials shall be used only for the above-mentioned purposes. CONSINEE shall use those materials only for secondary purposes, which are initially approved by the CONSIGNOR in writing.

2. Prior to the dispatch of the biological materials to the CONSINEE, Turkish Medicines and Medical Devices Agency and Ethics Committee approved informed consent forms, which belong to the persons for whom the biological material is provided, should be obtained. This consent form should explain all the purposes of use of the biological samples.

3. CONSINEE cannot provide the biological material to the third parties without prior written approval of the CONSIGNOR.

4. Biological materials shall be dispatched by the CONSIGNOR to the CONSINEE without the identity or any descriptive information of the individuals.

5. CONSINEE shall use the biological materials in accordance with as the United Nations Human Genome and Universal Declaration of Human Rights.

6. CONSINEE acknowledges and agrees that the biological materials to be dispatched under this agreement shall be utilized for research purposes and have some risks associated with their usage. Appropriate preventive actions should be taken for those risks.

7. CONSINEOR and CONSINEE shall mutually agree that the biological materials cannot be used as a source for any commercial profit and the rights relating to a joint publication or a patent right that may arise may be the only exception for that CONSINEOR and CONSINEE shall mutually agree on those rights prior to trial initiation.

8. CONSINEE agrees to return or dispose of all materials and to evidence such acts accordingly in the event of termination of the agreement or withdrawal of written consent of the volunteer referred to in item 2.

9. This agreement shall be terminated in the event of termination of the trial, violation on the terms of related regulations or noncompliance with agreement clauses of either of the parties.

10. CONSINEE and CONSIGNOR shall be responsible from the execution of this Agreement and performances hereunder. In case of conflict, both countries of the parties’ courts are authorized.
Good Human Tissue Practice

Collection
- Informed Consent
- Supplier Database

Procurement

Source

Disposal
- Return to Donor / Biobank
- End of Use Certificate
- Disposal Certificate

Use
- Informed Consent
- Sample Identity / Labelling
- MTA
- SOW / SAO

Storage
- Storage Period
- How Long ?
- Location ?
- Archive (GCP)
- Return (ICF) !

Transport
- Can we Export ?
- Must we Return to Biobank

Further / Future use
- Informed Consent
- Can we Store ?
- Can we Use ?
- Ethical Approval

Who Owns Samples
Donor / Subject
Biobank (Source)
Client or Lab (USER)
Q&A

Covance Inc., headquartered in Princeton, NJ, USA, is the drug development business of Laboratory Corporation of America Holdings (LabCorp). COVANCE is a registered trademark and the marketing name for Covance Inc. and its subsidiaries around the world.