We Share for HVAC System
HVAC 系 统 微 分 享

Policy,Design& Qualification

上海里知工程咨询有限公司
Shanghai Leedzone Engineering Consultant Co. ,LTD.

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

Topic for weshare 微分享主题

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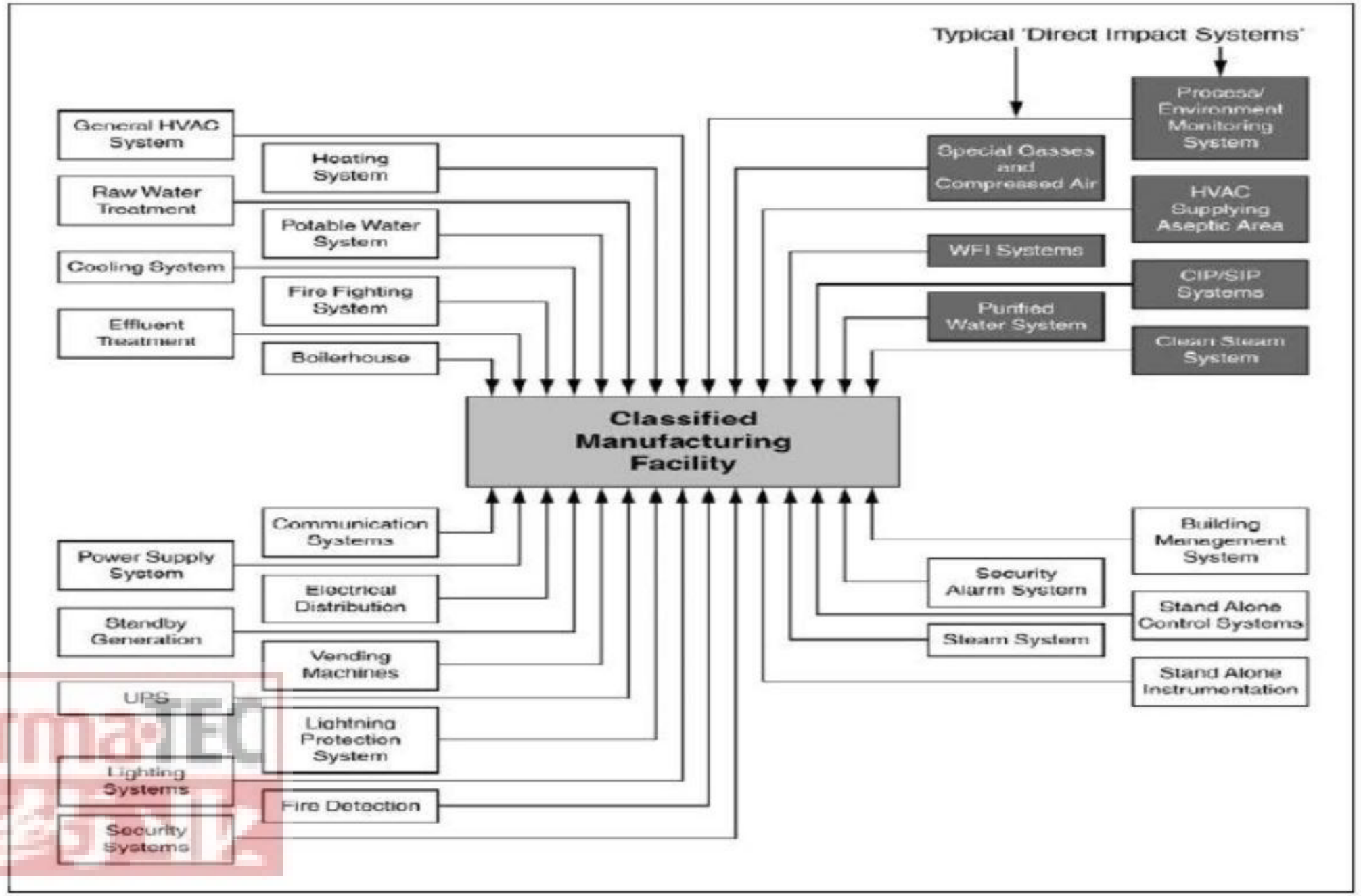
1. HVAC System for Cleanroom On GMP GMP洁净空调系统主要组成
2. HVAC System Zoning 空调系统分区
3. GMP ZONE Concept for PAL (Personnel Air Locker) GMP区域人净概念
4. GMP ZONE Concept for Material GMP区域物净概念
5. Recovery Time 自净时间
6. Bio Safety Level 生物安全级别

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

1. HVAC System for Cleanroom On GMP Aspect
洁净空调系统

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

Figure 8-1 Typical Facility Engineering Systems that Support Classified Space Production



EUGMP Vs ISO cGMP Vs ISO

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EU GMP

Cleanness	At rest	In operation	Remark
Grade A	ISO 5	ISO 5	The local zone for high risk operations.
Grade B	ISO 5	ISO 7	For aseptic preparation and filling.
Grade C	ISO 7	ISO 8	Clean areas for carrying out less critical stages in the manufacture of sterile products.
Grade D	ISO 8	Not defined	

FDA

TABLE 1- Air Classifications[a]

Clean Area Classification (0.5 um particles/ft^3)	ISO Designation[b]	≥ 0.5 µm particles/m^3	Microbiological Active Air Action Levels[c] (cfu/m^3)	Microbiological Settling Plates Action Levels[c,d] (diam. 90mm; cfu/4 hours)
100	5	3,520	1[e]	1[e]
1000	6	35,200	7	3
10,000	7	352,000	10	5
100,000	8	3,520,000	100	50

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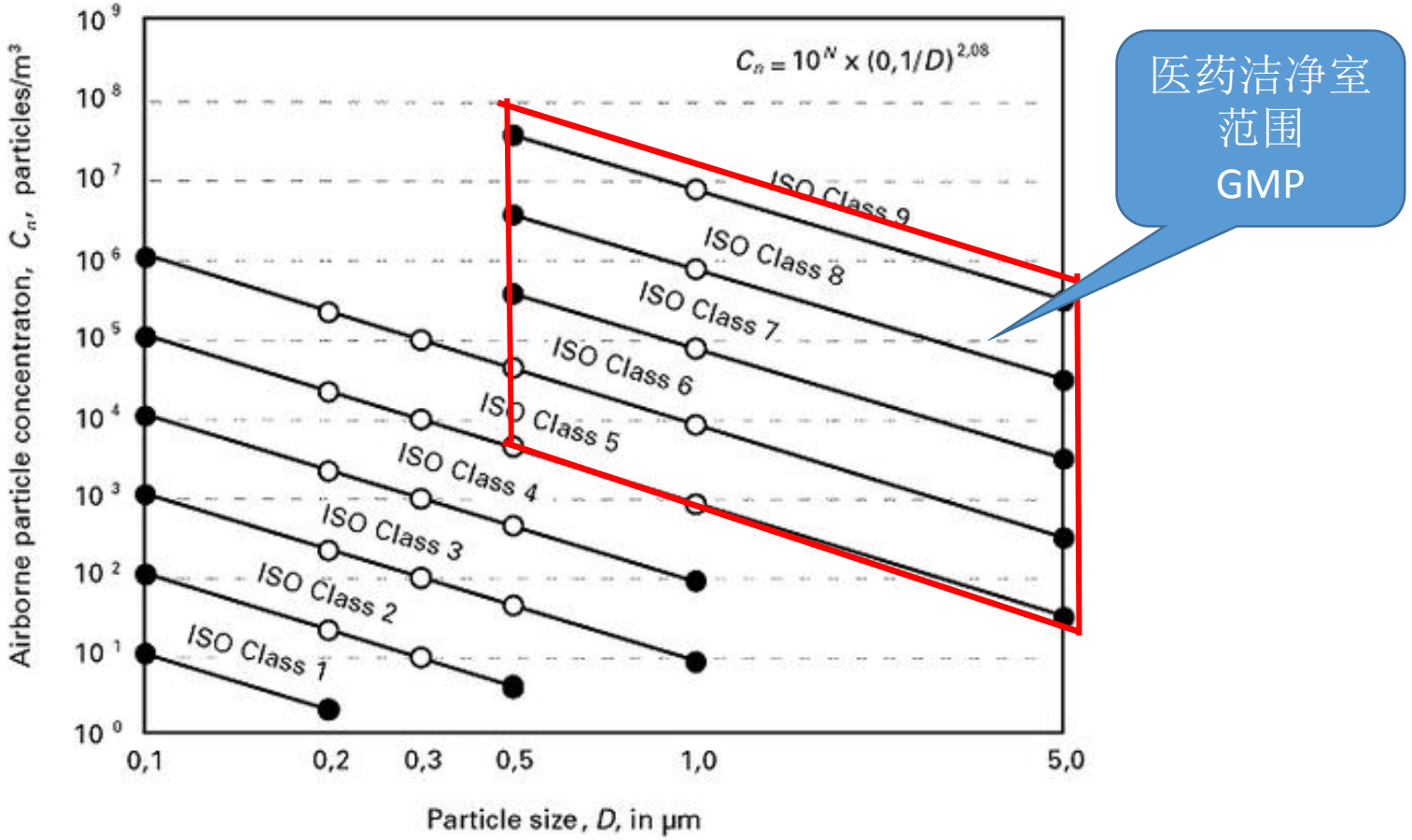
E-Mail: sunny.ke@leedzone.net

ISO14644-1



PS：ISO14644是针对所有工业洁净室，医药洁净室通常是ISO5以上，受控粒子粒径通常为0.5um.

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E-Mail: sunny.ke@leedzone.net

Main Code and Guideline of HVAC

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International:

- ASHEAR
- EU GMP
- United States Code of Federal regulations
  - ✓ 21 CFR parts 210 and 211 - manufacture, packaging and holding of drugs
  - ✓ 21 CFR parts 808, 812 and 820 - medical devices
  - ✓ 21 CFR part 11 - electronic records and signatures

Enforced by the United States Food and Drug Administration (FDA)

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

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General HVAC Requirements
洁净空调系统一般要求

1. the protection of the products from any contamination
   保护产品不受污染
2. the protection of the operators from the products
   保护操作者不受产品危害
3. the protection of the environment
   保护环境

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E-Mail: sunny.ke@leedzone.net

Key Points for Cleanroom洁净系统控制要素

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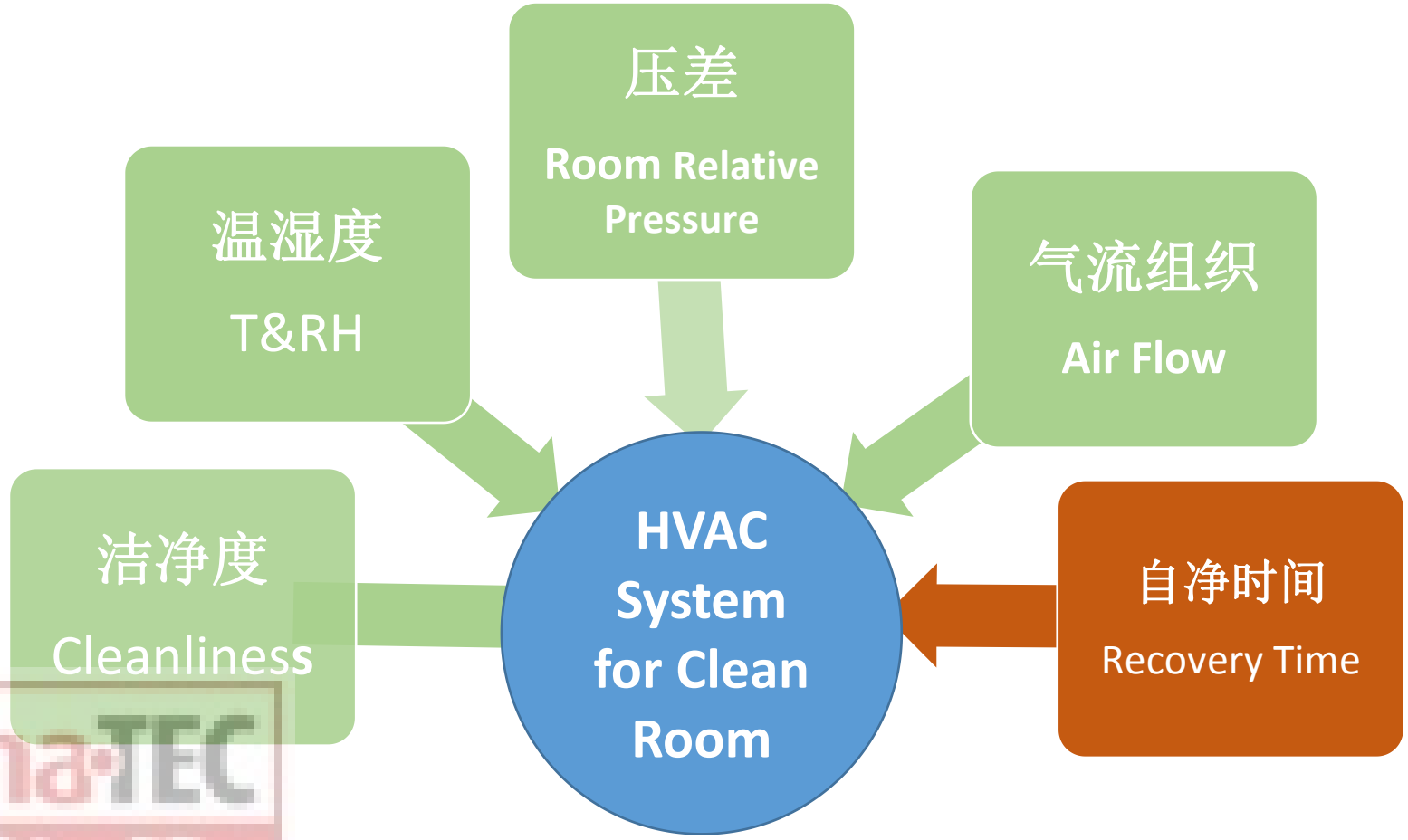

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E-Mail: sunny.ke@leedzone.net

Room Parameter principle for HVAC system
房间参数确定原则

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- **Design parameter :设计参数**
- **Normal Operating Range 正常运行参数范围;**
- **Operating Range: 运行参数范围**
- **Alert Range: 警戒范围**
- **Alarm Range: 报警范围**

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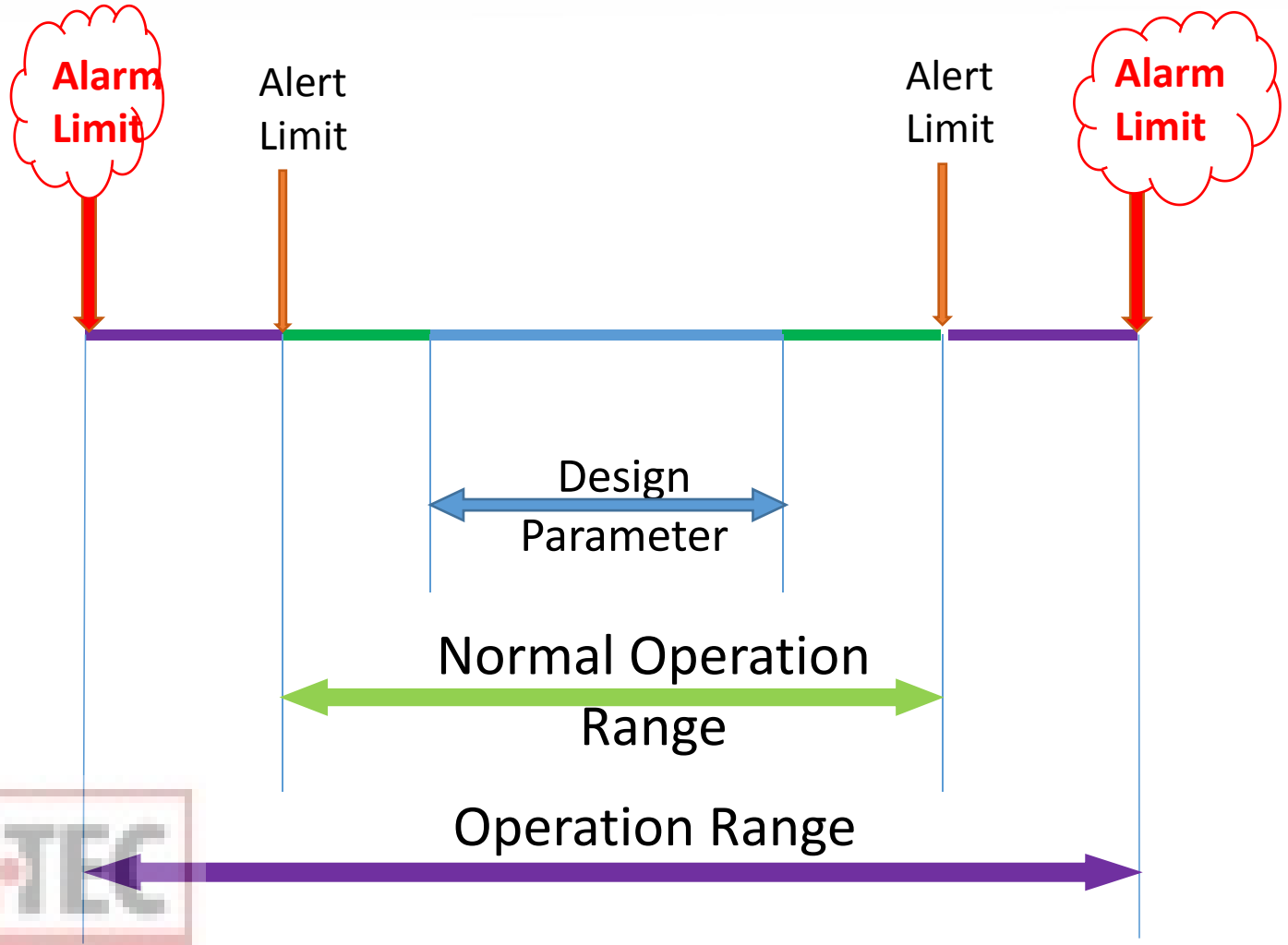
E-Mail: sunny.ke@leedzone.net

Key Points for Cleanroom洁净系统控制要素



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E-Mail: sunny.ke@leedzone.net

Room pressure 压差

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Room Pressure Differential/压差

相邻洁净区房间之间的压差应为 **10-15** Pa（指导值）。

------**EU GMP**

洁净区与非洁净区之间、不同等级洁净区之间的压差应不低于**10** Pa，相同洁净度等级不同功能的操作间之间应保持适当的压差梯度，以防止污染和交叉污染。

-----**中国新版GMP**

相邻洁净区房间之间的压差应为**12.5** Pa

-------**FDA**

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

Recovery time 自净时间

EU GMP，WHO，CFDA
推荐值为 **15~20** 分钟

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

2. HVAC System Zoning
洁净空调系统分区

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

HVAC系统分区原则：

空调系统的分区根据不同工艺要求，进行分区。不能为了分区而分区，要知道为什么要这样那样分区。找到最合适的空调分区。

- Different Classified Zone不同的洁净级别
- Different Process Requirement不同生产工艺
- Different or Same Cleanroom不同或同一洁净区
- Different Shift工作时间
- Support Area 辅助区域

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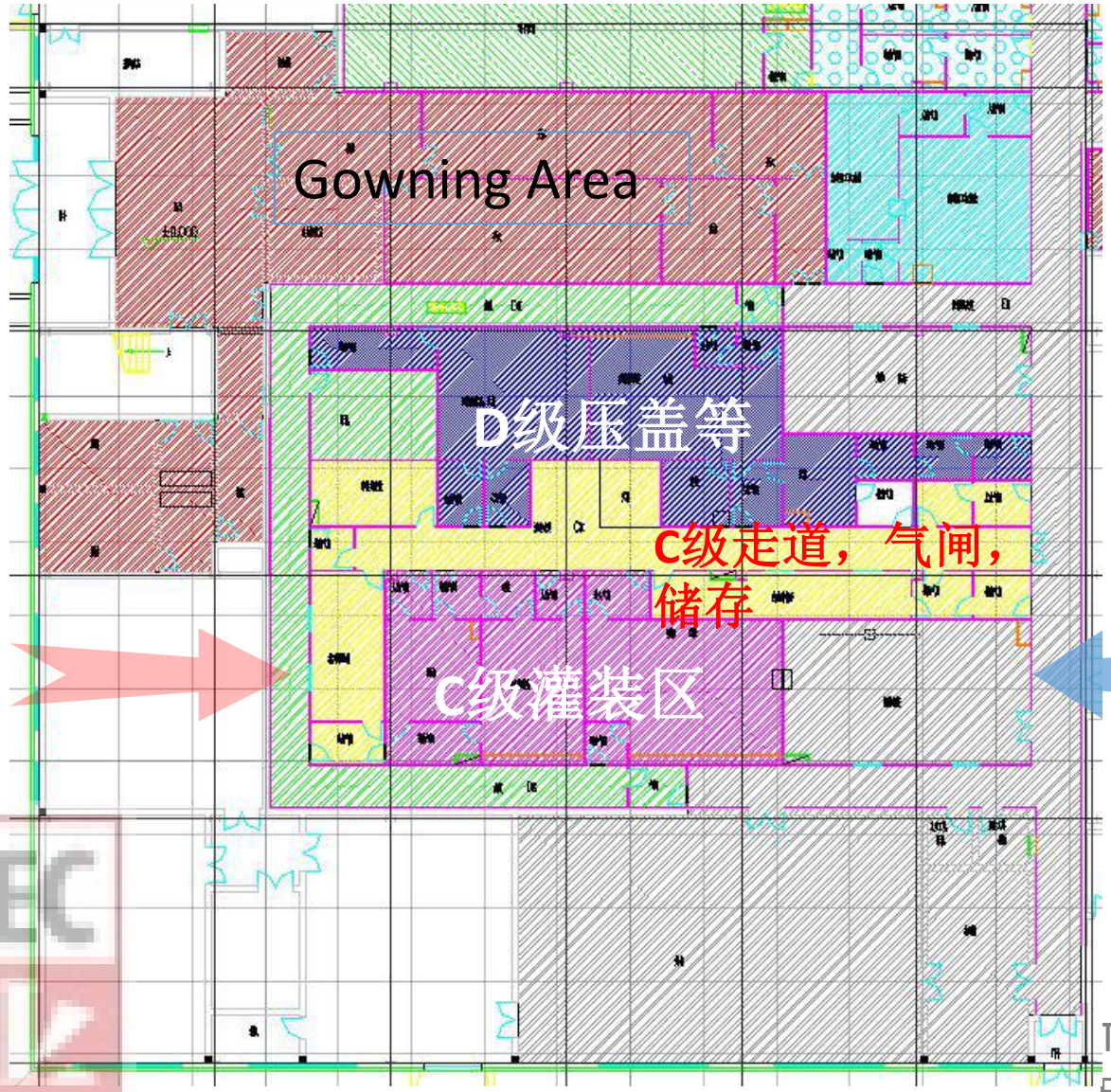
E-Mail: sunny.ke@leedzone.net

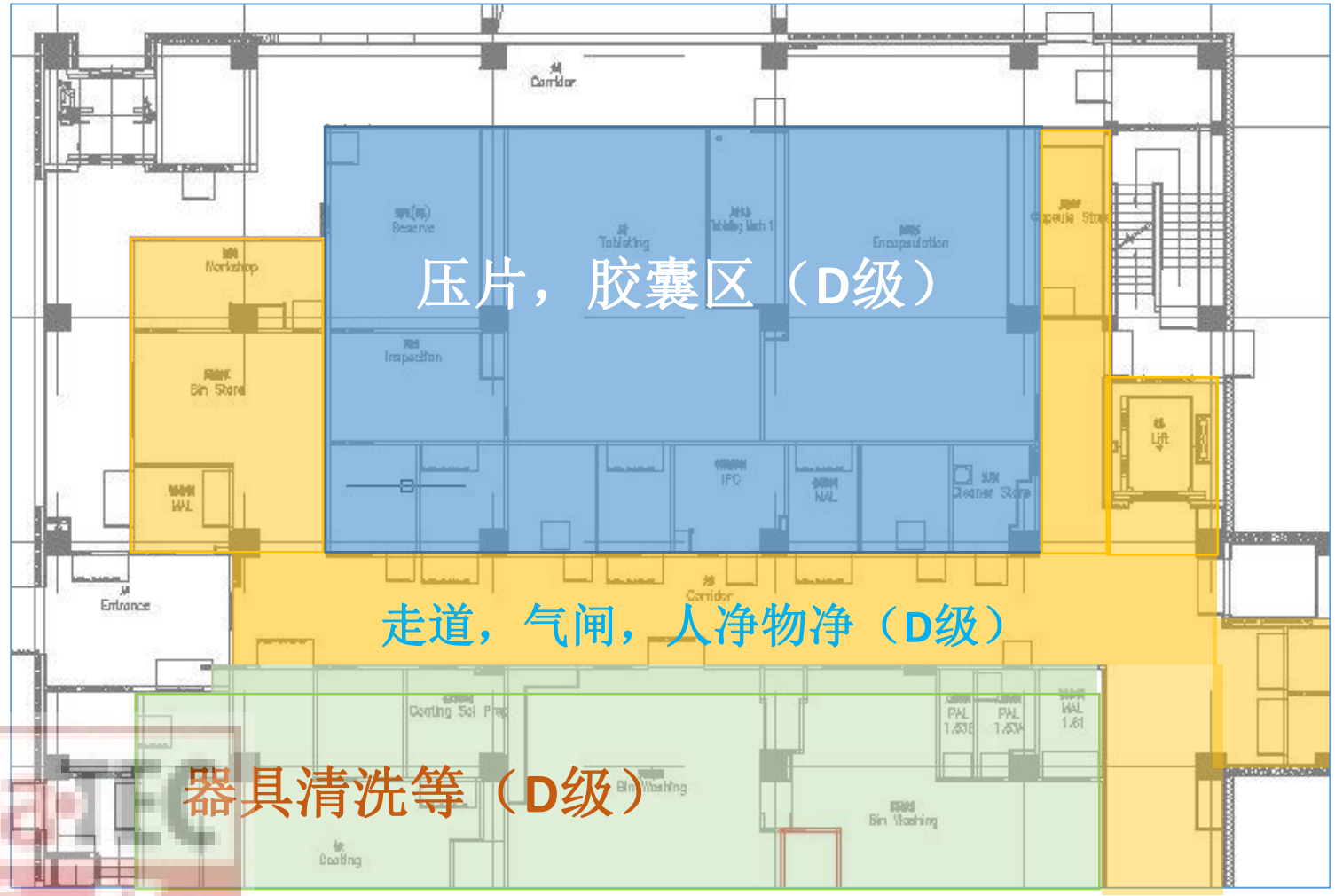


D 级走道

CNC区域

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

Sample-OSD：



Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

Sample-单抗API：

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

3. GMP ZONE Concept for PAL (Personnel Air Locker)

GMP区域人净概念

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

GMP ZONE Concept for Personnel GMP区域人净概念

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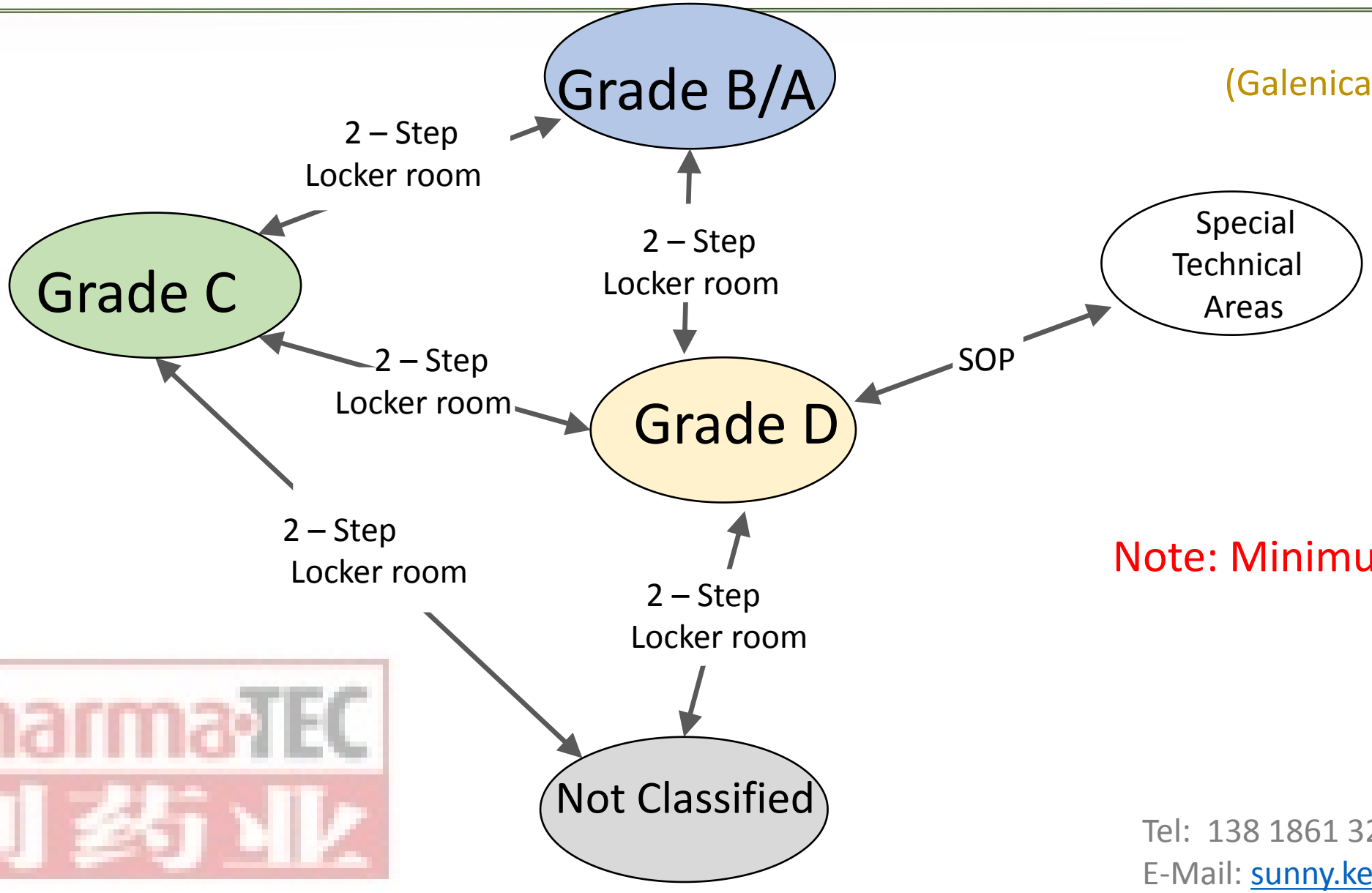
(Galenical Plants制剂车间)



Note: Minimum Requirement !

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

4. GMP ZONE Concept for Material
GMP区域物净概念

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

GMP ZONE Concept for Materials GMP区域物净概念

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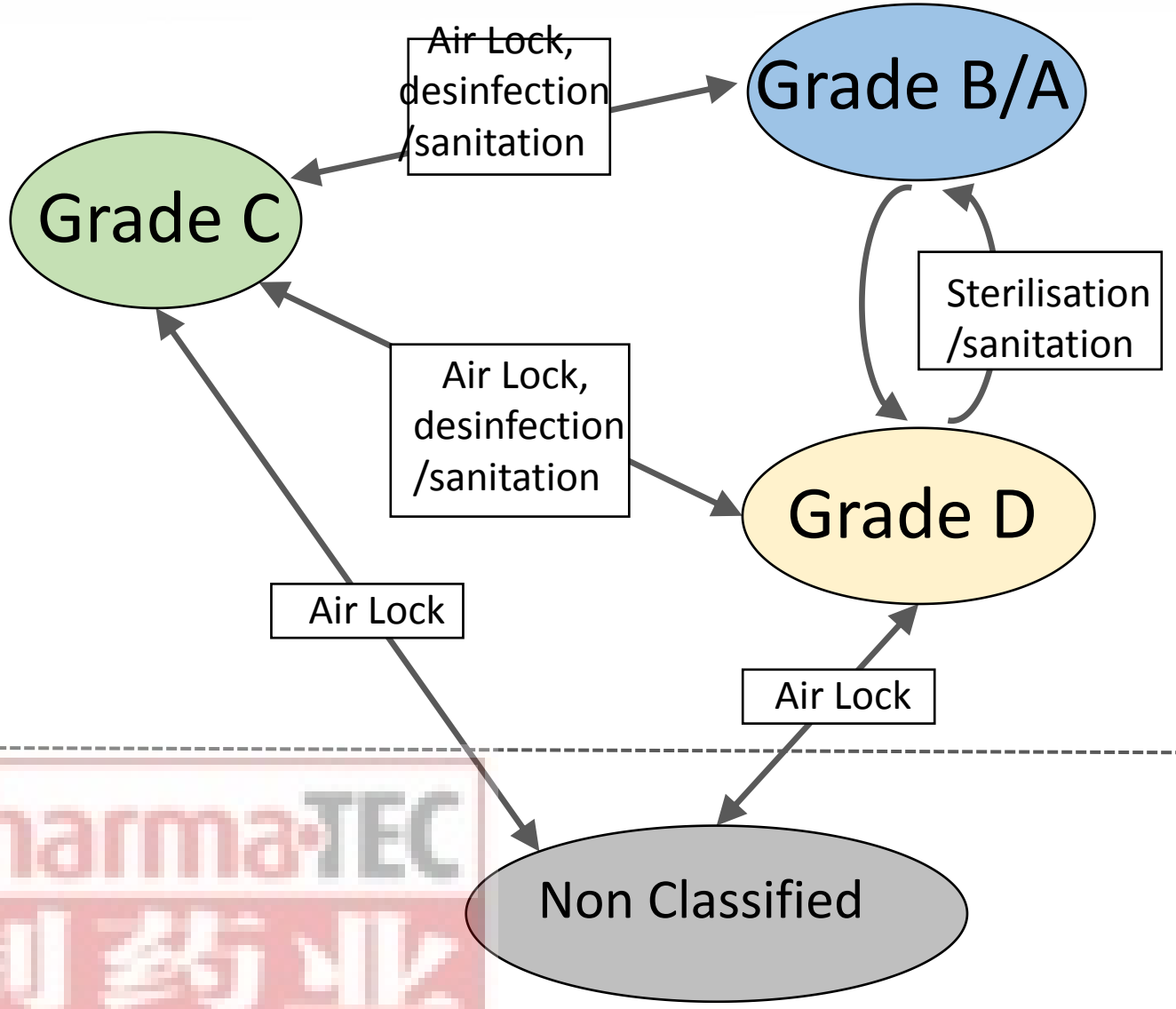

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

5. Recovery Time of HVAC System

洁净空调系统自净时间

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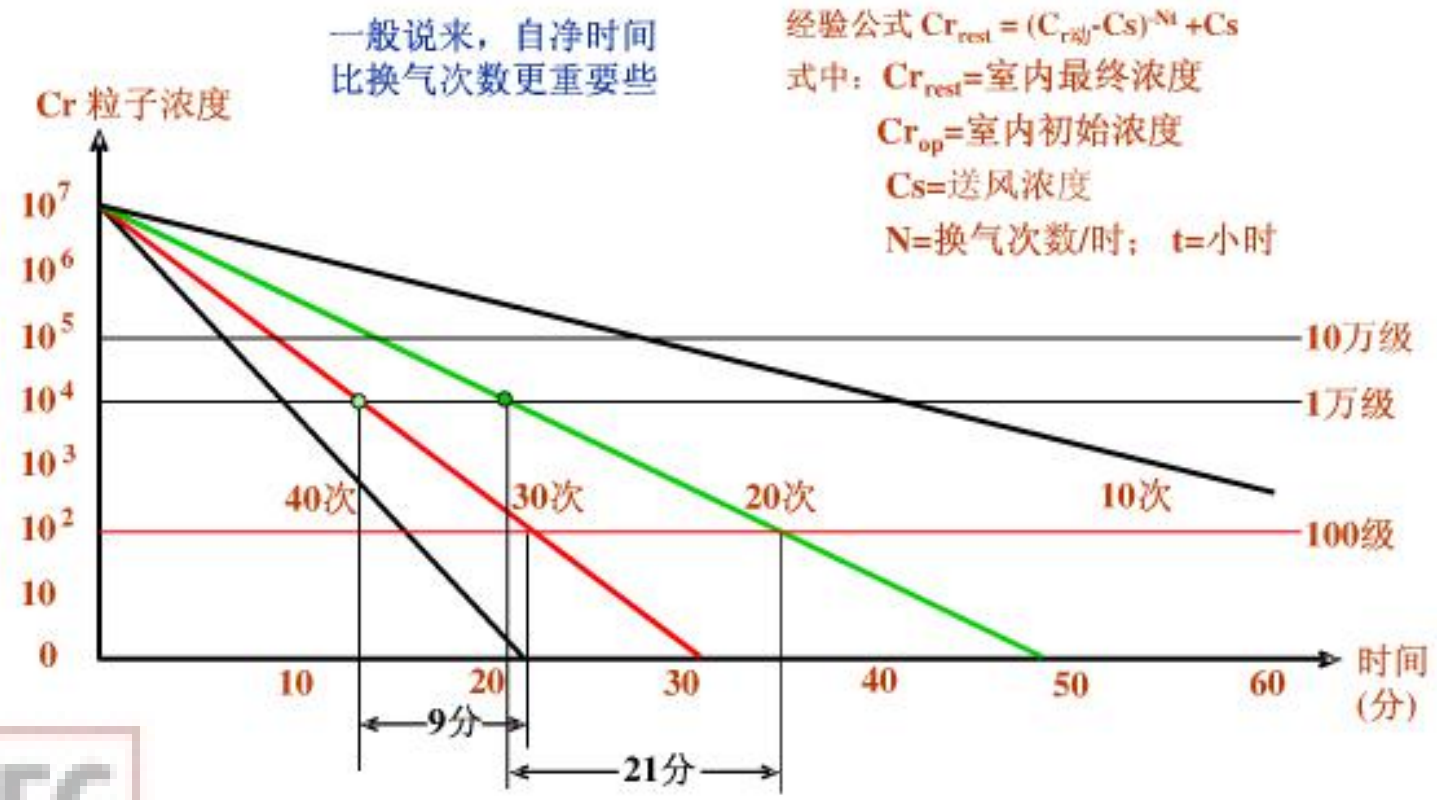
E-Mail: sunny.ke@leedzone.net

Recovery time VS Air Change Rate 自净时间 和换气次数：



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E-Mail: sunny.ke@leedzone.net

Regulation of Recovery time 自净时间法规

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EU GMP

Annex 1：Manufacture of sterile medicinal products：
无菌药品

14. The particle limits given in the table for the "at rest" state should be achieved after a short "clean up" period of **15-20 minutes** (guidance value) in an unmanned state after completion of operations.

表中"静态"下微粒限值，应在操作完成无人员的状态下，**15~20分钟**（指导值）达到。

15. The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended **"clean up period"** should be attained.

对C级和D级的动态监测，应根据质量风险管理的原则进行。监测要求和预警/动作限值将根据实际的操作情况。但是应达到推荐的"自净限值"。

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E-Mail: sunny.ke@leedzone.net

Regulation of Recovery time 自净时间法规

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【WHO】

Annex 4： WHO GMP for sterile pharmaceutical products

无菌药品

4.7.6 The airborne particle conditions given in Table 1 for the “at rest” state should be achieved in the absence of the operating personnel after a short “clean-up” or “recovery” period of about **15-20minutes** (guidance value), after completion of the operations. The particulate conditions given in table 1 for grade A “in operation” should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment.....

4.7.8 . The monitoring of Grade C and D areas in operation should be performed in accordance with the principles of quality risk management. The requirements and alert/action limits will depend on the nature of the operations carried out, but the recommended “**clean up period**” should be attained.

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

Regulation of Recovery time 自净时间法规

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新版GMP　附录1：无菌药品

第三章 洁净度级别及监测

第十条 应当按以下要求对洁净区的悬浮粒子进行动态监测：

（七）生产操作全部结束、操作人员撤出生产现场并经**15～20分钟**（指导值）自净后，洁净区的悬浮粒子应当达到表中的“静态”标准。

（八）应当按照质量风险管理的原则对C级洁净区和D级洁净区（必要时）进行动态监测。监控要求以及警戒限度和纠偏限度可根据操作的性质确定，但自净时间应当达到规定要求。

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

Regulation of Recovery time 自净时间法规

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Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacture Practice (cGMP)无菌药品

Air change rate is another important cleanroom design parameter. For class 100,000(ISO 8) support rooms, airflow sufficient to achieve at least **20 air changes per hour** is typically acceptable. Significantly higher air change rates are normally needed for class 10,000 and class 100 areas.

- Airflow patterns within the room to ensure sufficient mixing in turbulent cleanroom design, especially if air change rates are below **20/hour**, or if local sites of high airborne particles are observed.
- Recovery period from in-use to at-rest (common in EU facilities). **The European GMP suggests 15 to 20 minutes** as acceptable recovery time. Recovery time is a good indicator of the air system's overall effectiveness (its "robustness").

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

Recovery time 自净时间小结：

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EU GMP　World Health Organization　CFDA　FDA

自净时间(指导值)：
15～20分钟

最小换气次数（ISO8）：
≥ 20 times/h

注意：根据14644-3：（针对所有工业洁净室）
由初始浓度（N0），室内达到稳定的浓度（N），实际换气次数（n），可得到计算自净时间（t0），与实测自净时间（t）进行对比，一般的，如果t≤1.2t0,为合格。

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

6. Bio-Safety Level
生物安全级别

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

Regulation for BSL 生物安全级别

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GB50346生物安全等级

WHO生物安全等级

CDC&NIH生物安全等级

ISPE生物安全等级

ICHQ7生物安全等级

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

CDC&NIH生物安全等级

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Table 1: Application of this Guidance to API Manufacturing

Type of Manufacturing	Application of this guidance to steps (shown in gray) used in this type of manufacturing				
Chemical manufacturing	Production of the API Starting material	Introduction of the API starting material into process	Production of Intermediate(s)	Isolation and purification	Physical processing, and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing, and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing, and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/comminuting			Physical processing, and packaging
Biotechnology: fermentation/cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing, and packaging
"Classical" fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing, and packaging

Increasing GMP requirements

Tel: 138 1861 3241 Sunny ke
E-Mail: sunny.ke@leedzone.net

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Thank you for your attention!
Come to share with us.

PROJECT CATEGORIES 服务的工程类型

- ◆Pharmaceutical/ biopharmaceutical 生物工程
- ◆Medical device industry project 医疗器械项目
- ◆Monoclonal Antibody API 单克隆抗体项目
- ◆Vaccine projects 疫苗项目
- ◆Food and Nutrition Project 食品和营养项目
- ◆R&D Centers Project 研发实验楼项目
- ◆Electronics Project 电 子工程项目
- ◆Hospital & surgery 医院及手术室项目

Tel: 138 1861 3241 Sunny ke
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